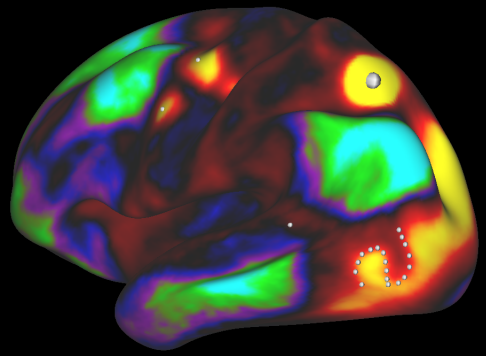
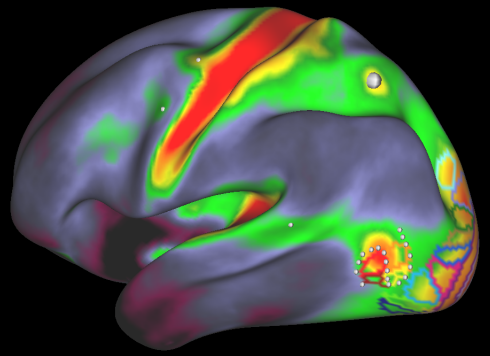
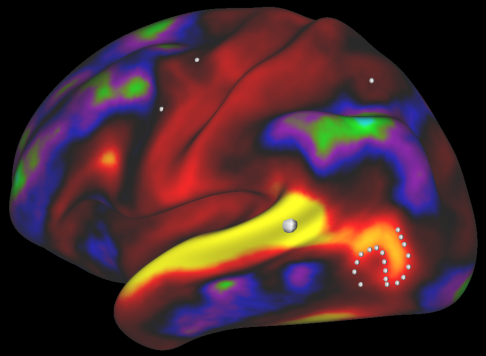
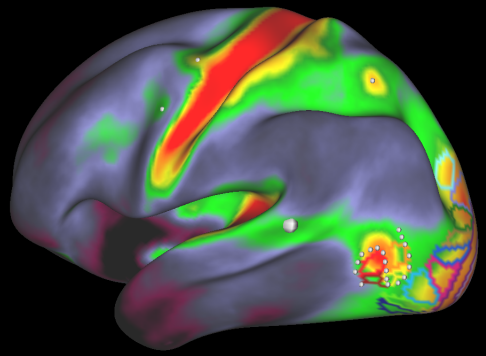




# Non-invasive Cortical Parcellation and Registration with Myelin Maps and Other MRI Modalities

*Matt Glasser*
*Department of Anatomy and Neurobiology*
*Washington University Medical School*



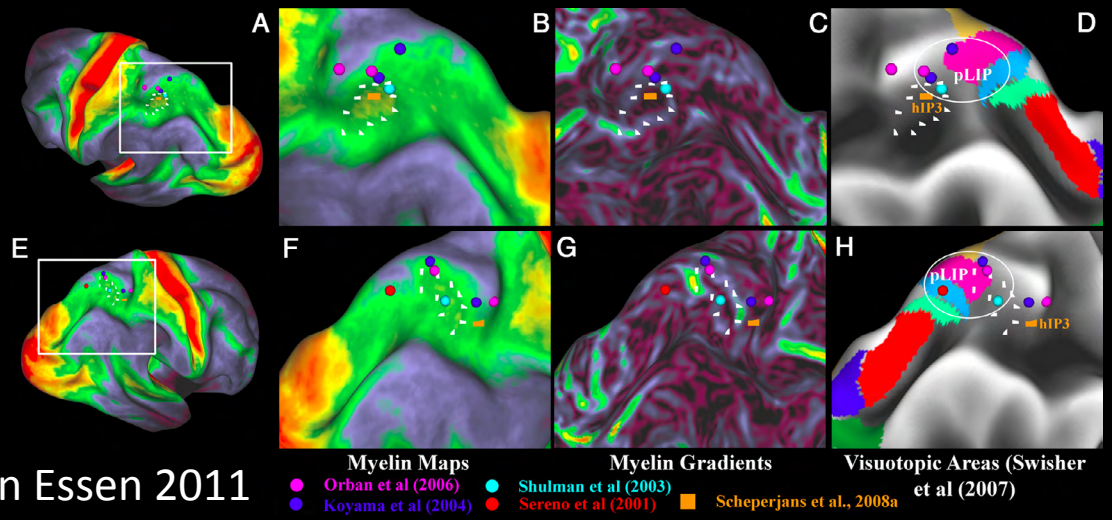


# Learning Objectives

- Volume-based vs CIFTI grayordinates-based neuroimaging analysis paradigms & why we should parcellate
- Non-invasive MRI-based methods for mapping cortical myelin content
- Myelin maps across subjects and species, and multi-modal cross-subject registration and parcellation
- Group registration “drift” and implications for cross-study comparisons

