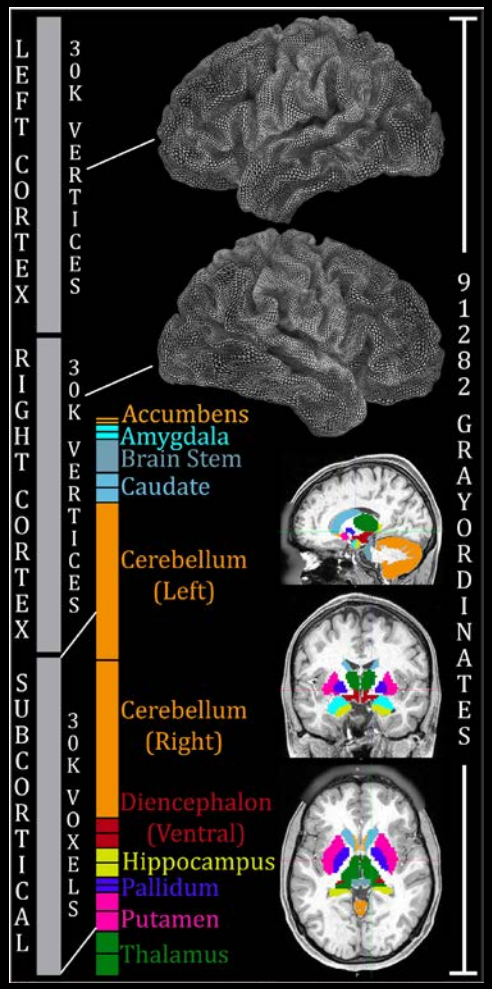
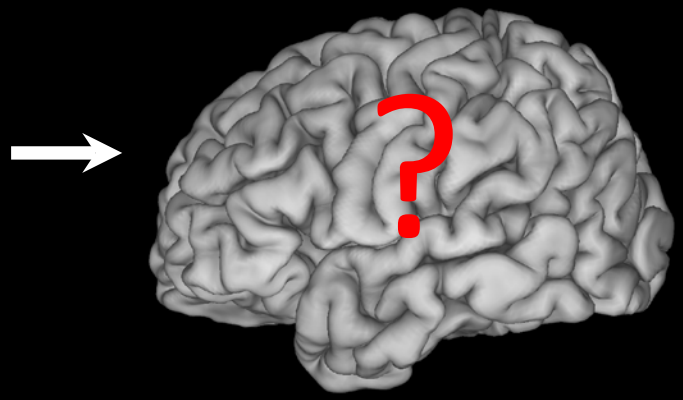
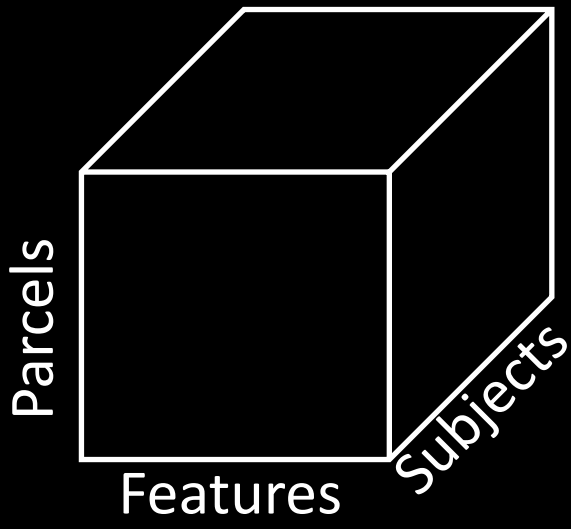
Brain Parcellation



Matt Glasser:

Lecture 2 of 3





Motivation

- In lecture 1, we learned about careful processing for preserving the high spatial and temporal resolution of the HCP data
- We also learned about the CIFTI grayordinates analysis paradigm and how it improves spatial localization across subjects and studies
- Now we'll focus on the cool neuroanatomy that we can see with this approach
- We'll discuss the statistical benefits of parcellation
- We'll see how parcellation can improve communication about the brain across studies and between investigators

Lecture Topics

- Why parcellate, when to do a parcellated analysis, and how should one parcellate
- Cortical architecture, myelin maps, and gradients as putative areal boundaries
- fMRI-based modalities and gradients
  - Function
  - Connectivity
  - Topography
- The HCP's multi-modal parcellation and sample parcellated analyses

Why Parcellate Your Neuroimaging Data?

- Dense data (i.e. grayordinate-wise or voxelwise) is very large
  - At 2mm there are 228,483 brain voxels in MNI space and 91,282 grayordinates
  - A dense timeseries is 91282 x 4800 x 4 = ~1.6GB and a dense connectome 91282 x 91282 x 4= ~32.5GB
  - These datasets require a lot of RAM, disk space, and CPU time to process
  - There are probably not substantially more than 500 brain parcels (a parcellated connectome would be 500 x 500 x 4 = ~1MB)
- Dense data has relatively low SNR, reducing statistical sensitivity
  - People often resort to spatial or temporal blurring to deal with the unstructured noise in dense data
  - Why not use the brain's neuroanatomical organization to our advantage by averaging within brain areas instead?
  - Boost SNR cleanly without averaging across brain areas (or, even worse, CSF, white matter, and other tissue types)—a much better form of smoothing
- Analysis of dense data requires an enormous number of statistical tests
  - Correcting for multiple comparisons conservatively leads to high significance thresholds (e.g. Bonferroni), reducing statistical power
  - Lots of less conservative methods, that give different results

Why Parcellate Your Neuroimaging Data?

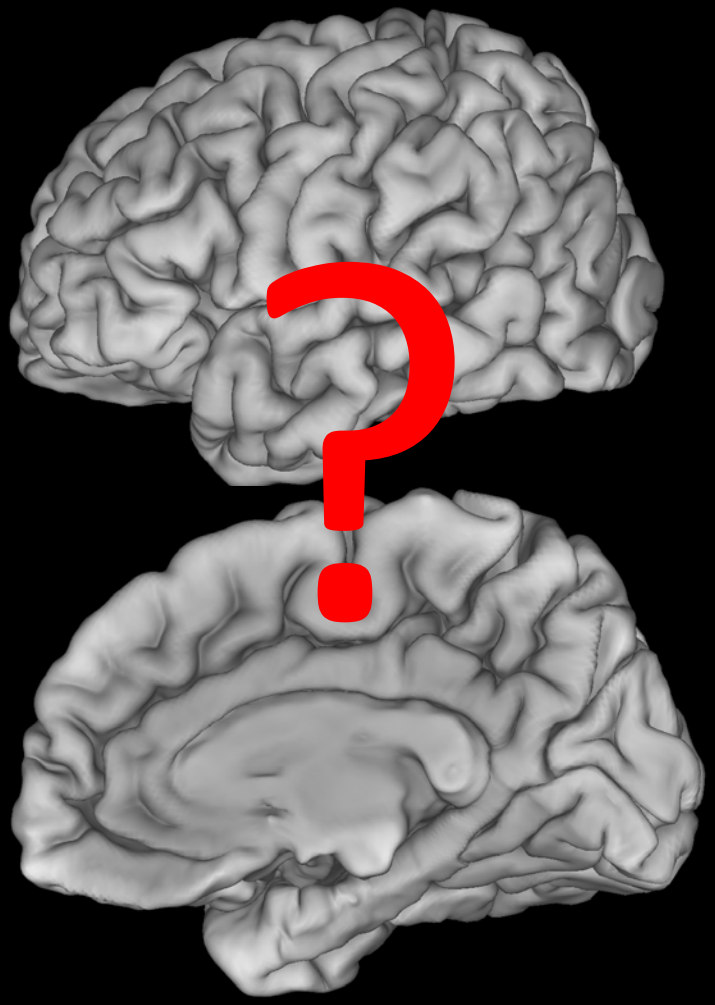
- Traditional neuroimaging analysis goes something like this
  - Smooth a dense dataset because the data have low SNR and are poorly aligned, blurring across cortical areas or even across tissues
  - Run computationally expensive voxel-wise statistical analysis
  - Have to correct voxel-wise analysis for a large number of multiple comparisons using statistical assumptions
  - Threshold to produce clusters and report these clusters as if they were the "brain areas" involved
- Wouldn't it be simpler, faster, and more sensitive to short circuit all this and just parcellate the dense dataset before running the analysis?
- Parcellations also help us make sense of complex brain data and facilitate communication between investigators
  - It's hard to compare notes if you're not even sure you are talking about the same thing
  - If we know how to find a brain area then we can study its properties in detail and try to understand what it does

When to Use "Dense" Analyses vs Parcellated Analyses

- Dense (i.e. grayordinate-wise) Analyses (minority of studies):
  - Analysis of fine details in MRI datasets smaller than a brain area--e.g. connectional topographies, intrareal heterogeneity
  - To make a parcellation
- Parcellated (i.e. area-wise) Analyses (most studies):
  - Any time the results will be presented as answering the question "what brain areas are …" (e.g. MNI data table)
  - Analysis of brain area activity, connectivity, and networks
  - Analyses of brain/behavior or brain/genetic relationships
  - Best place for integration of MRI and MEG data
- Keep in mind that one can always do a dense analysis on a restricted area if a parcellated analysis suggests something interesting (though one cannot do the reverse)

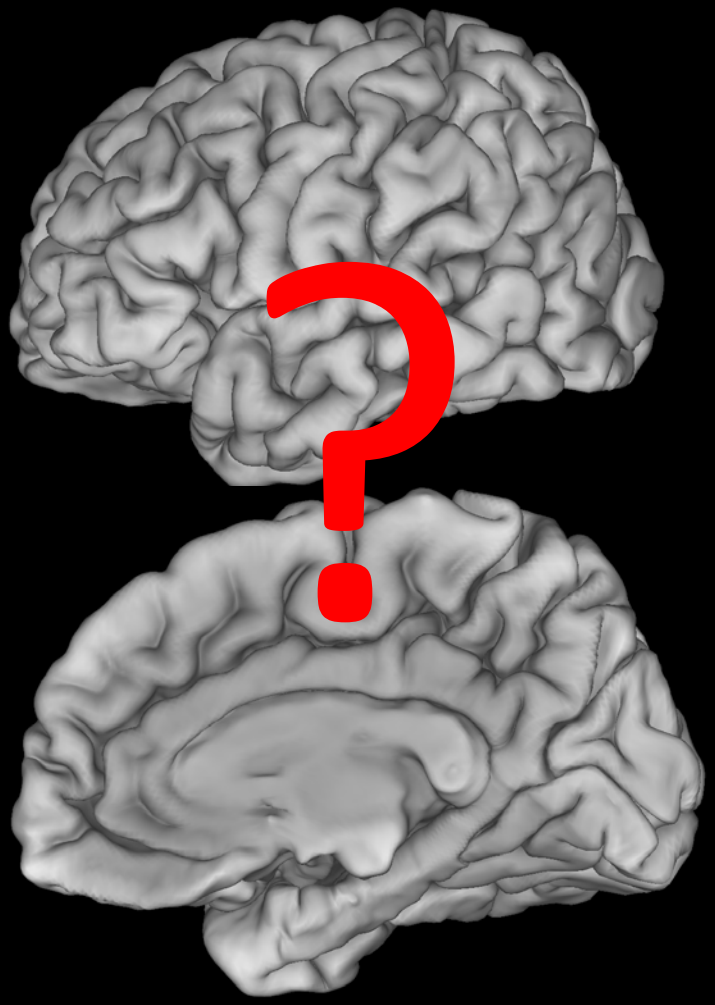
How Might One Parcellate the Brain?

- Recall from David's introduction that 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



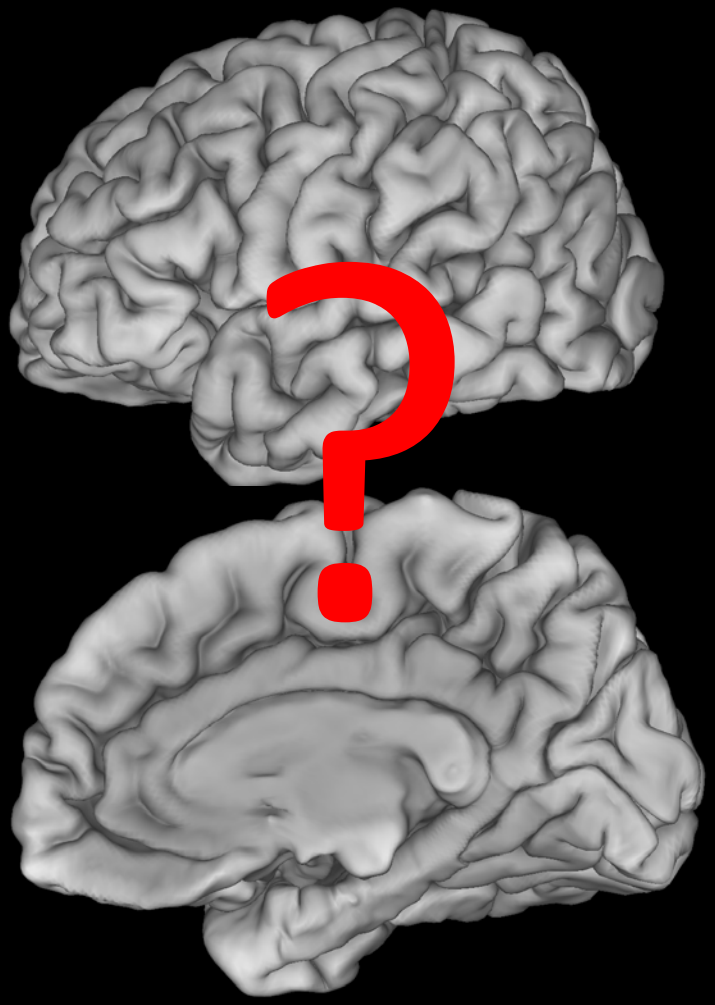
How Might One Parcellate the Cortex?

- 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
  - This is very different from using a statistical threshold to determine the boundary of an area



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



Summary of Why, When, and How to Parcellate

- Parcellation reduces the complexity of neuroimaging data while increasing statistical sensitivity and power and simplifying data analysis
- Parcellation improves communication between investigators
- Use a parcellated analysis when you are interested in brain effects at the areal or network level
- Use a dense analysis only when you have a specific hypothesis about effects that are finer grained than cortical areas
- Take advantage of multiple modalities when parcellating to increase confidence in objectively defined areal boundaries
- Identify cortical areas after defining them with respect to the extent literature when possible

Lecture Topics

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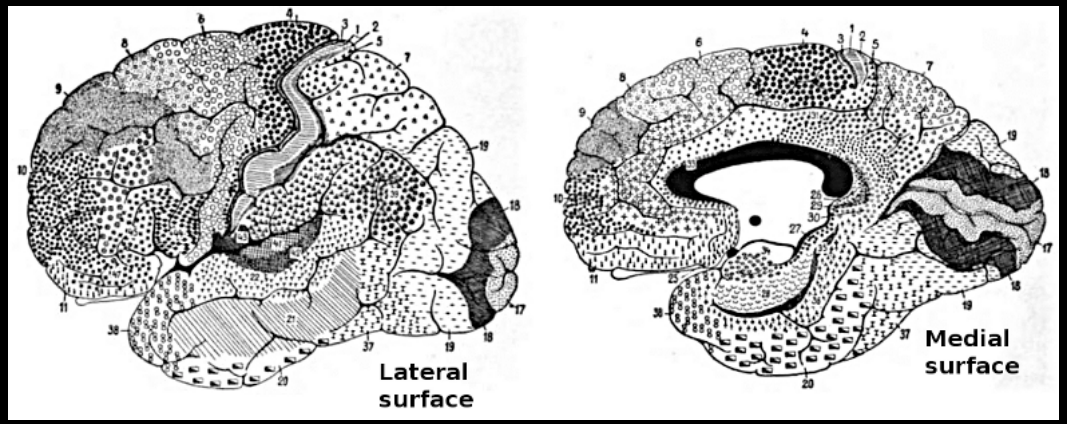
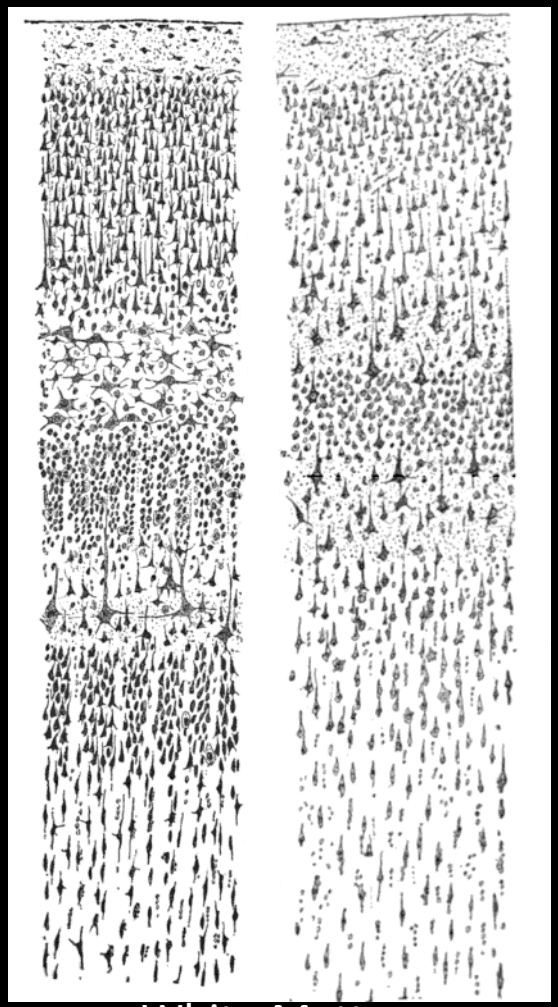
What Is Meant by the Architecture of A Cortical Area?

- Cortical areas can be distinguished based on differences in their cytoarchitecture or myeloarchitecture
- Cytoarchitecture refers to the location and quality of the neuronal cell bodies in the six cortical layers, revealed in appropriately stained tissue sections.
- Korbinian Brodmann used differences in post-mortem cytoarchitecture to make his famous hand-drawn map of 46 human cortical areas over 100 years ago

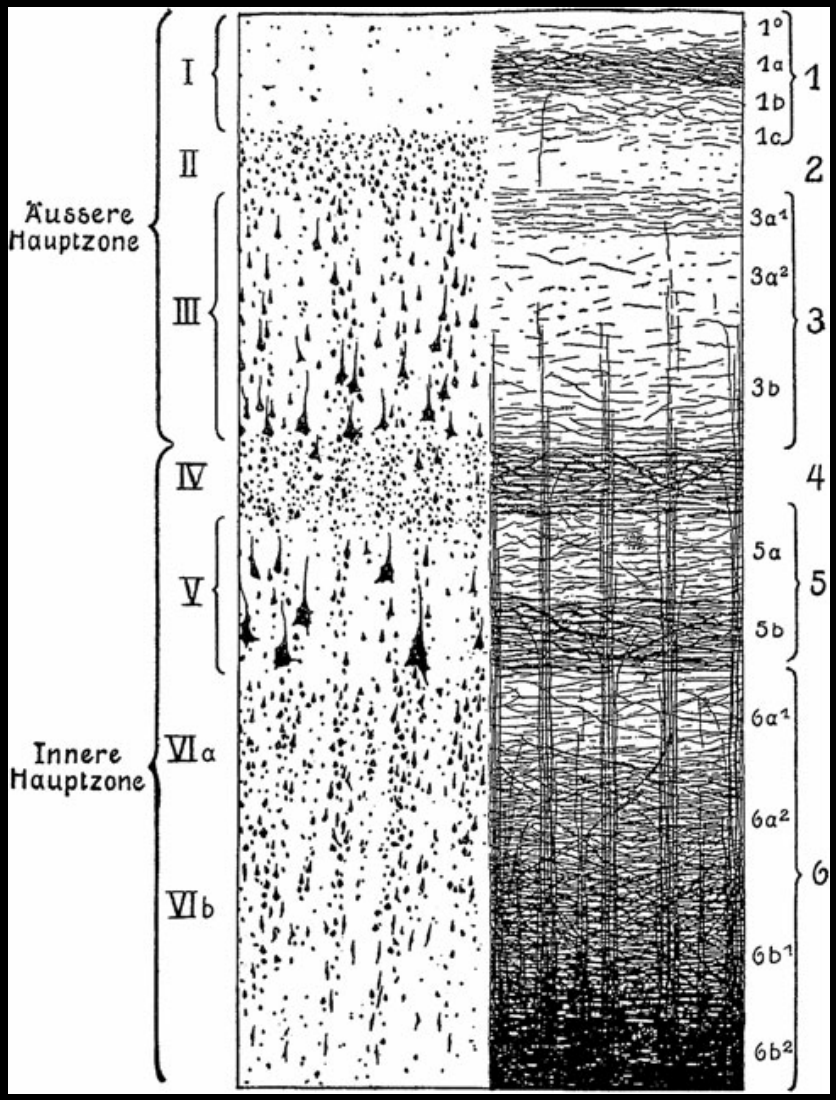


Brodmann 1909



What about Myeloarchitecture?

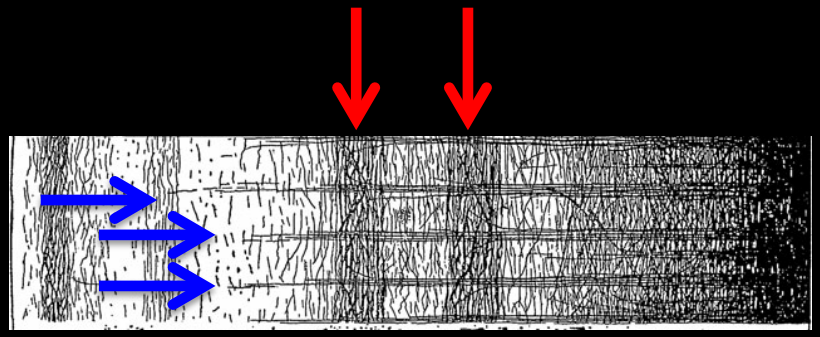
- Instead of staining for neuronal cell bodies, one stains tissue for myelinated axons.
- Cortical areas have differing amounts of myelinated fibers and differences in their distribution within the cortical layers
- Unlike cytoarchitecture, we have access to cortical myelin content maps in living subjects



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

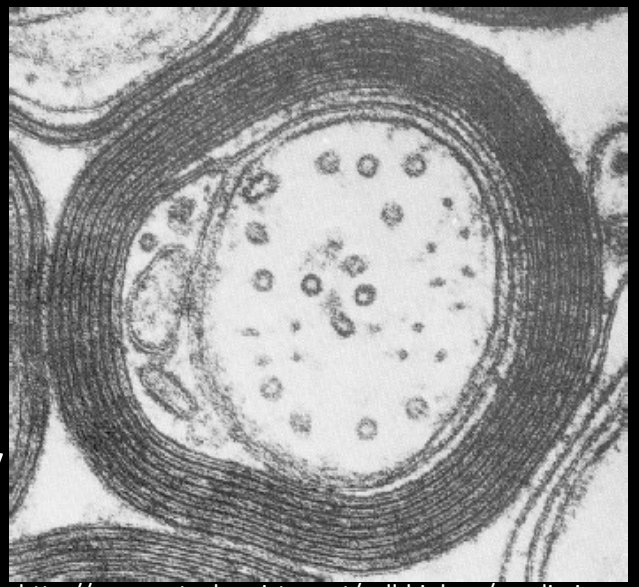


Pial Surface

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

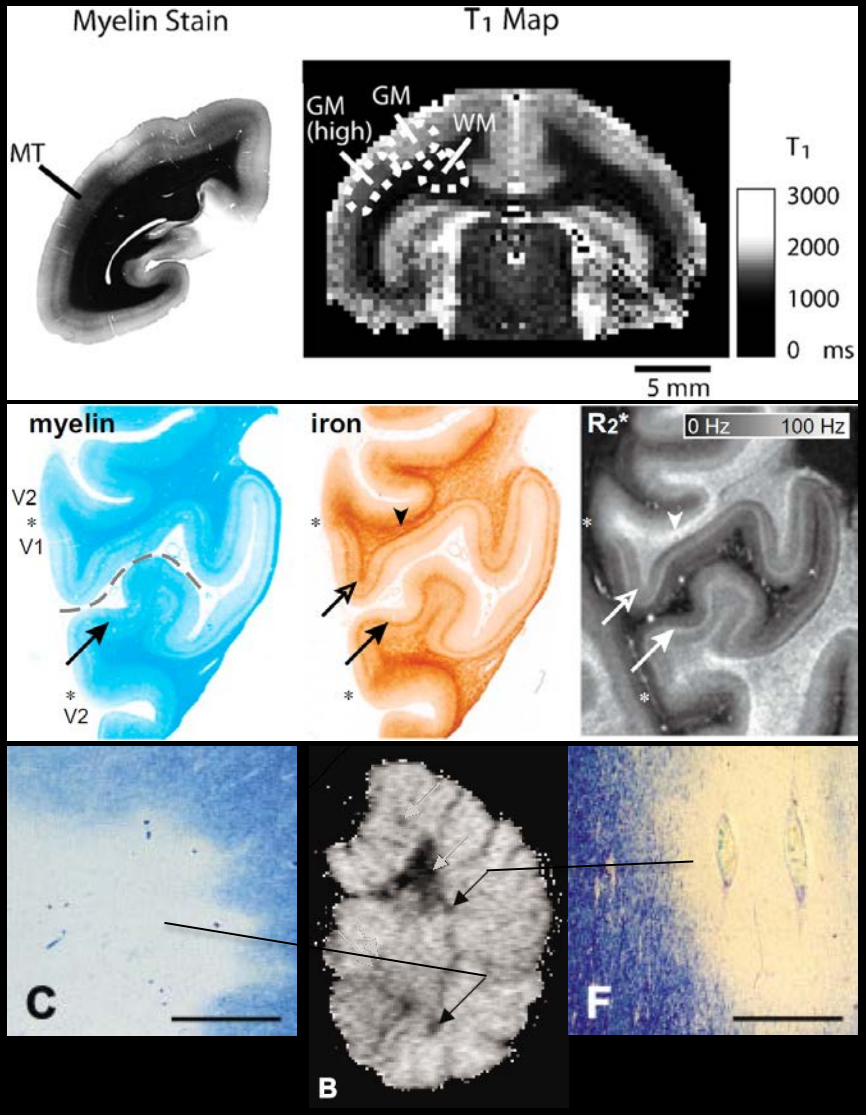


http://www.cytochemistry.net/cell-biology/myelin.jpg

- These properties lead to several forms of MR contrast:
  - T1 contrast (in T1 maps or T1w images)
  - T2* contrast (in T2* maps or T2*w images)
  - Magnetization Transfer (in MT maps or some kinds of T2w images)

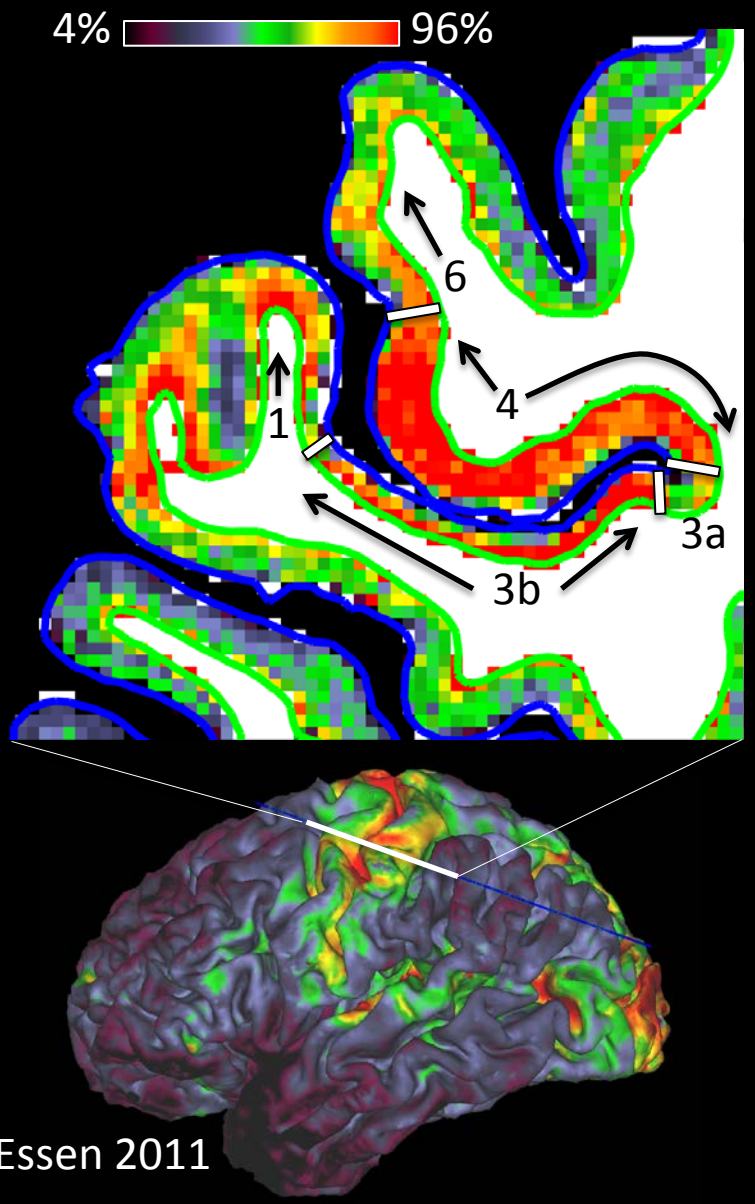
Histological Validation of MRI-based Myelin Contrast

- Bock et al 2009 compared T1 maps and T1w images to myelin stained sections of the same animal, showing similar patterns in both
- Fukunaga et al 2010 compared myelin and iron stained sections to R2* (1/T2*) maps showing close correspondence of all three modalities
- Schmierer et al 2004 compared myelin stained tissue in MS patients to MT maps, showing demyelination in MT-defined lesions