# Analysis Paradigms: Volume-Based

- Central Tenets:
  - Compare across subjects with volume registration of T1w image to group template
  - Smooth the data, attempting to correct for misalignments, increase SNR, and satisfy statistical assumptions
  - Compare across studies using 3D standard space coordinates (typically) or volume-based probabilistic maps
- Limitations:
  - Poor cross-subject and cross-study alignment of cortical areas because of substantial intersubject variability of folding patterns and areas vs folds
  - Smoothing mixes signals from different tissue types and across different brain areas
  - Substantial uncertainty in spatial localization (did two studies find the same area or not?)

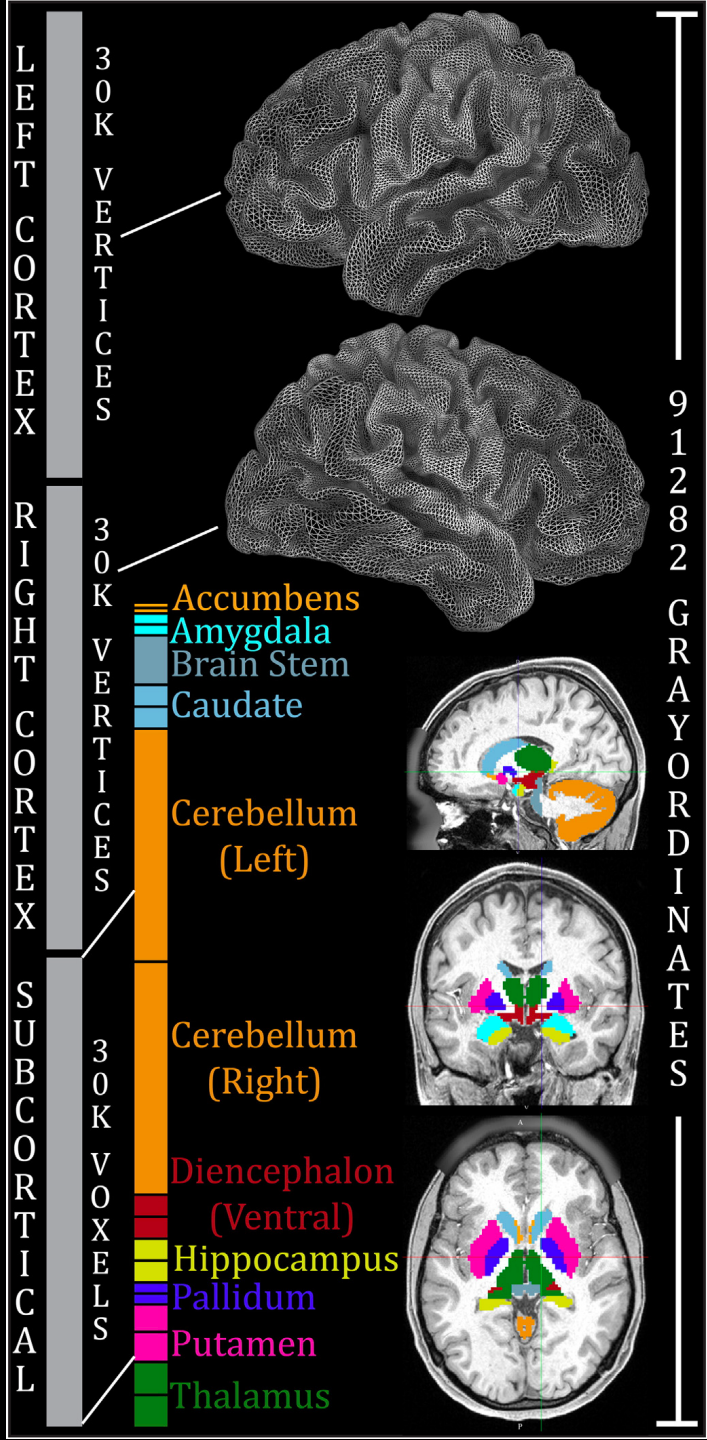



Glasser and Van Essen 2011

# Analysis Paradigms: CIFTI Grayordinates-based

- Central Tenets:
  - Consider gray matter data according to the geometric model best suited for it, surfaces for the sheet-like cerebral cortex and volumes for globular subcortical nuclei
  - Register individuals' cortical data using surface registration, ideally using areal features, and subcortical data using nonlinear volume-based registration
  - Avoid spatial smoothing--parcellation is the best form of "smoothing" for increasing SNR
  - Compare across subjects and studies using the extents of areas, a more definitive and stringent test--do these areas have the same borders?