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

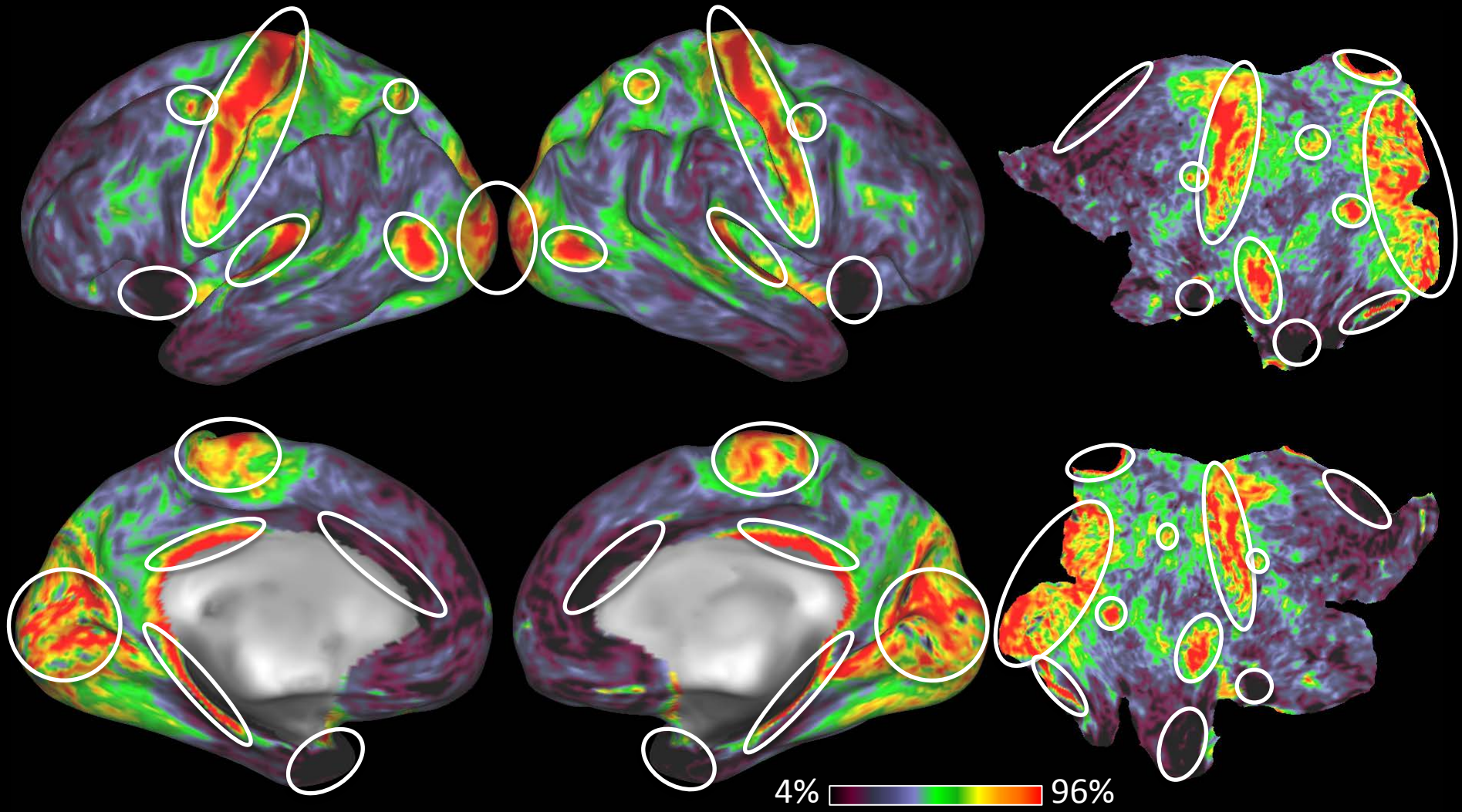


$$\frac{\text{T1w}}{\text{T2w}} \approx \frac{x * b}{(1/x) * b} = x^2$$

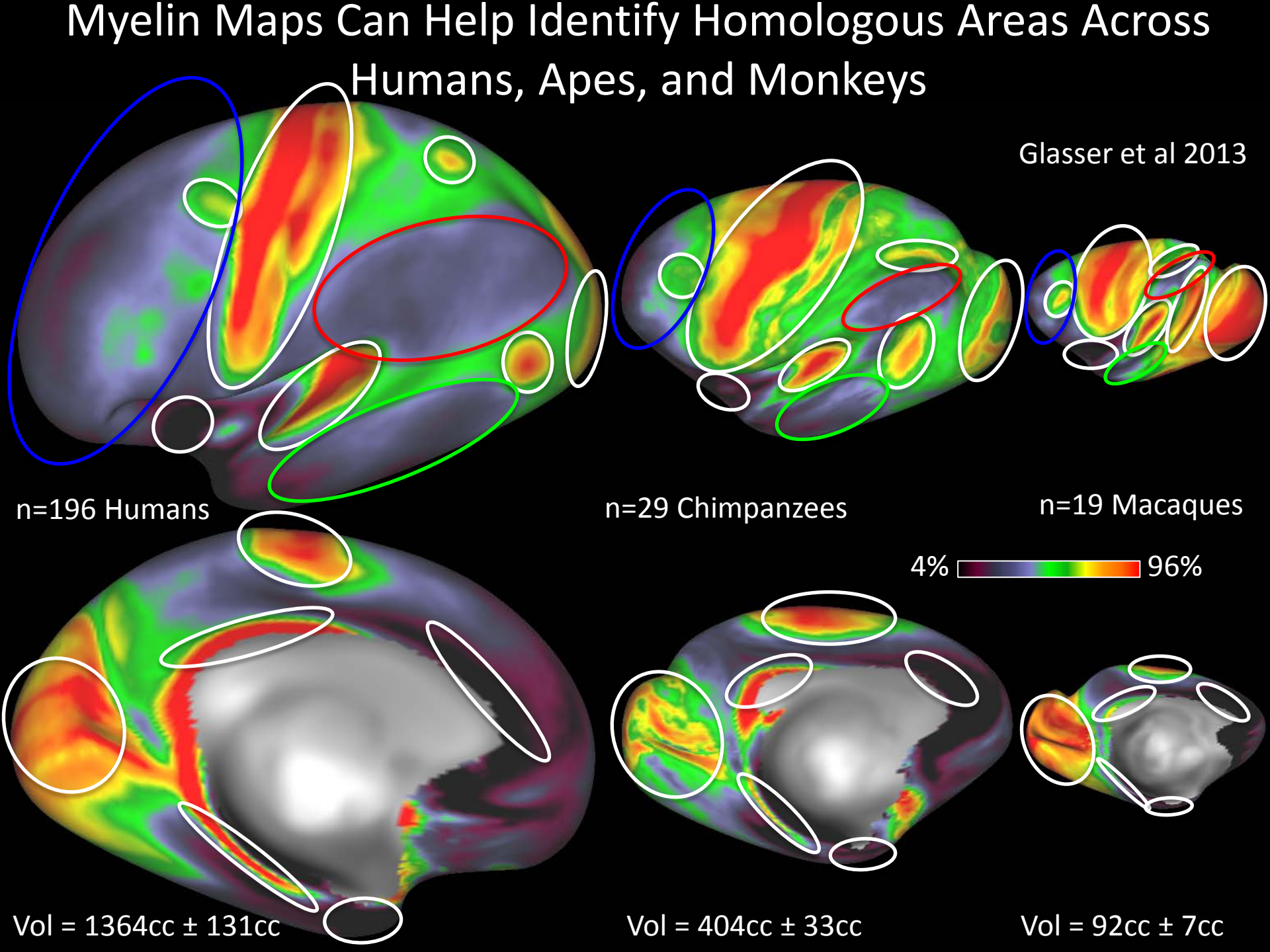
Glasser and Van Essen 2011

Myelin Maps of an Individual HCP Subject

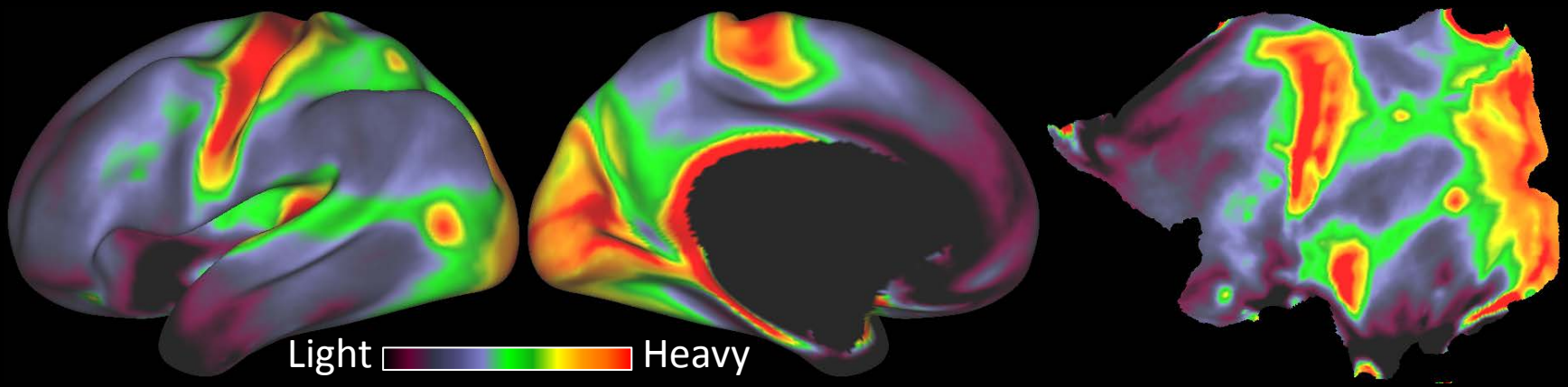
- Many cortical areal features are visible, including:



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



Architectonic → Myelin

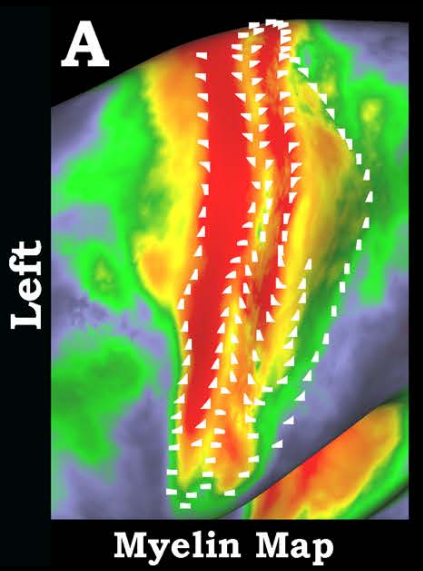


- If we want to define cortical areal borders, we're interested in where myelin content changes
- The spatial gradient tells us objectively where the transition in myelin content occurs
- The local maximum of the gradient is the most likely location of a potential areal border
- Some transitions are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

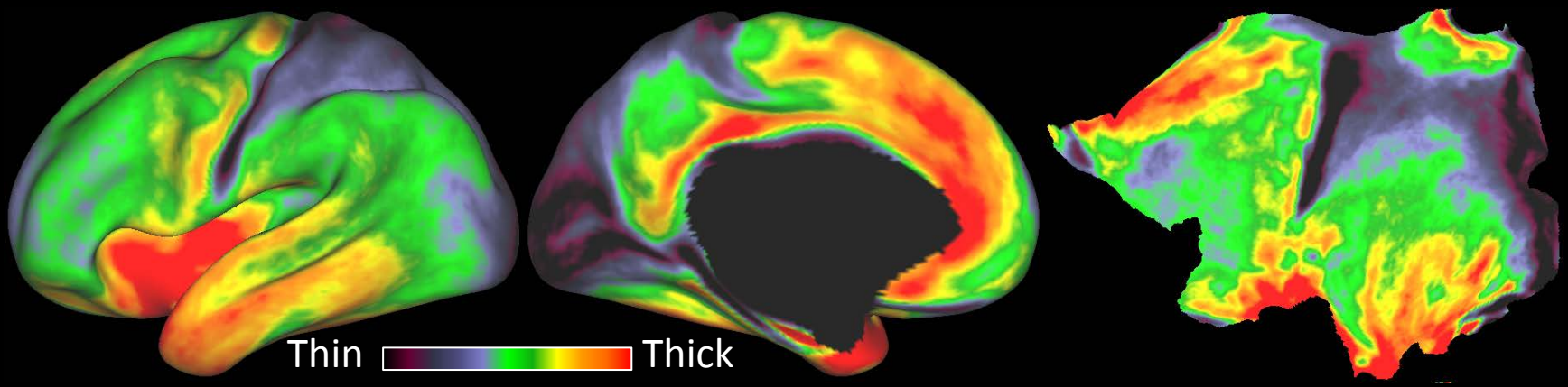
Neuroanatomical Validation of Myelin Maps

Glasser and Van Essen 2011
(69 In Vivo Humans)

Fischl et al 2008
(10 Post Mortem Humans)



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)

Summary of Cortical Architecture

- Cytoarchitecture and myeloarchitecture can be used to define cortical areas and their boundaries often agree
- Myelin content can be measured with MRI in living brains
- Early sensory and motor areas tend to have more myelin whereas higher cognitive areas tend to have less
- Lightly myelinated higher cognitive areas have expanded much more through evolution than have early sensory/motor areas
- Gradients reveal the most likely locations of areal boundaries
- Questions About Cortical Architecture?

Lecture Topics

- Why parcellate, when to do a parcellated analysis, and how should one parcellate
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- fMRI-based modalities and gradients
  - Function
  - Connectivity
  - Topography
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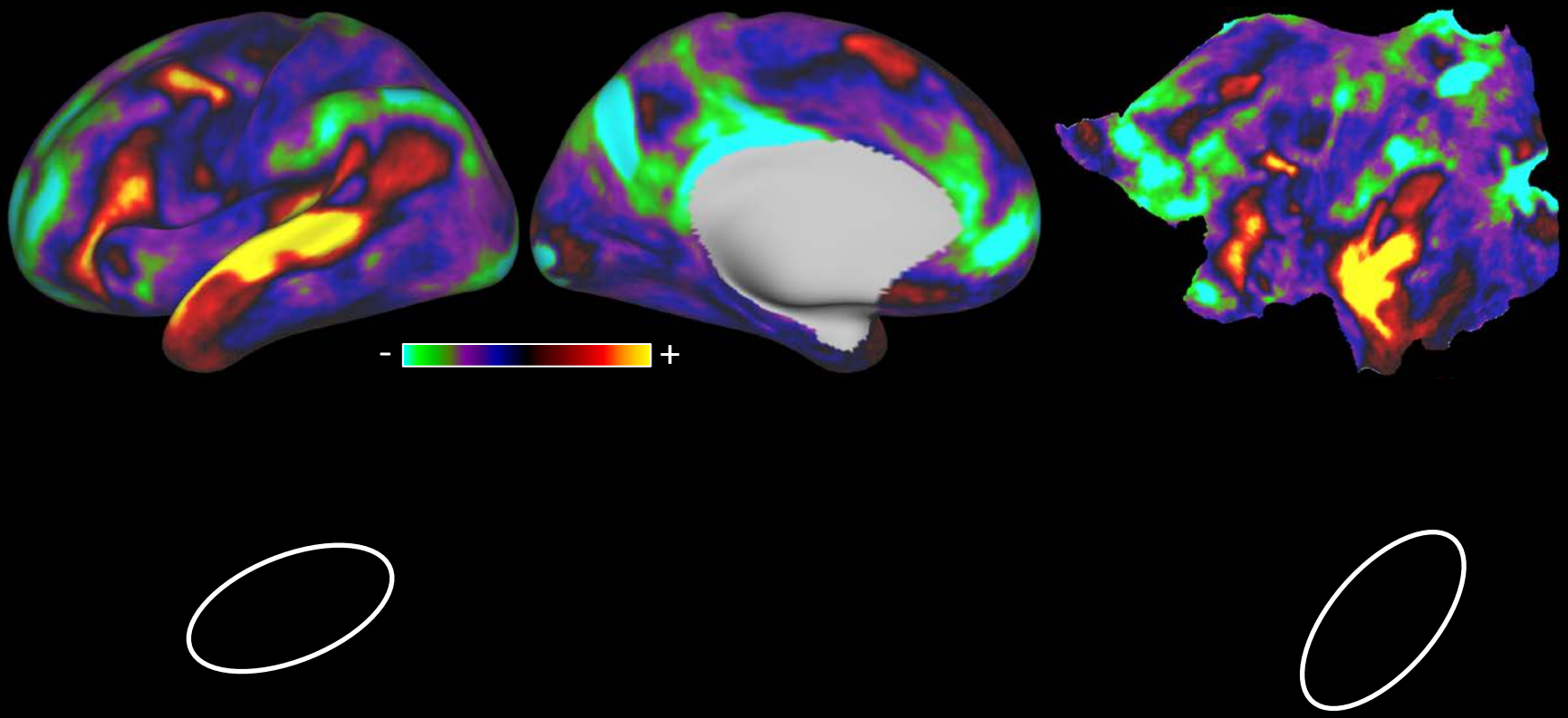
What about Function, Connectivity, and Topography?

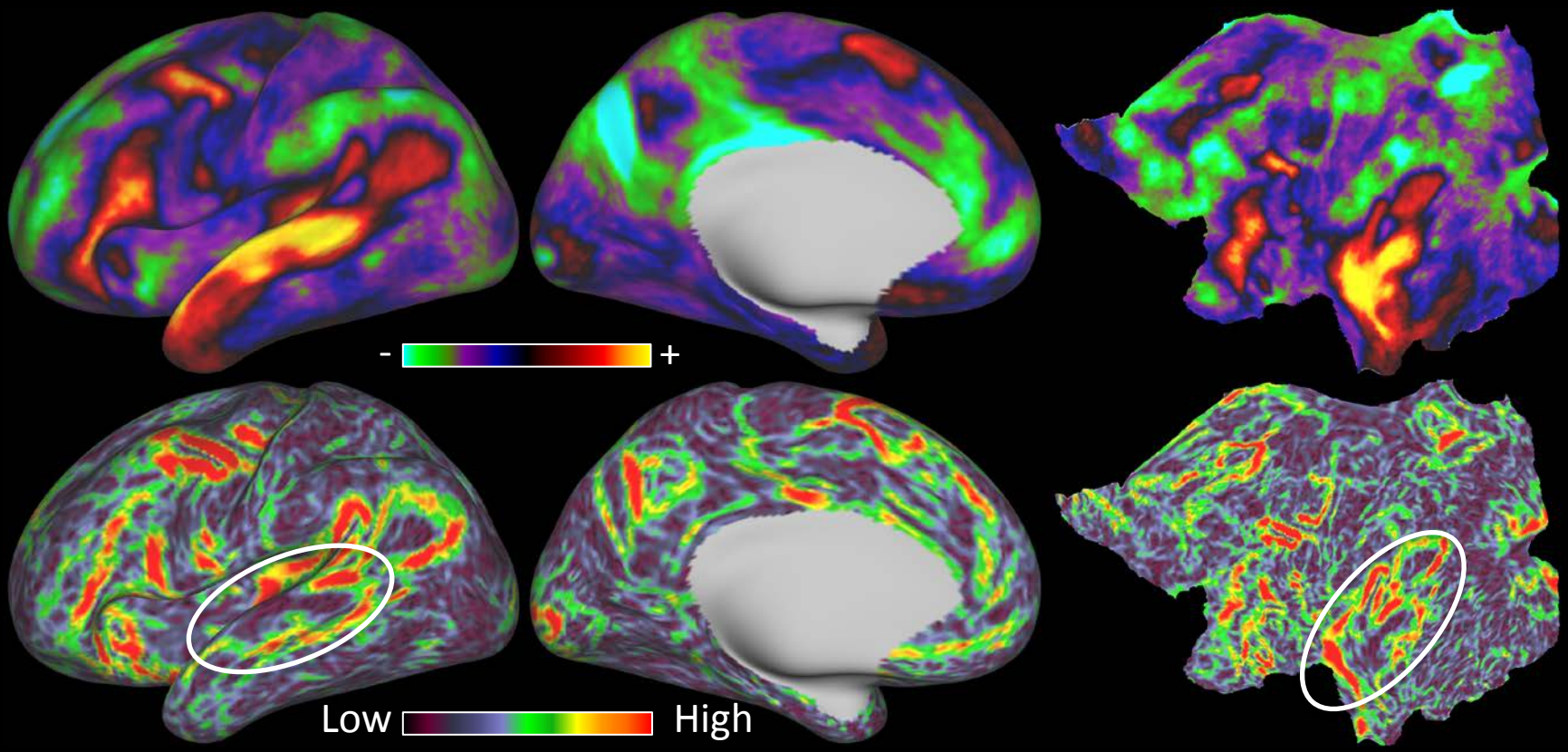
- fMRI is a particularly powerful modality for parcellation and can be analyzed to reveal
  - Function – Regression between timeseries and task design intended to activate regions involved in a particular function
  - Connectivity – Correlation between timeseries of different grayordinates, often when the subject is at rest
  - Topography – Correlation or Regression between timeseries to reveal patterns in connectivity (or function) within areas that define maps, one per area, of visual space, sound frequency, body surface, etc
- Each of these techniques has strengths and weaknesses for parcellation
  - Function
    - Strength: Tells you something about what an area is doing, more robust to structured noise
    - Weakness: Not very efficient in terms of CNR & brain coverage / unit time
  - Connectivity
    - Strength: Very efficient in terms of CNR & brain coverage / unit time
    - Weakness: Cannot tell you about function by itself, not robust to structured noise (data cleanup is critical, as Steve will tell you in the next lecture)
  - Topography
    - Strength: When present it is particularly definitive for parcellation and identification
    - Weakness: Not always present or not yet understood

Function → task fMRI → STORY vs REST



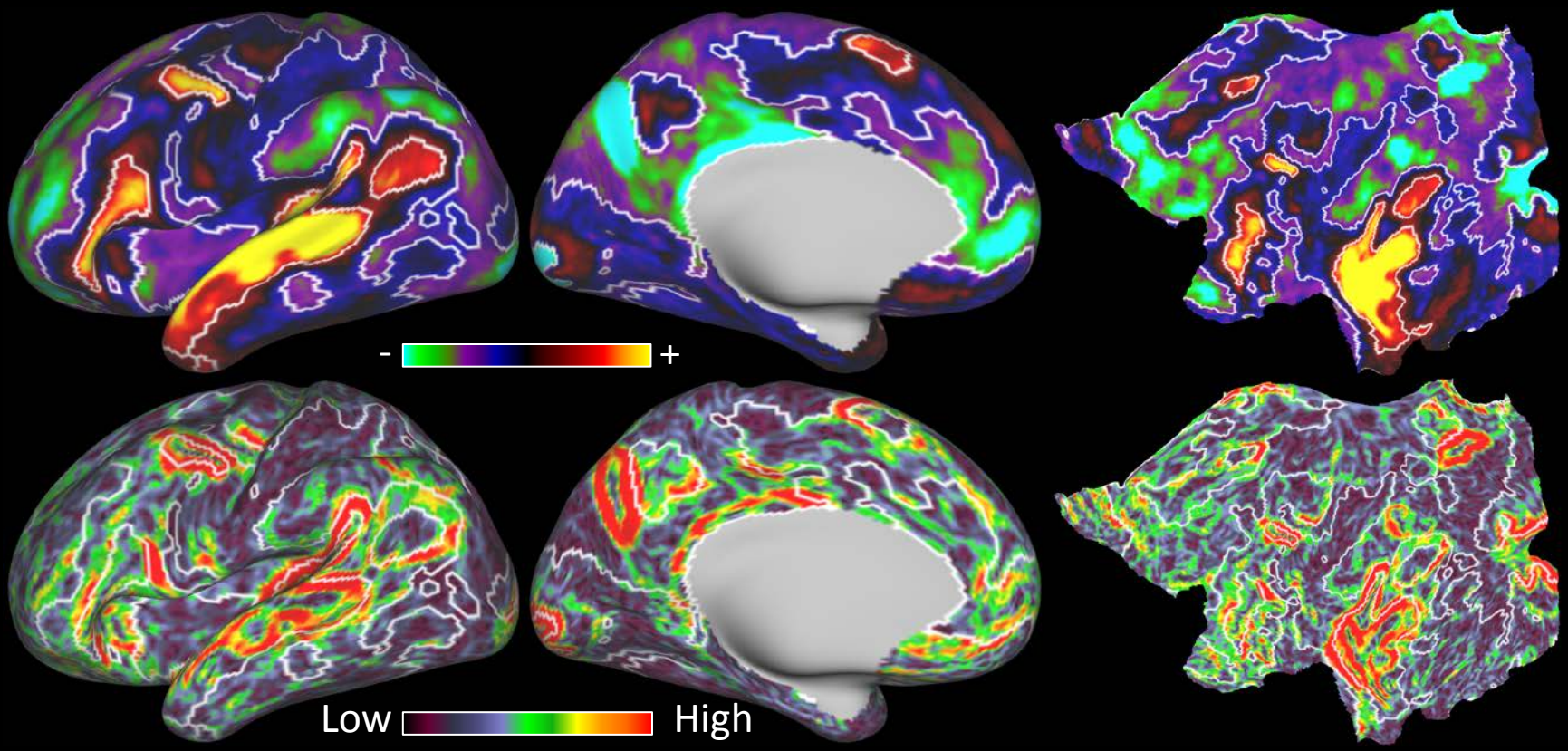
- Positive areas have more activity during the task relative whereas negative areas have more activity during resting
- tfMRI contrast beta maps (i.e. effect size maps) produce gradients just like the architectonic maps
- Why not use z-statistical significance maps for making gradients?

Function → task fMRI → STORY vs REST → Gradients



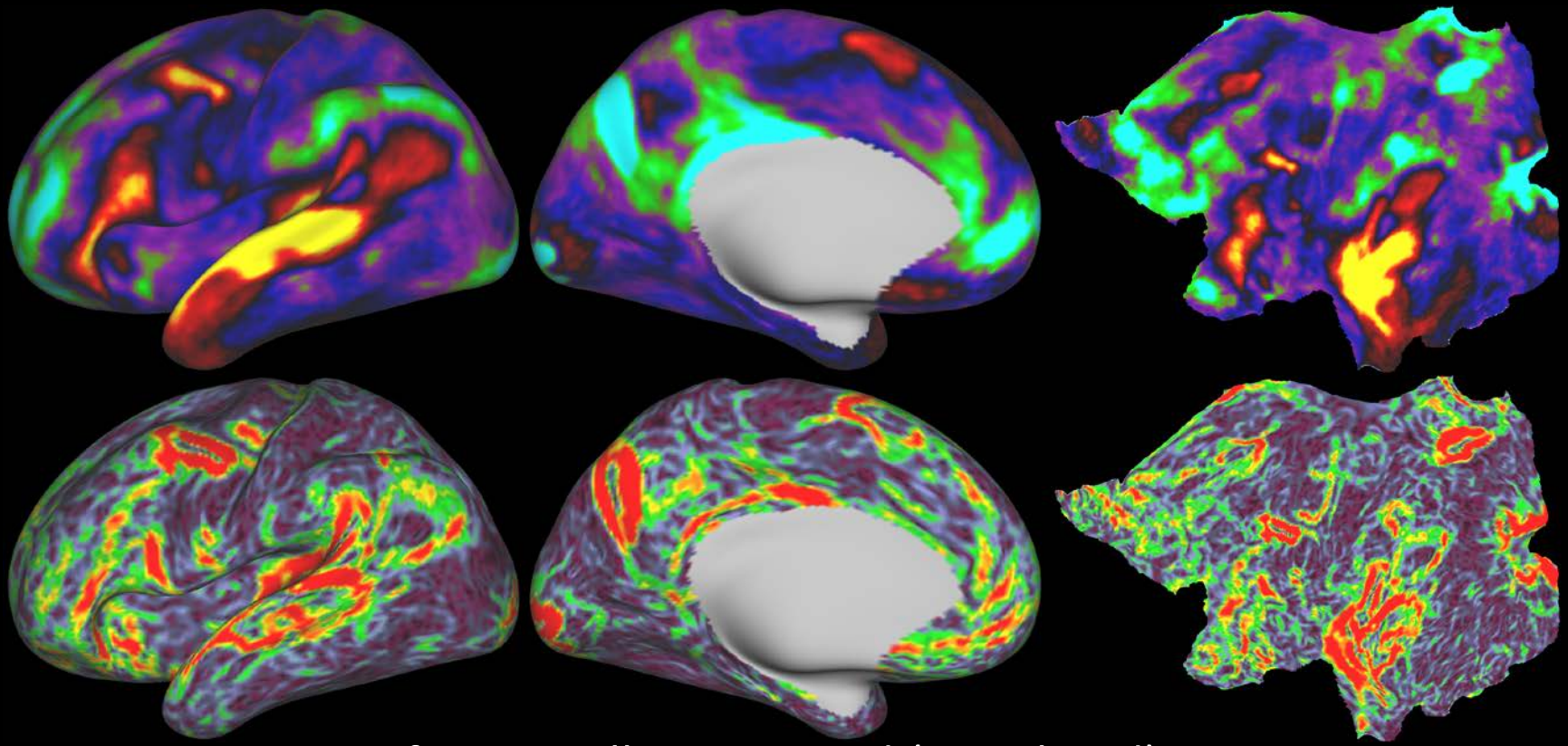
- Gradients of statistical significance maps are not the same as gradients of effect size maps
  - zstat maps have had a number of nonlinear transformations applied to them to scale them according to sample size and measurement precision
- In parcellation, we are interested in the location where the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

Function → task fMRI → STORY vs REST → Gradients



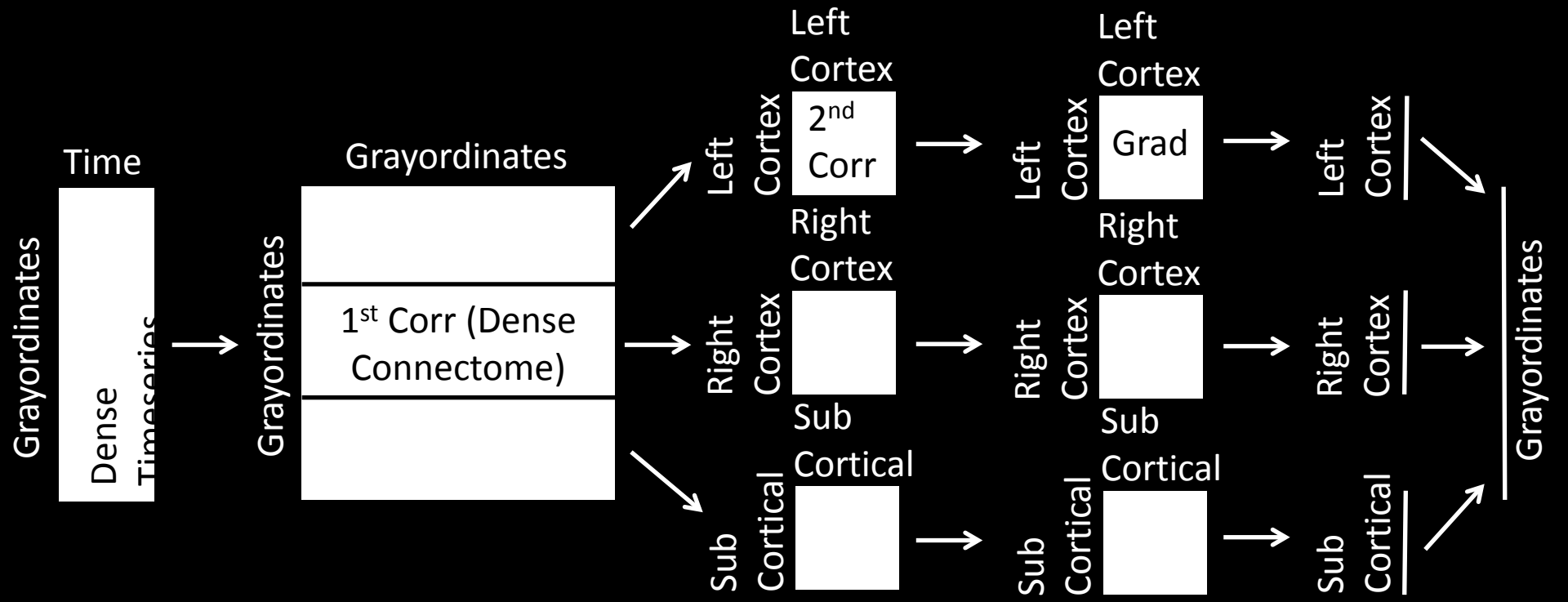
- What about defining regions based on statistically thresholded zstats?
- Even a very conservative zstat threshold (two tailed Bonferroni correction of 91282 grayordinate tests) often has little to do with the strongest effect size gradients
  - "Every thing is significant" because of the large number of subjects
- At the same time the threshold contour is not as reproducible as the effect size gradients
- Any questions about tfMRI and gradients?

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 that areas that activate together are often functionally connected

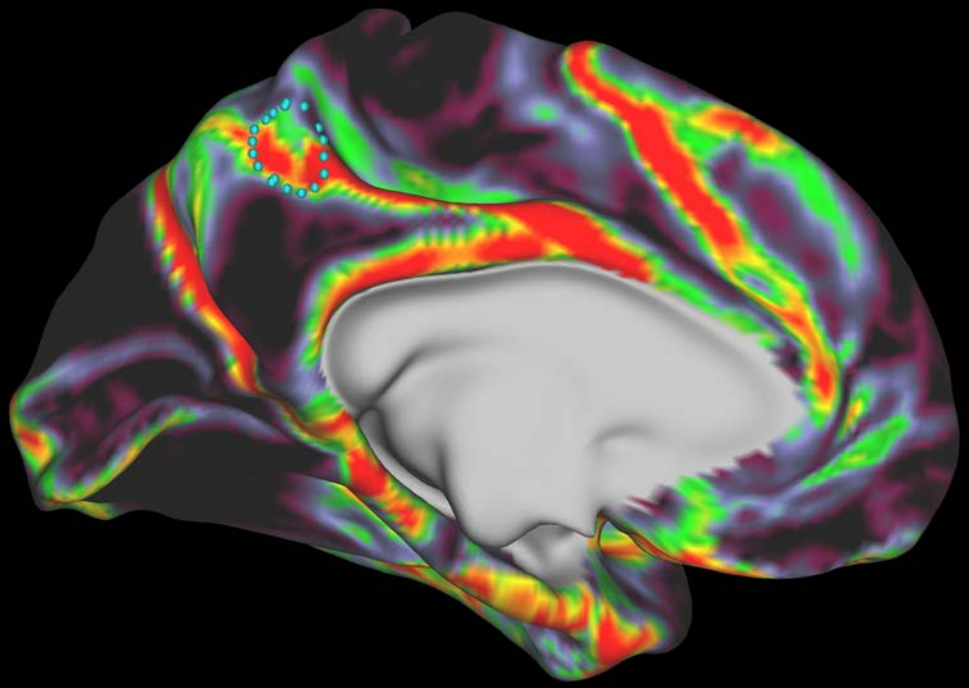
Resting State Functional Connectivity Gradients: Full Correlation Methods



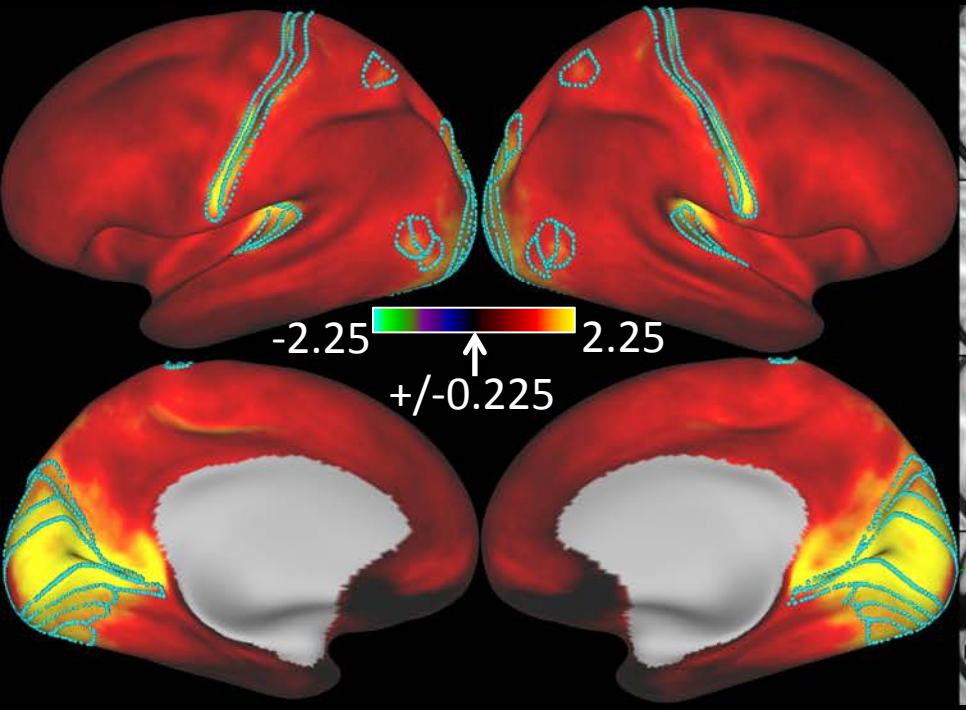
- 1) Correlate Dense Timeseries to Make Dense Connectome
- 2) Correlate Left Cortical functional connectivity patterns to make 2nd order correlation matrix
- 3) Take gradient of Left Cortical 2nd order correlation matrix to make a gradient matrix
- 4) Average across gradient matrix to make mean gradient map (1 x Left Cortex)
- 5) Repeat steps 2-4 for right cortex and subcortical
- 6) Recombine to make full grayordinates gradient map (1 x Grayordinates)

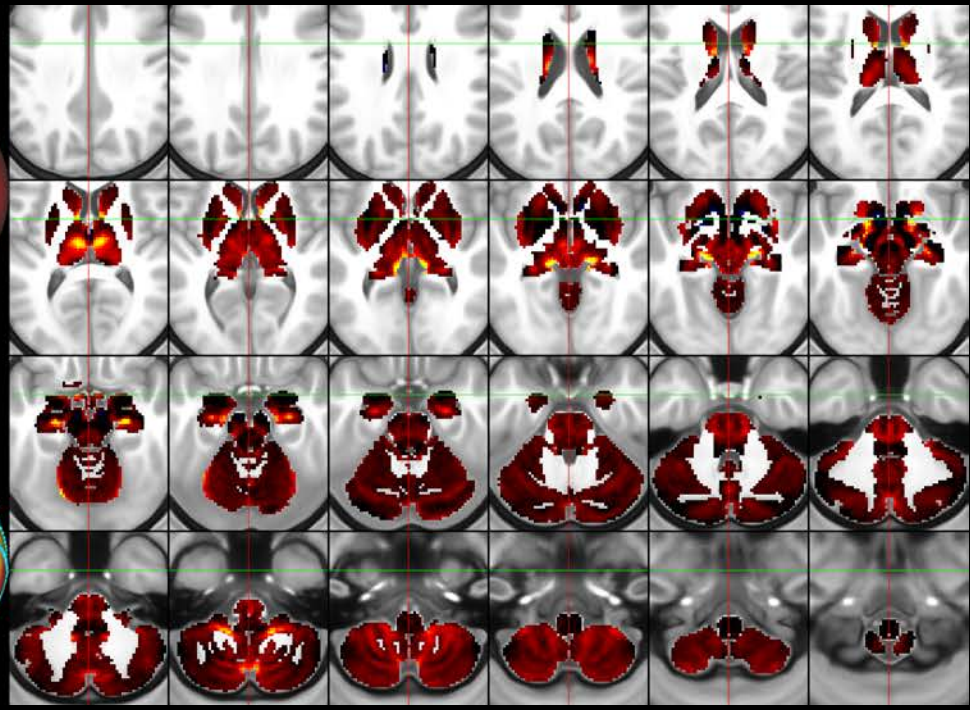
Tips for Resting State Gradients

- Data need to be cleaned of spatially specific artifacts (including veins) using a method like ICA+FIX (Tuesday morning practical)
- Avoid Fisher z transform (this nonlinear function will move gradients slightly)
- We don’t do global signal regression (MGTR), as this moves gradients more
- We prefer to stay closer to the original data, avoiding other kinds of nonlinear transforms on the gradients like edge detection



Why Do the Gradients Move?

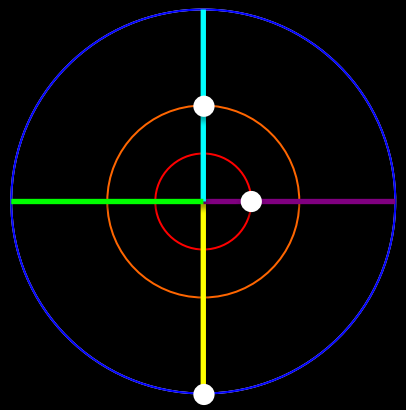




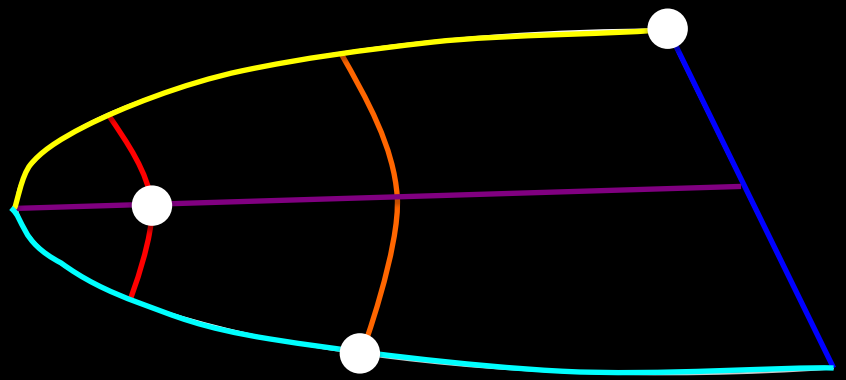
- Regression beta of global signal showing its spatial localization (yellow is at least 10x higher than black)
- In ICA+FIX cleaned data, global signal is particularly strongly correlated with
  - Visual, Auditory, and Somatosensory Cortices
  - LGN + MGN, and several other subcortical hotspots
- Particularly weakly correlated with the cerebellum
- Not clear how a global artifactual (i.e. non-neural/BOLD) process would produce this neuroanatomically specific localization and dramatic difference in correlation strength across different brain areas
- Could the global signal be related to how much the sensory systems are correlated with each brain area?
- Given the spatially specific localization of the global signal, it's not surprising that removing it moves gradients
  - Similar unintended consequences of removing the global signal could occur in other analyses, so caution is warranted
- Without the clean up stages in the ICA+FIX pipeline, the global signal is more localized to regions most effected by motion and related artifacts including the frontal pole and posterior cerebellum
- Questions about connectivity?