Glasser et al (2013) Neuroimage "HCP Pipelines Paper"



# Why Parcellate Your Data?

- Dimensionality Reduction:
  - At 2mm there are 228,483 brain voxels in MNI space and 91,282 grayordinates—a lot of statistical comparisons
  - Vs up to 500 brain parcels (e.g. ~200 cortical areas per hemisphere and ~100 subcortical areas)
- Improve SNR:
  - Averaging across parcels boosts SNR cleanly, without mixing in non-grey matter signal or signal from adjacent cortical areas
- Neuroimagers' Sanity/Communication:
  - Parcels help us make sense of very complex brain data
  - e.g. V1 is the first cortical area and has specific properties we can study

# When to Use "Dense" Analyses vs Parcellated Analyses

- Dense (i.e. grayordinate-wise) Analyses:
  - Analysis of fine details in MRI datasets--e.g. connectional topographies, intrareal heterogeneity
  - Form substrate for brain parcellation
- Parcellated (i.e. area-wise) Analyses:
  - Analyses of brain networks and large scale organization and activity
  - Analyses of brain/behavior or brain/genetic relationships
  - Best place for integration of MRI and MEG data

# Learning Objectives

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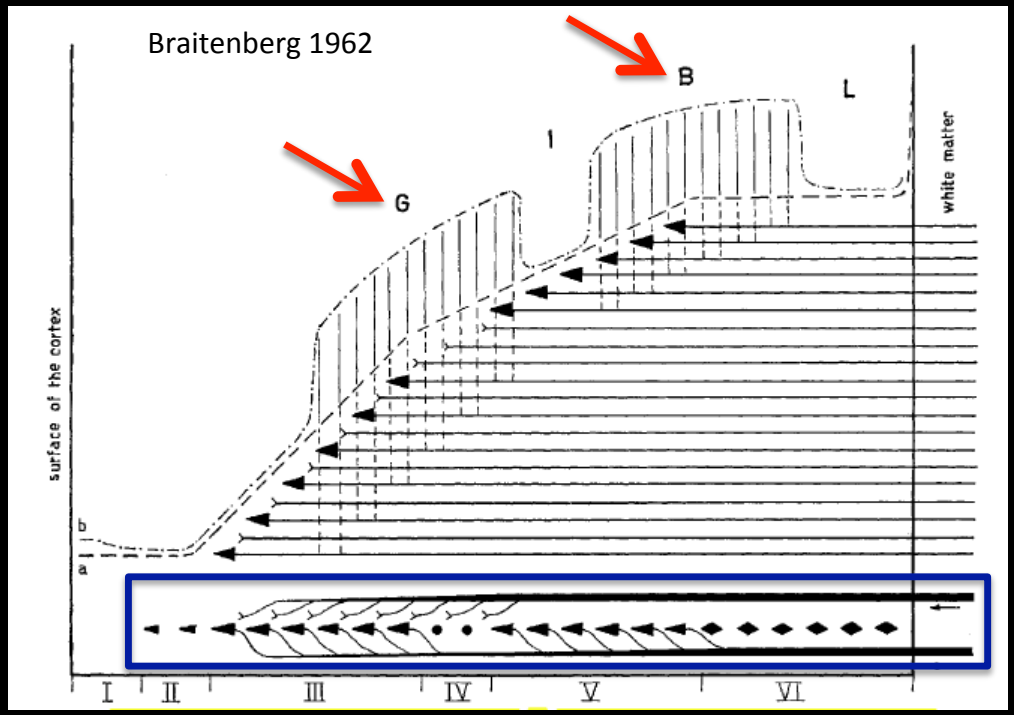
# A Brief History of Histological Myelin Mapping of the Cerebral Cortex: The Vogts