How to Measure Topographic Organization in Cortical Areas

- Unlike the sharp gradients that form areal boundaries, topographic connectivity gradients tend to be smoothly varying and occur inside cortical areas
- Many describe spaces outside of the body, for example visual space (the Visual Field) is represented spatially in primary visual cortex
- Stimulating a specific part of the visual field leads to neuronal activity in specific parts of the visual cortical areas because corresponding parts of these areas are strongly connected
- This topographic organization can be measured using a task paradigm or with connectivity



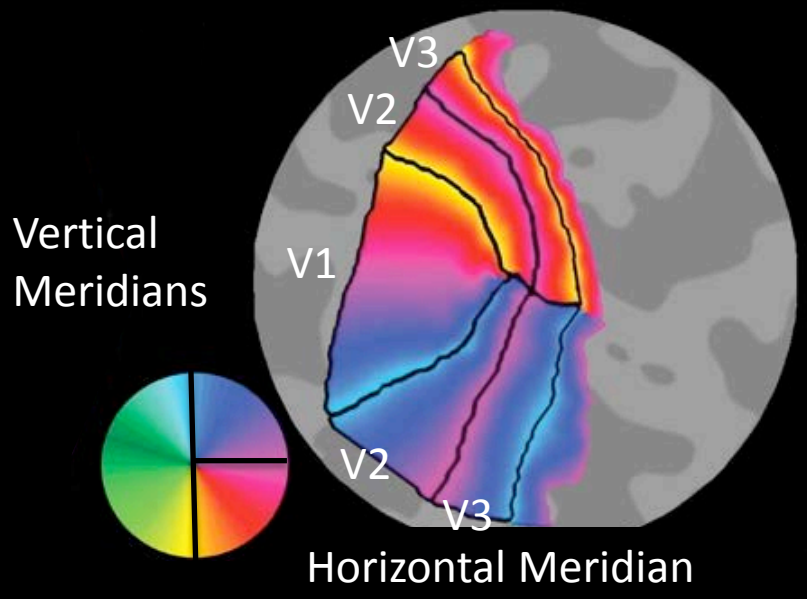
Visual Field



Primary Visual Cortex

Topographic Maps Can Tell Us the Locations of Areal Borders

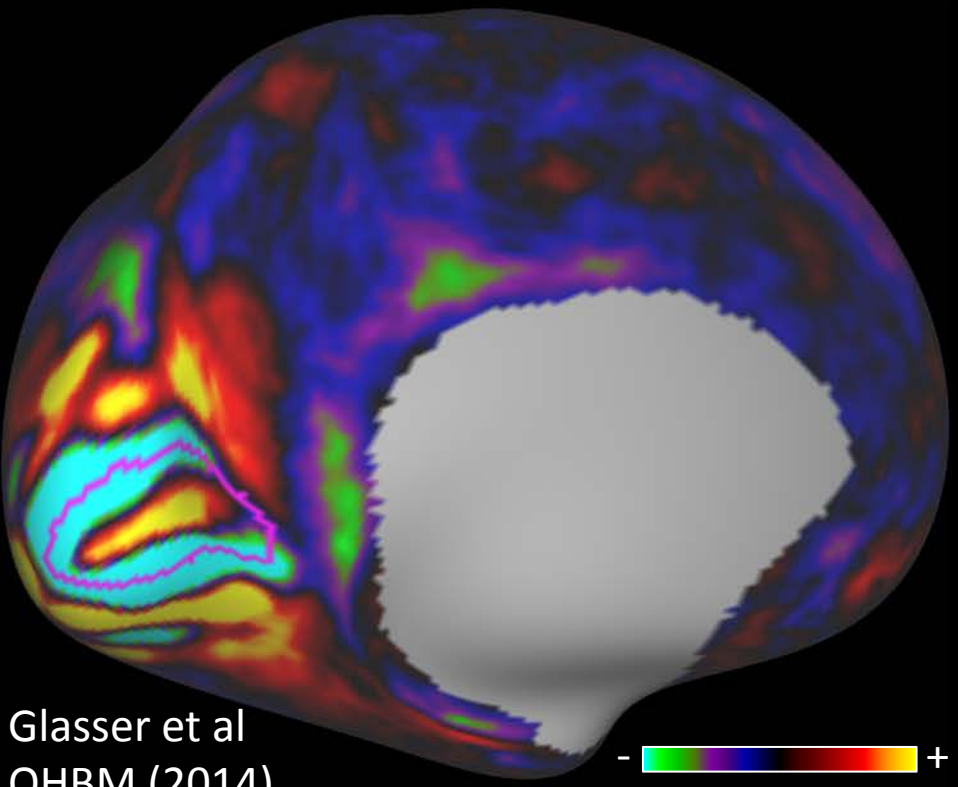
- Polar angle reversals define boundaries between visual areas
  - e.g. vertical meridians between V1 and V2
  - horizontal meridian between V2 and V3
- Visual areas generally have both central and peripheral eccentricity representations
- Retinotopic fMRI is available in the 7T HCP data



Schira et al 2009

Visual Topography in Resting State fMRI with ICA

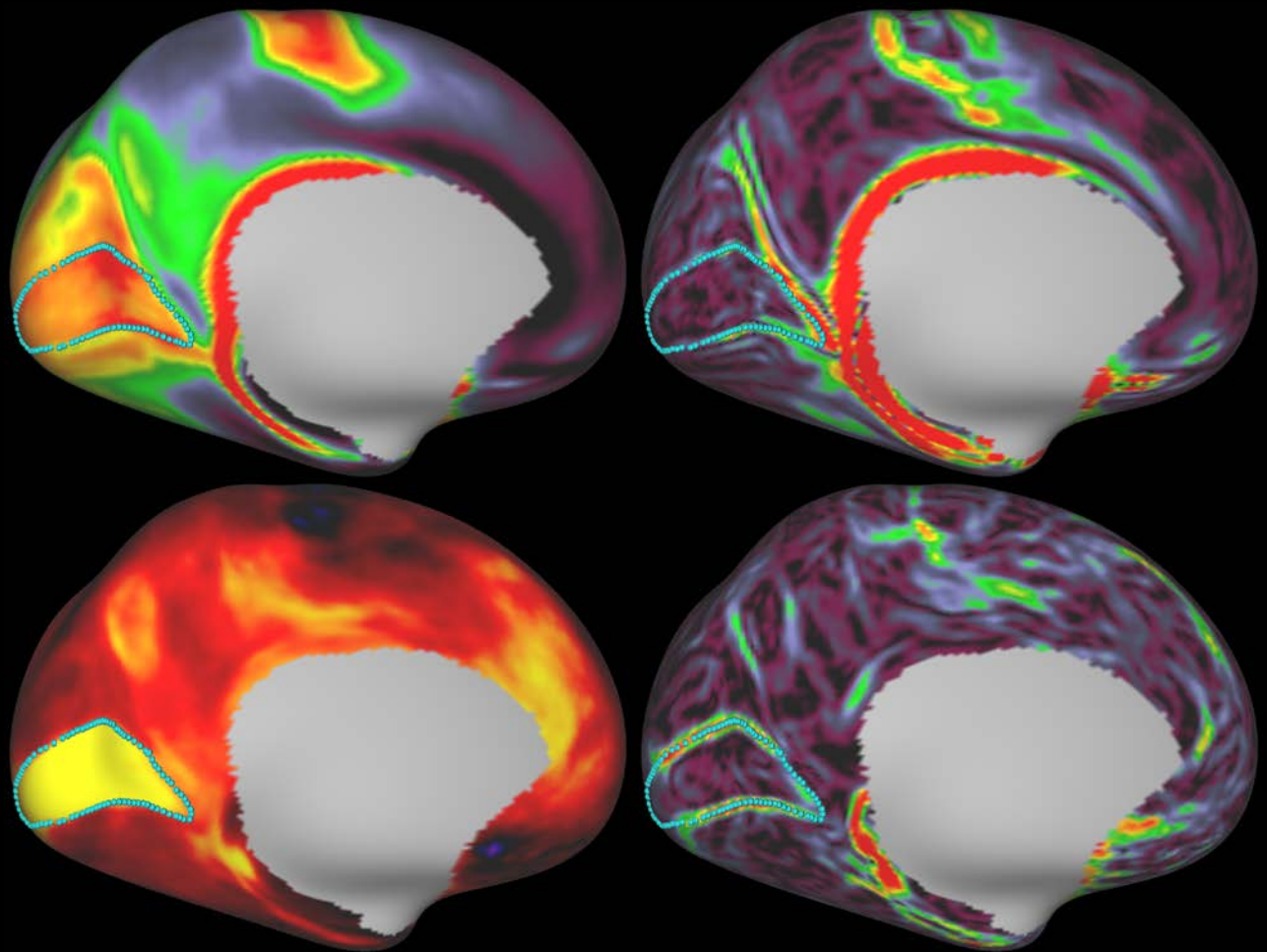
- ICA is used to separate spatially overlapping resting state signals
- With HCP quality data and processing methods, it is possible to see signals related to polar angle in a d=137 group ICA
- Horizontal meridians are positive whereas vertical meridians are negative
- Purple outline is architectonic V1 (from Fischl et al 2008)
- Eccentricity related signals are also visible (previously reported in Yeo et al 2011)



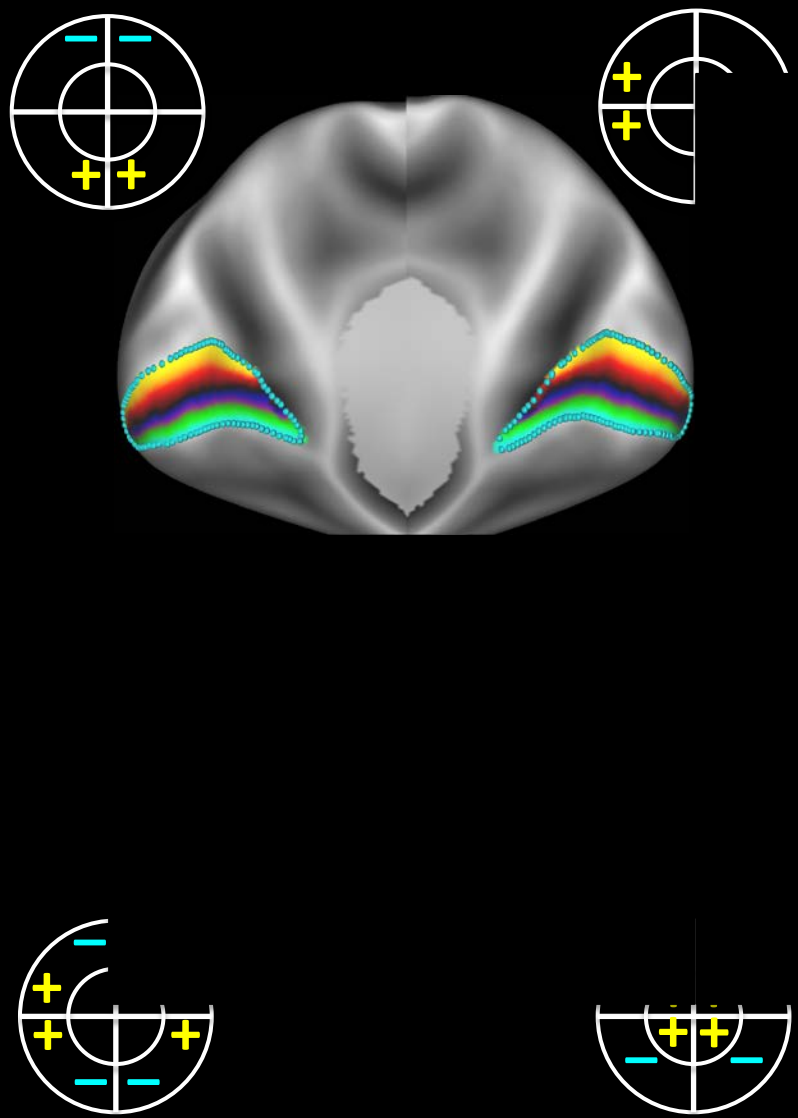
Glasser et al
OHBM (2014)

Using Resting State Visual Topography for Parcellation: Finding V1

- First define V1 with multi-modal gradients
  - Myelin Maps
  - LGN seed for functional connectivity
- V1 ROI is a blue outline
- The whole brain resting state gradients also show a boundary around V1
- Task fMRI also shows a partial V1 boundary

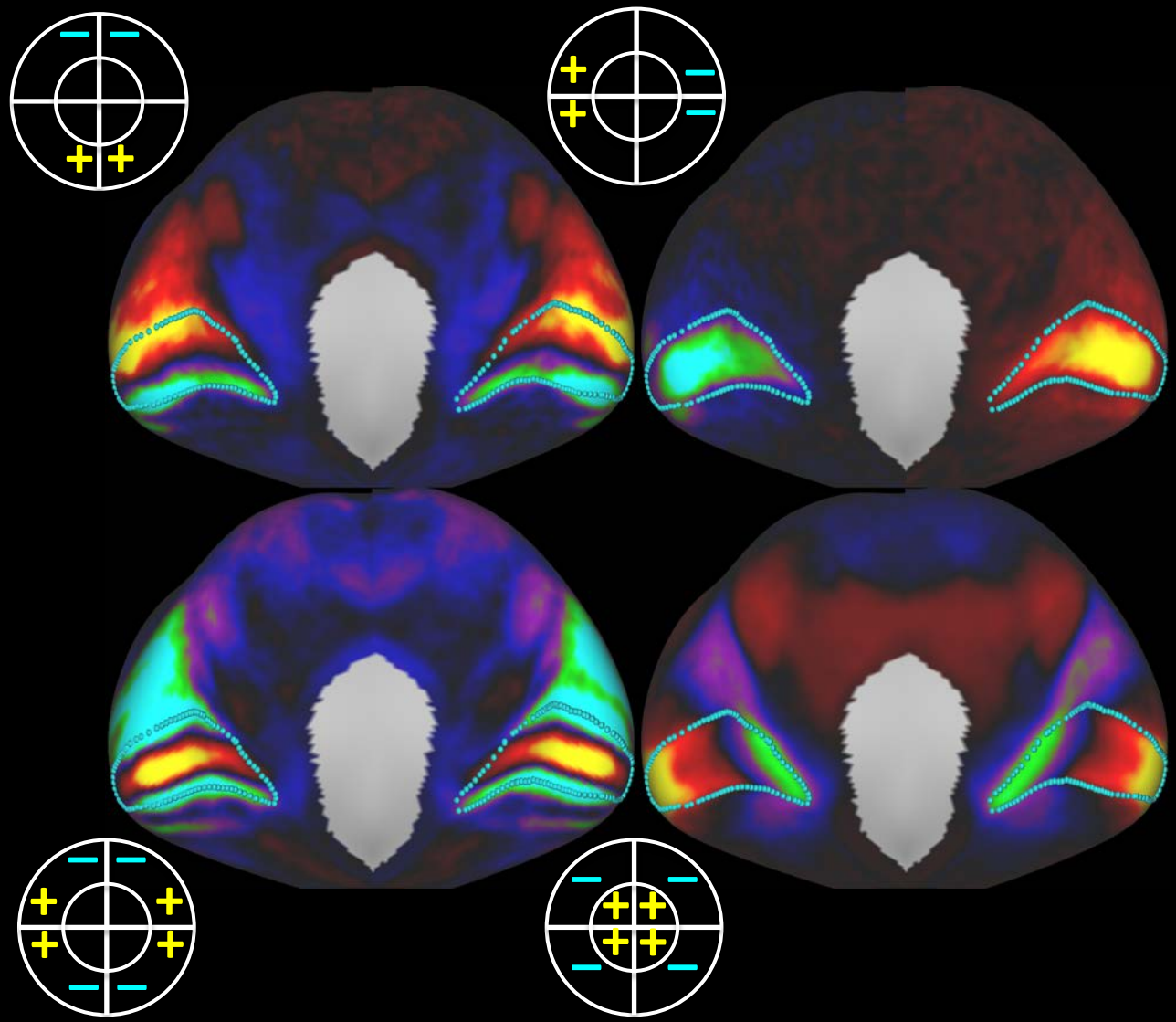


Define a Coordinate Space in V1 and Generate Visuotopic Spatial Regressors



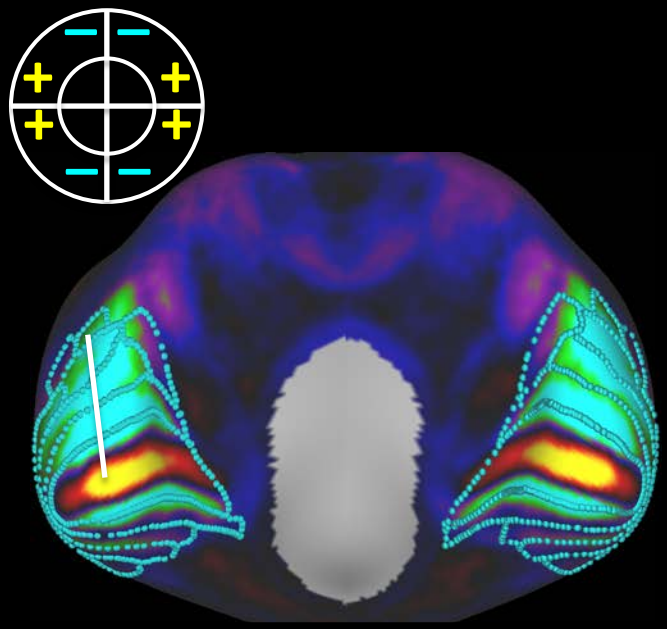
- Using known neuroanatomy:
  - Lower vs Upper Vertical Meridian
  - Left vs Right Horizontal Meridian
  - Horizontal vs Vertical Meridian
  - Foveal Vs Peripherial
  - Also all of V1, higher order harmonics
- Regressors are linear in V1 space
  - Retina space has a nonlinear transformation from V1 space

Use Spatial Regressors to Generate Whole Brain Spatial Maps

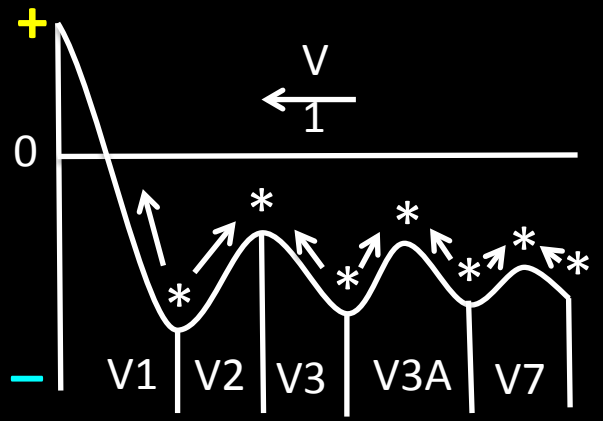


- Use a weighted dual regression (weighted by vertex areas)
  - First spatial multiple regression
  - Then temporal multiple regression
- Visuotopic patterns are present outside of V1
  - These patterns are biased somewhat by other resting state signals
- Lets focus more on horizontal vs vertical…

From Whole Brain Spatial Maps to Visual Area Boundaries

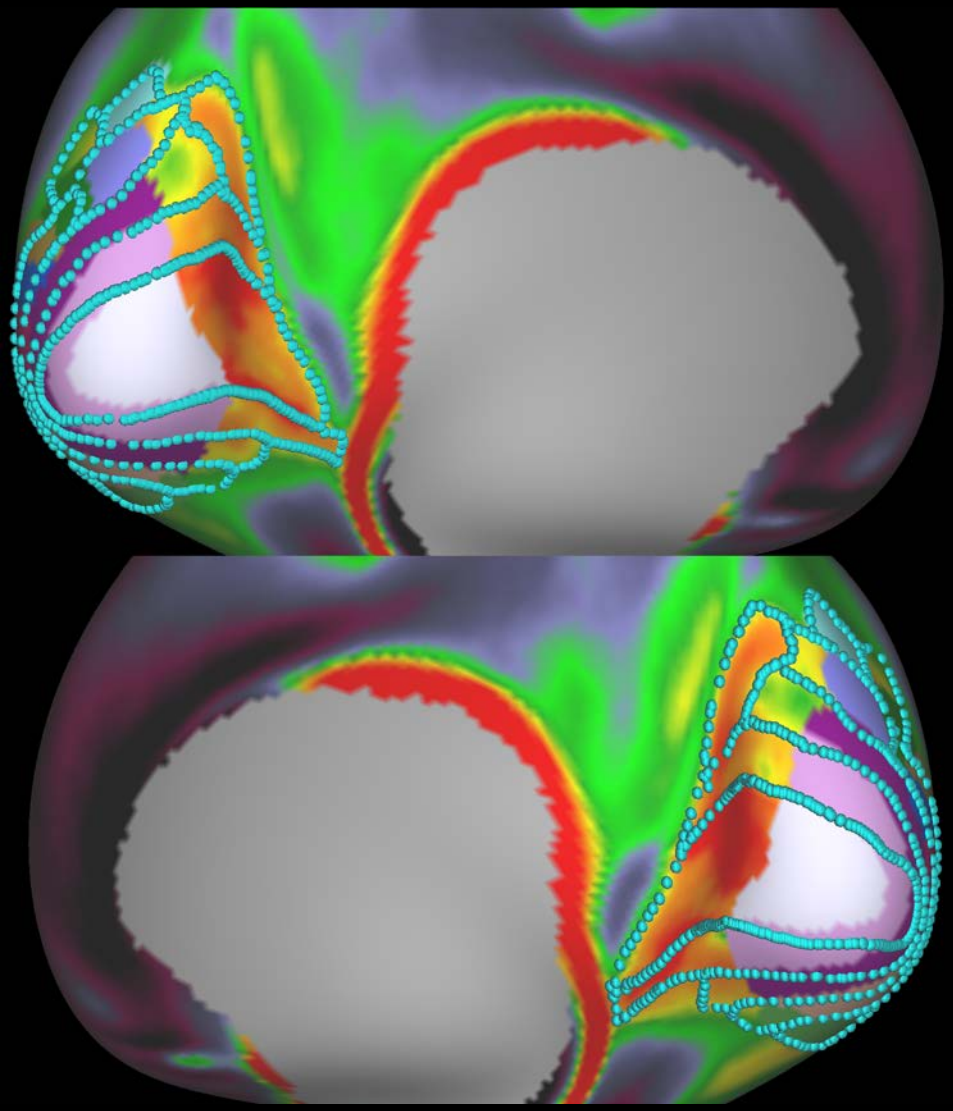


- Horizontal vs Vertical meridians
  - Profile along line
- Areal boundaries (meridians)
  - Local minima in the gradient magnitude (*)
  - Reversals of the gradient vectors (seen as the dot product of the gradient vector with a reference vector pointing towards V1)
  - Many visual areas can be defined using this information (V2, V3, V3A, V3B, V4, V6, V7, V8, etc)
- Retinotopic visual cortex is heavily myelinated



Comparison with Retinotopic fMRI Parcellation from Another Study

- Comparison with 12 subject group average retinotopic parcellation from Orban's group (non-HCP)
  - Registered with MSM areal-feature-based registration and dedrifted
- Generally good agreement including V1, V2, V3, V4(v), V3A(D), V7
  - Incomplete peripheral coverage in retinopic fMRI because it is hard to stimulate the peripheral retina within the confines of an MRI scanner
  - Fovea is also hard to map because of microsaccades
- Resting state visuotopic parcellation can map both regions better
- Questions about Topography?

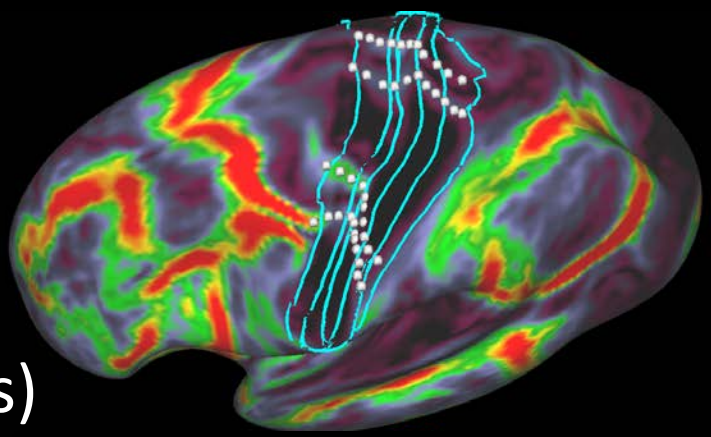


Multi-modal Parcellation: Putting It All Together for One Cortical Area

- 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



Face

Hand

Foot

Architecture, Function, Connectivity, and Topography Summary

- Architecture, Function, connectivity, and topography are all possible to measure non-invasively with MRI
- Gradients represent putative areal boundaries
- Functional activity across many tasks can help in defining cortical areas
- Differences in functional connectivity across the cortex help to define cortical areas
- Topographic organization within areas revealed by a task paradigm or using connectivity can also help define them
  - Some areas could have topographic subareas defined
- All of the above depends critically on careful preprocessing within the CIFTI grayordinates neuroimaging analysis paradigm
- Questions about parcellation modalities or approach?

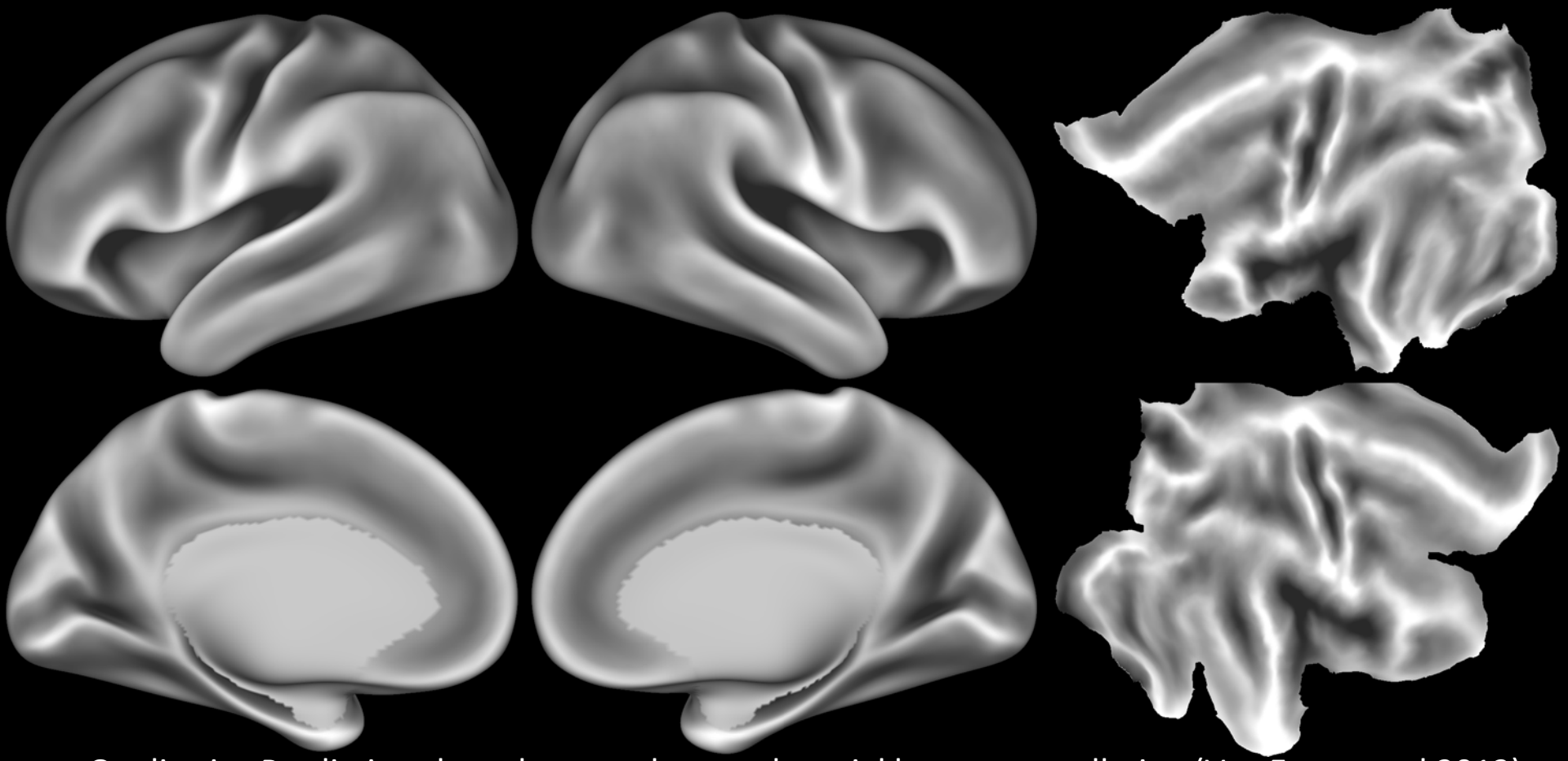
Lecture Topics

- Why parcellate, when to do a parcellated analysis, and how should one parcellate
- Cortical architecture, myelin maps, and gradients as putative areal boundaries
- fMRI-based modalities and gradients
  - Function
  - Connectivity
  - Topography
- The HCP's multi-modal parcellation and sample parcellated analyses

Multimodal Cortical Parcellation

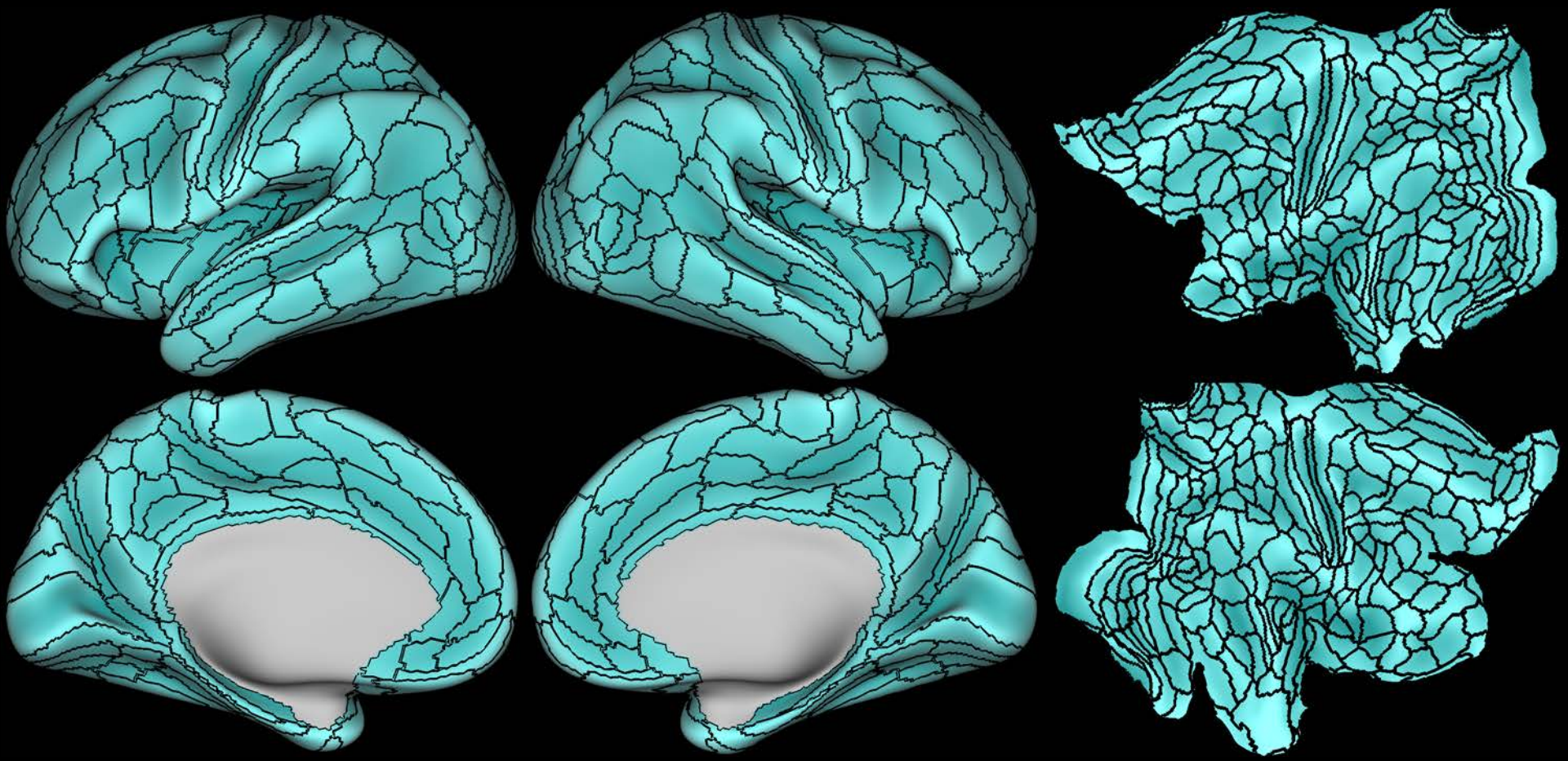
- The multi-modal parcellation was constructed from 210(P) subjects brought into the standard grayordinates space using MSM areal-feature-based registration
- Borders were defined using gradients in group average
  - Architecture (myelin maps and thickness with curvature regressed out)
  - Function (86 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



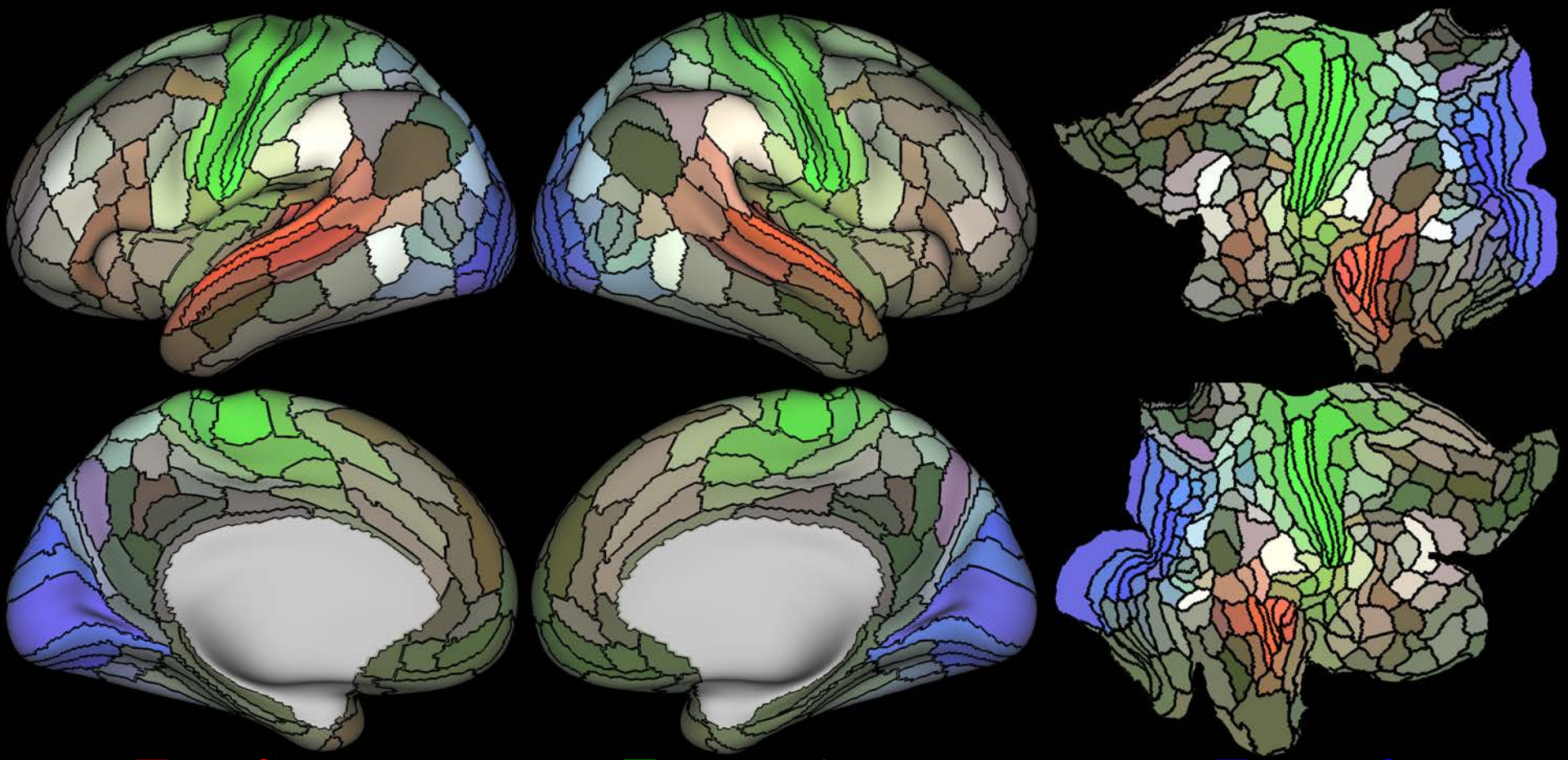
- Qualitative Predictions based on monkeys and partial human parcellation (Van Essen et al 2012):
  - 150-200 human cortical areas per hemisphere
  - Wide variability in areal size and shape
  - Will be examples of inter-areal heterogeneity (e.g. early sensory topographies)

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

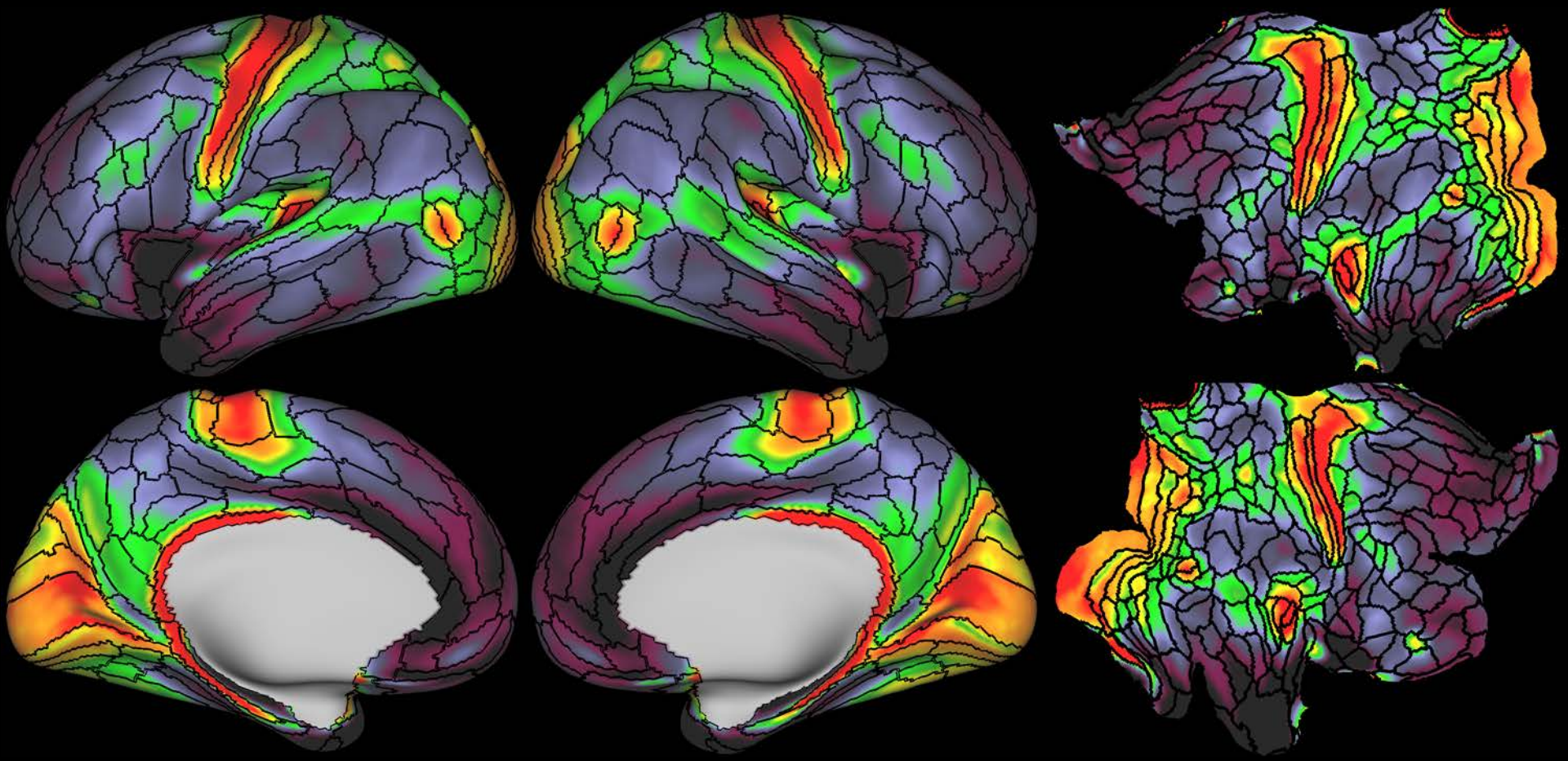


■ Auditory ■ Sensori-motor ■ Visual

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

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

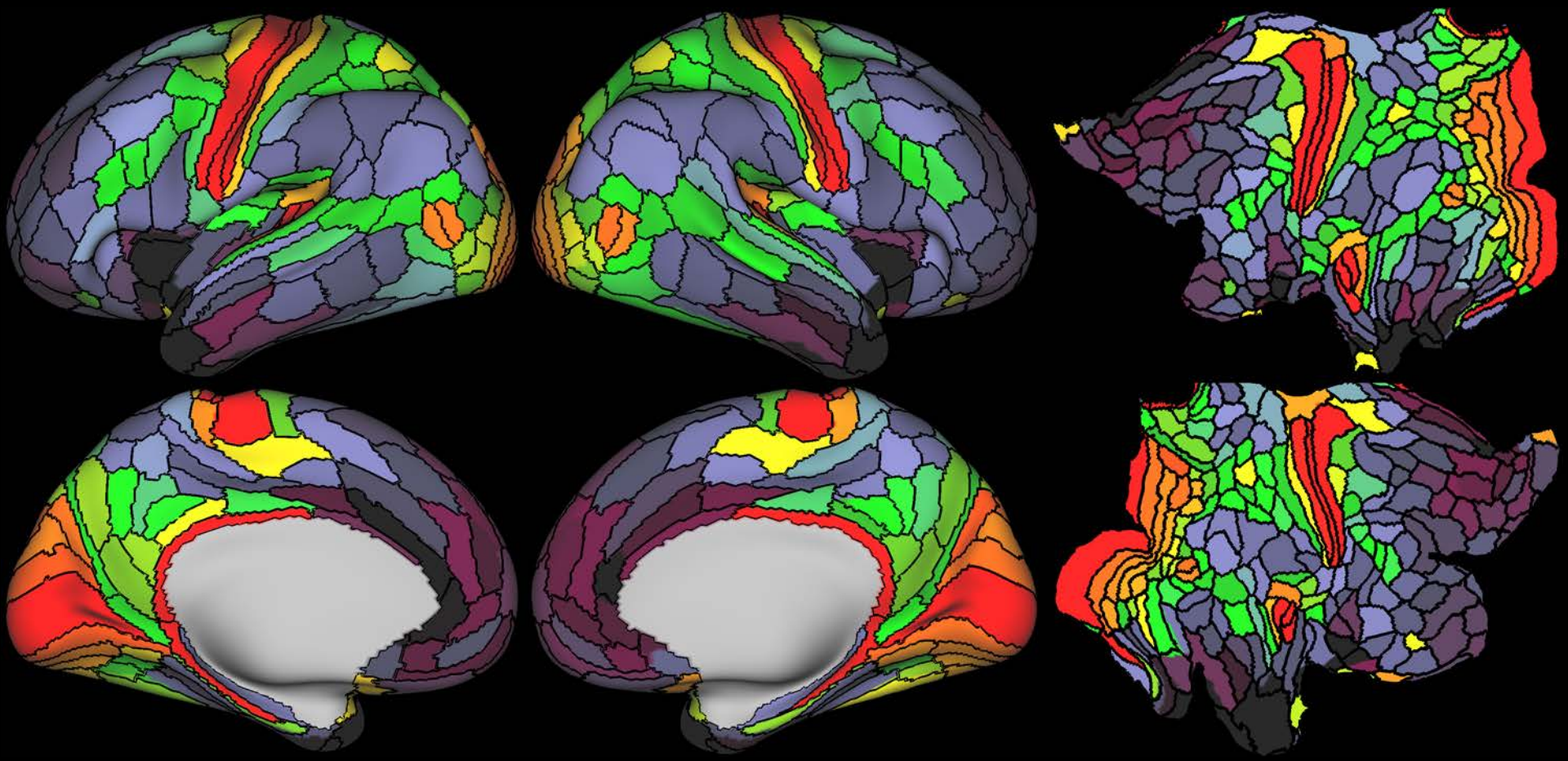
Parcellated Analyses



Dense Myelin Map

Light — Heavy

Parcellated Analyses

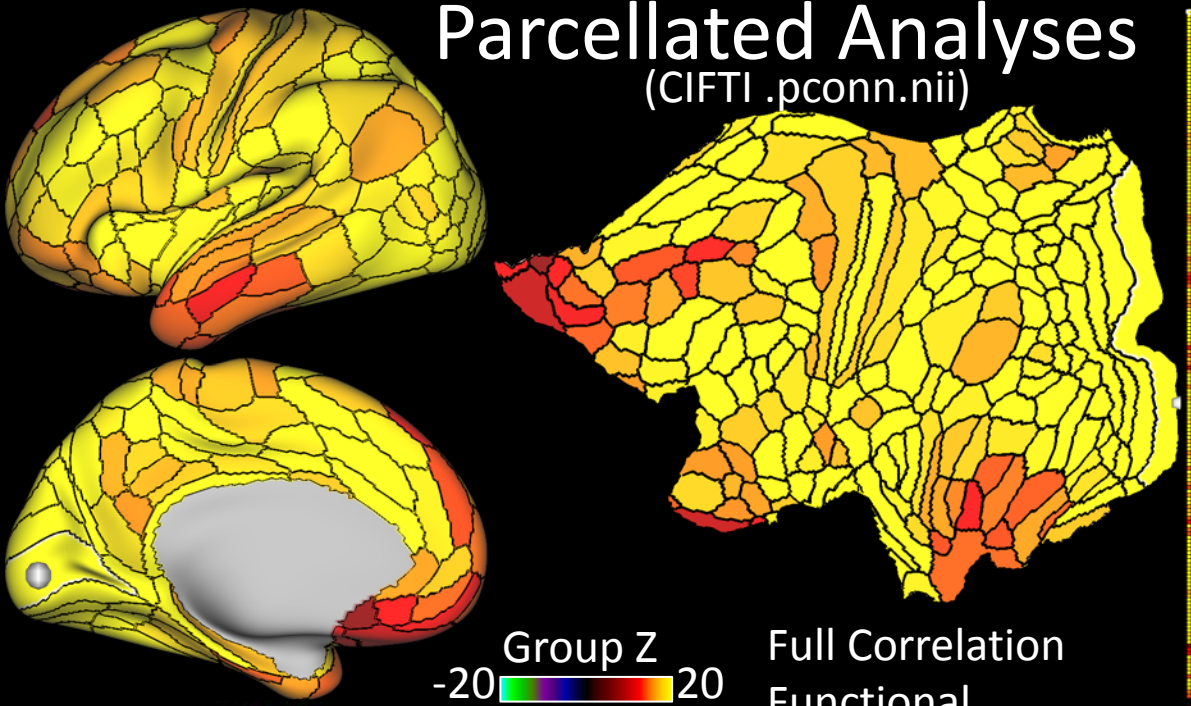


Parcellated Myelin Map

Light — Heavy

Parcellated Analyses

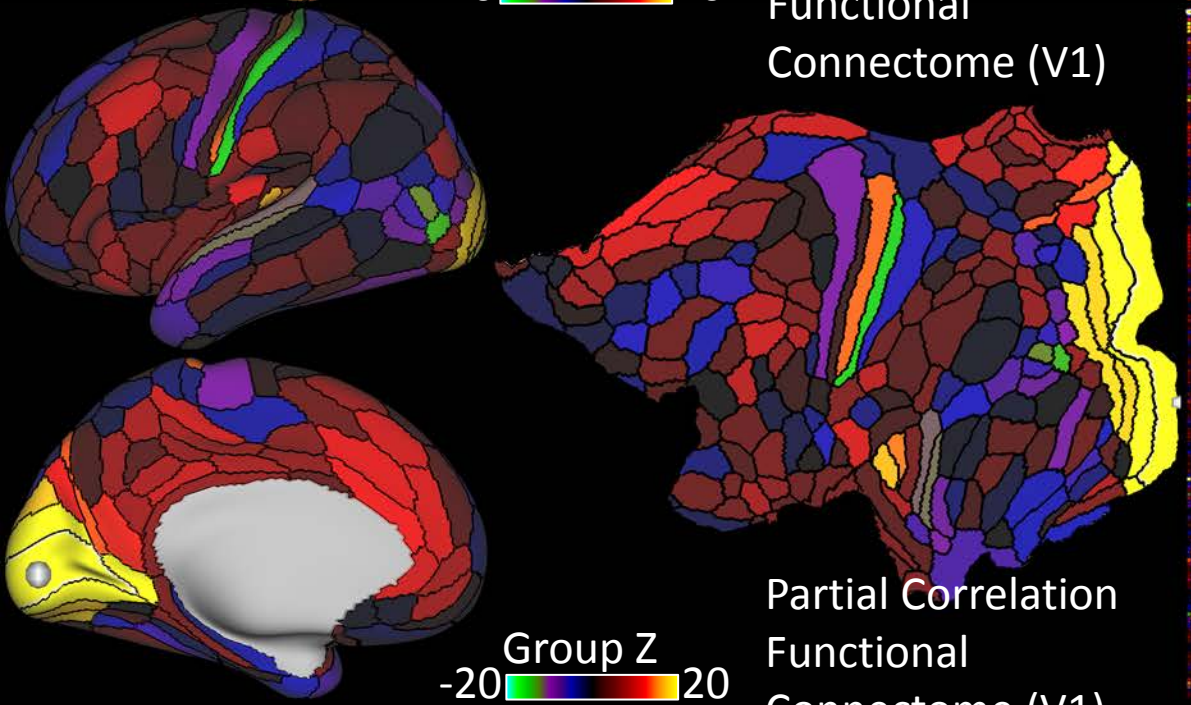
(CIFTI .pconn.nii)



Group Z

-20 20

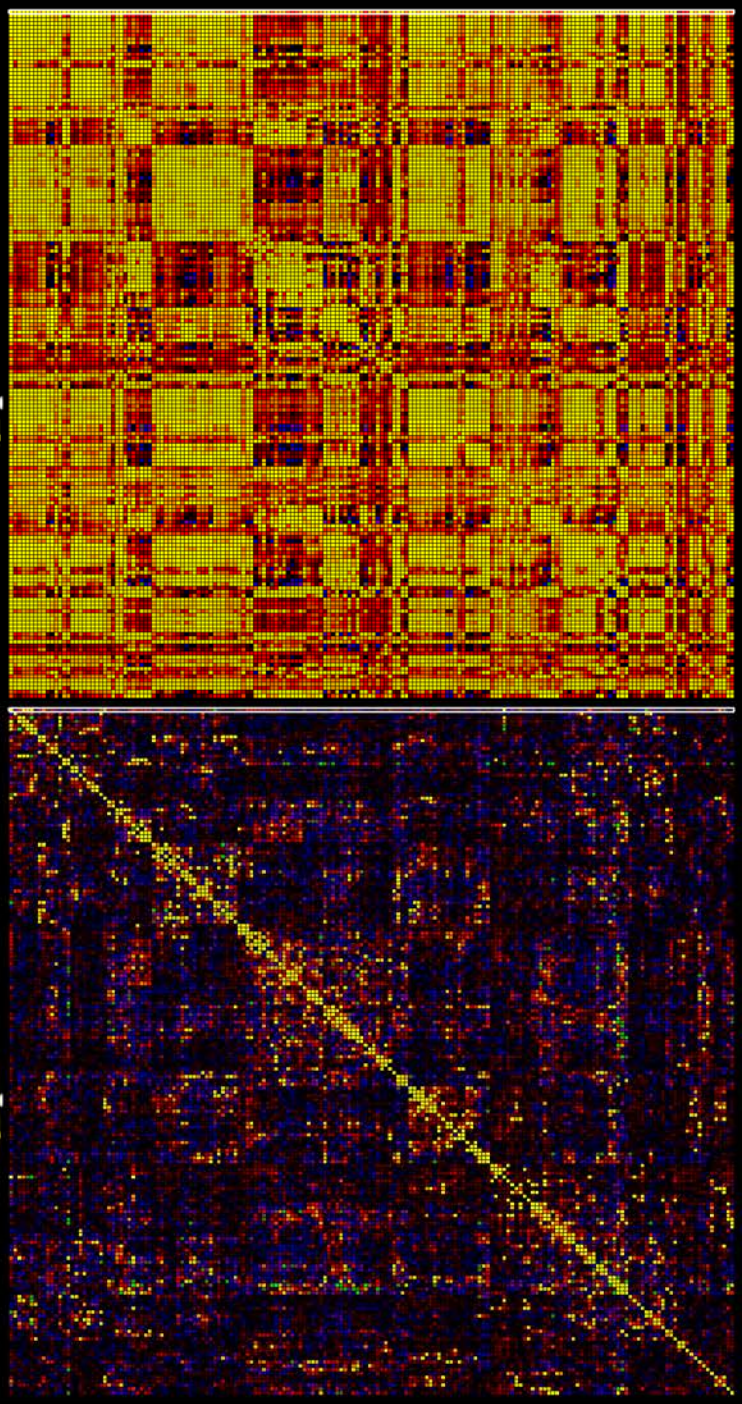
Full Correlation Functional Connectome (V1)



Group Z

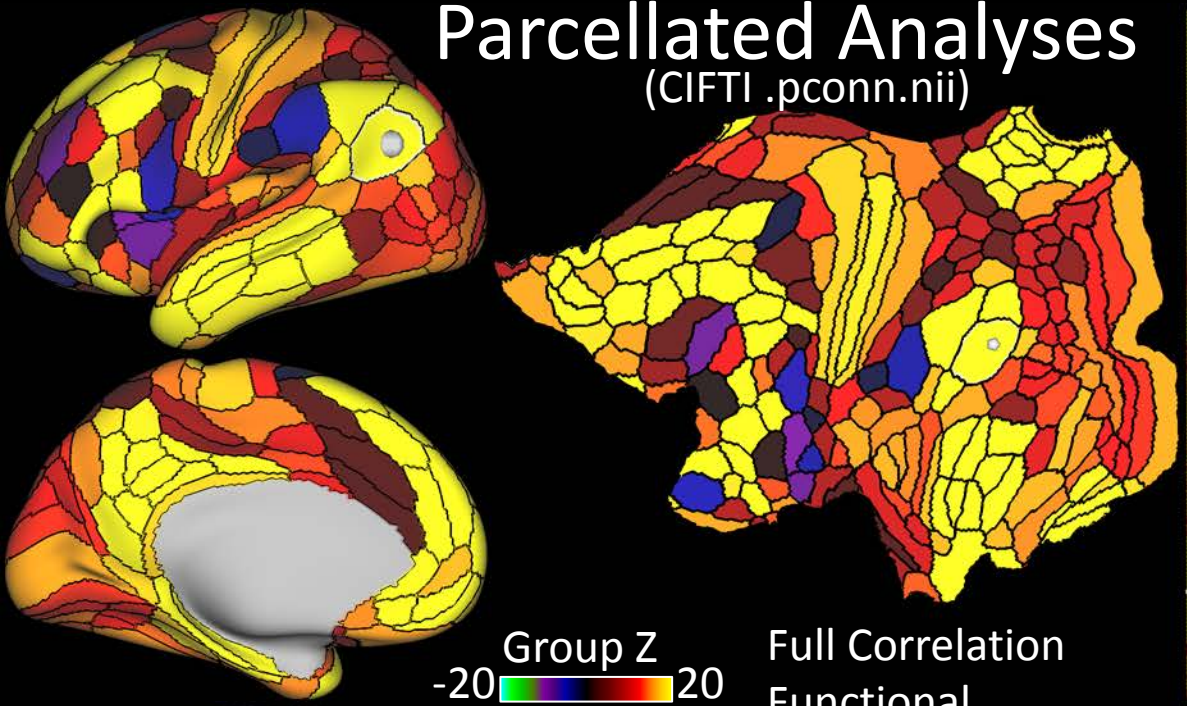
-20 20

Partial Correlation Functional Connectome (V1)



Parcellated Analyses

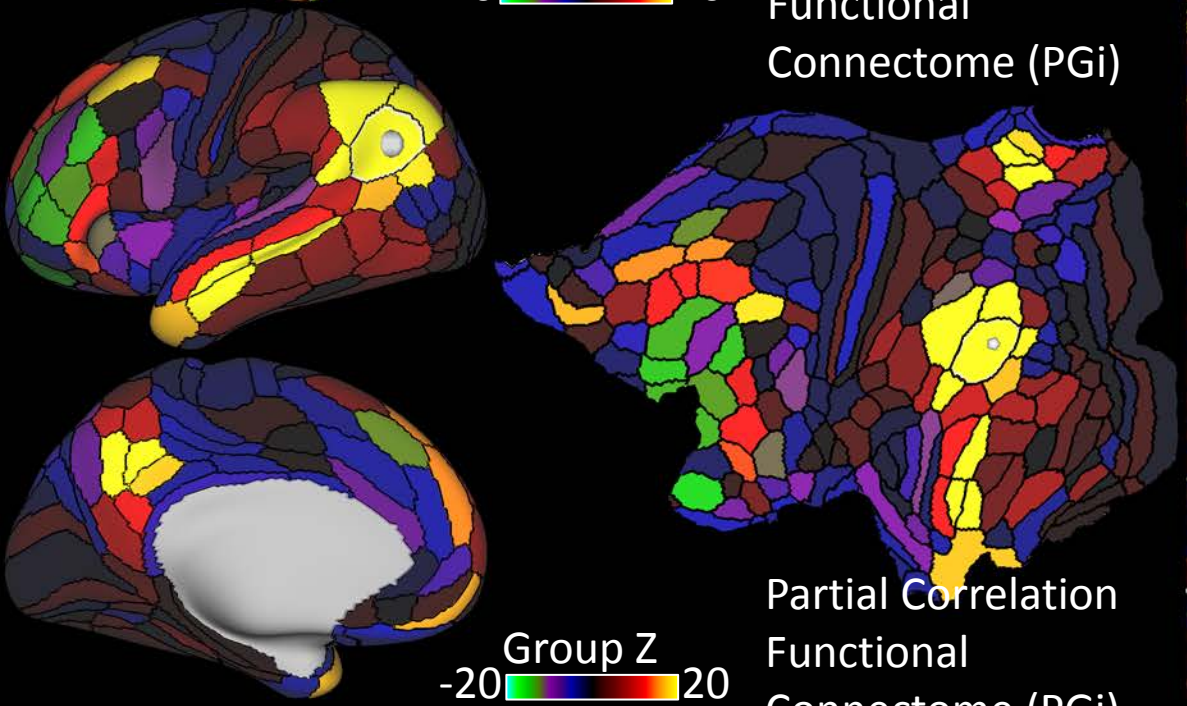
(CIFTI .pconn.nii)



Group Z

-20 20

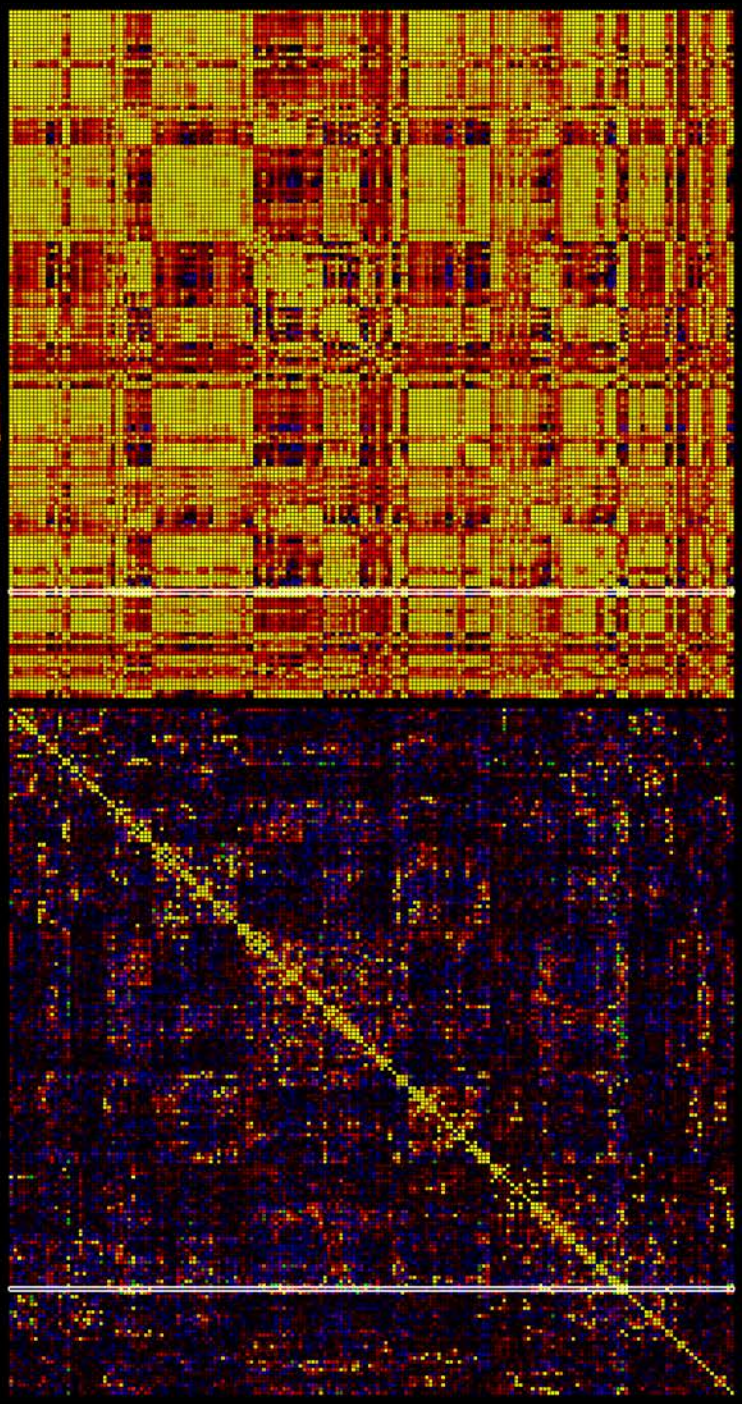
Full Correlation Functional Connectome (PGi)



Group Z

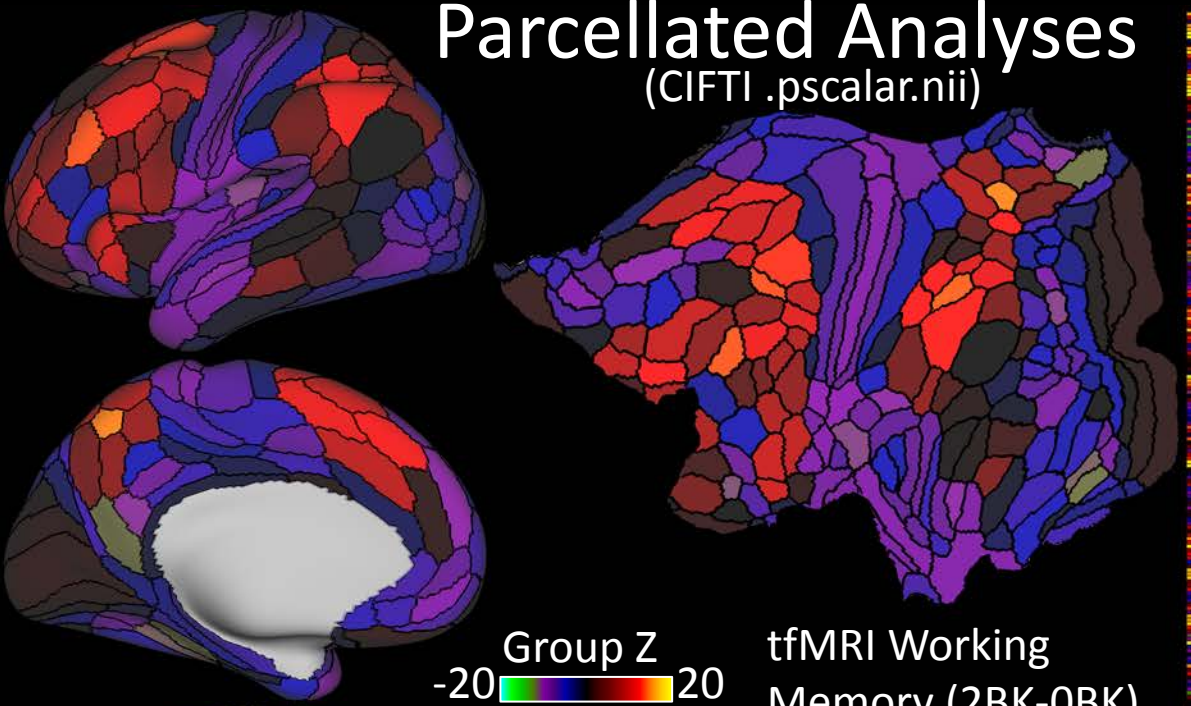
-20 20

Partial Correlation Functional Connectome (PGi)



Parcellated Analyses

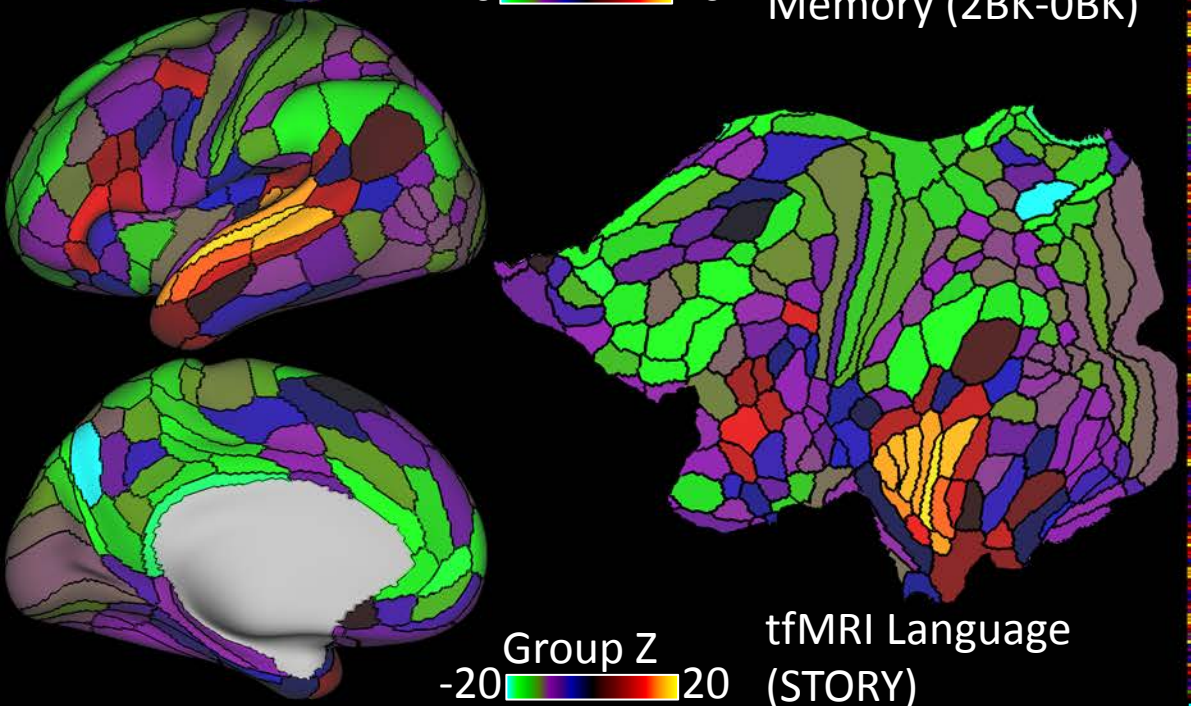
(CIFTI .pscalar.nii)



Group Z

-20 20

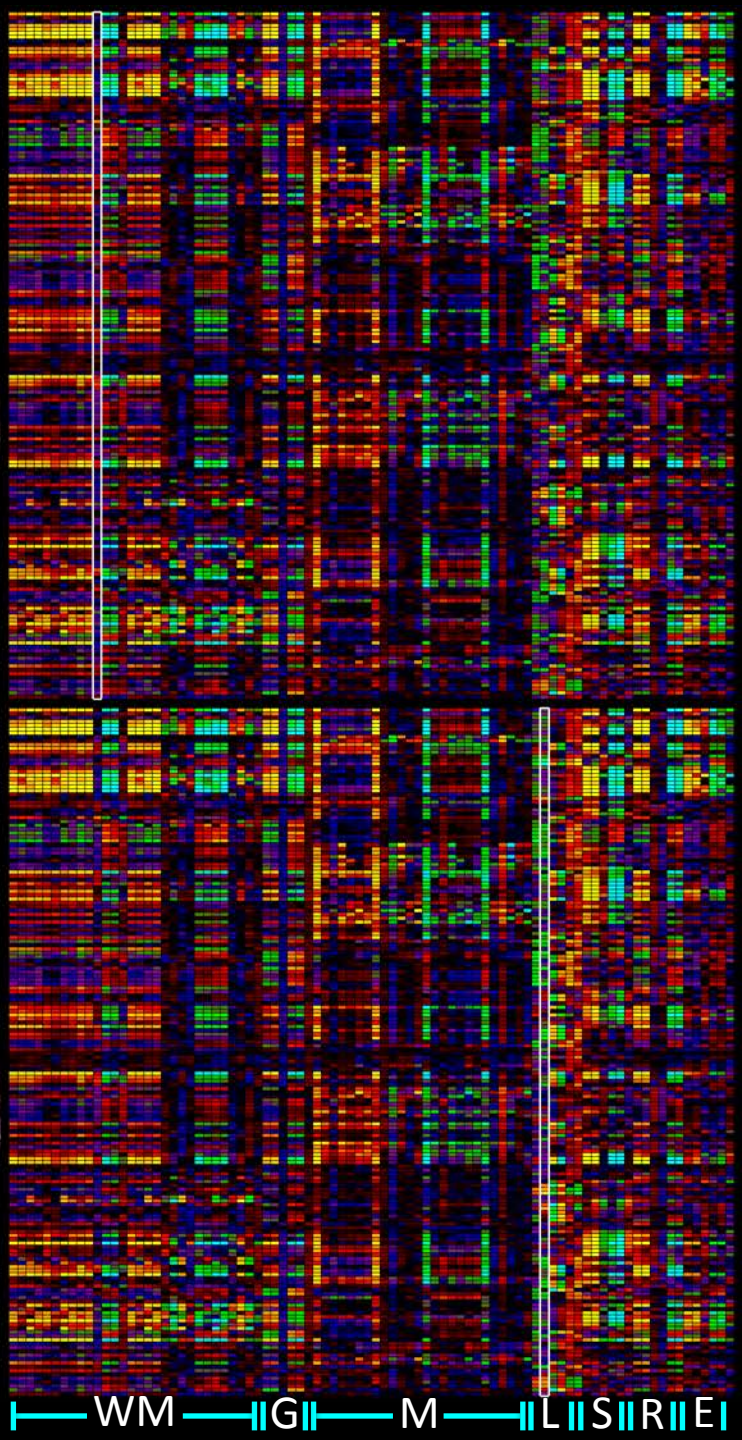
tfMRI Working Memory (2BK-0BK)



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!
  - The could apply to your own data if analyzed as suggested in this course
- The concept of Parcels X Features X Subjects will be important for lecture 3 tomorrow

Multi-modal Parcellation Summary

- 178 cortical areas were found in each hemisphere, within the expected range of 150-200
- These areas vary widely in size and shape and some areas have topographic heterogeneity
- Parcellated analyses can be performed with most modalities, architecture, function, or connectivity
- Minimal loss of detail at the areal level with a good parcellation
- Questions about multi-modal parcellation or parcellated analyses (validation tomorrow)

One Last Slide

- Careful preprocessing and analysis pays major dividends by preserving fine neuroanatomical detail
- You don't have to smooth your data
  - If you're after information at the coarse areal level, use a functionally relevant parcellation (simplicity, sensitivity, power, communication)
  - If you're after fine-grained patterns like visuotopy, smoothing is obviously a bad idea
- Understand what you are doing to your data
  - Many processing steps/transformations can shift/change gradients
- What's most important is that you use a functionally relevant parcellation when appropriate (even if it isn't the HCP's multi-modal parcellation)
- Next lecture will be all about validating the multi-modal brain parcellation
  - Including a method to define and identify these cortical areas in individual subjects
  - Any last questions?