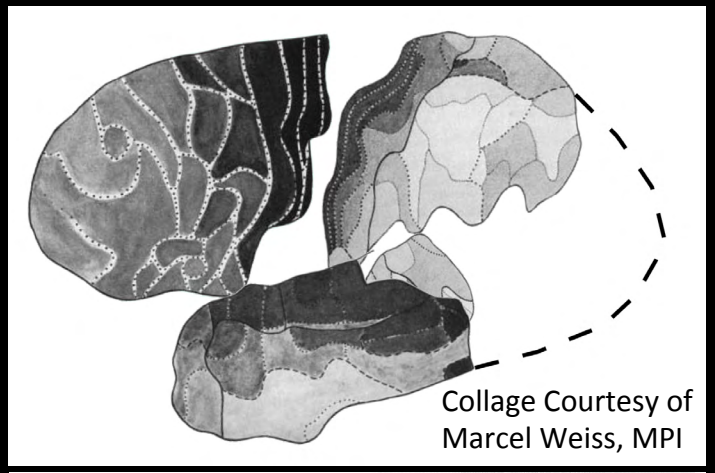
- Oskar and Cécile Vogt studied the myeloarchitecture (microscopic pattern of myelin-stained fibers within the cerebral cortex) in the early 1900s
- Myeloarchitecturally distinct cortical areas can be recognized based on differences in several parameters, including:
  - Overall myelin content
  - Number of tangential fibers bands (bands of Baillarger)
  - Density of radial fibers
- The Vogts argued that each cortical hemisphere contains around 200 myeloarchitecturally distinct areas
  - Korbinian Brodmann studied cytoarchitecture of the cortex in their institute, identifying 46 areas

MPI for Brain Research, Frankfurt

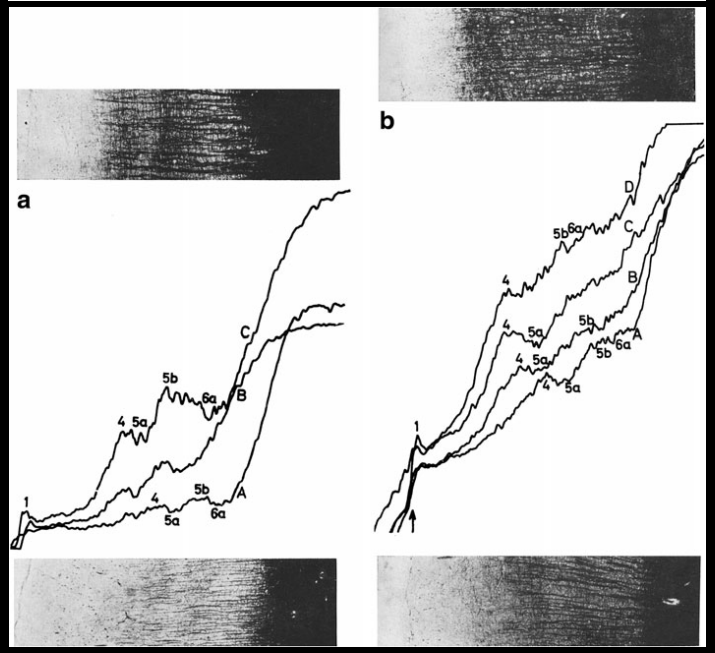


# A Brief History of Histological Myelin Mapping of the Cerebral Cortex: Hopf

- Adolf Hopf refined the Vogts' parcellations and produced:
  - The first surface maps of cortical myelin content
  - Quantitative light absorption traces of myelin staining through the cortical layers



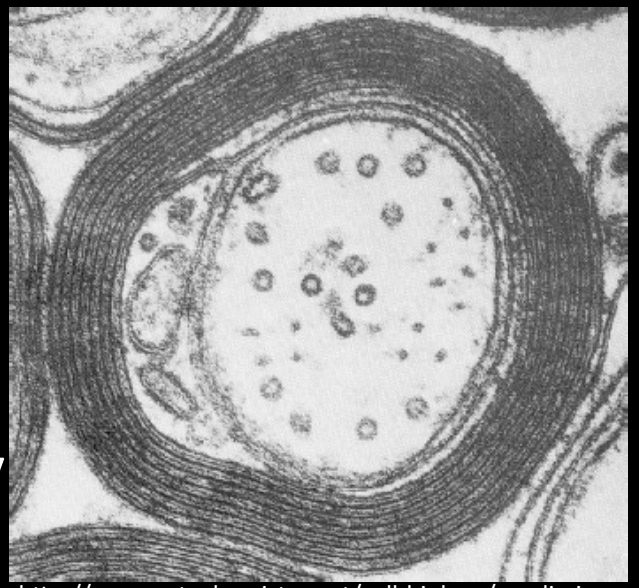
Collage Courtesy of Marcel Weiss, MPI




Excellent historical review:
Nieuwenhuys (2012) Brain Structure and Function

# 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

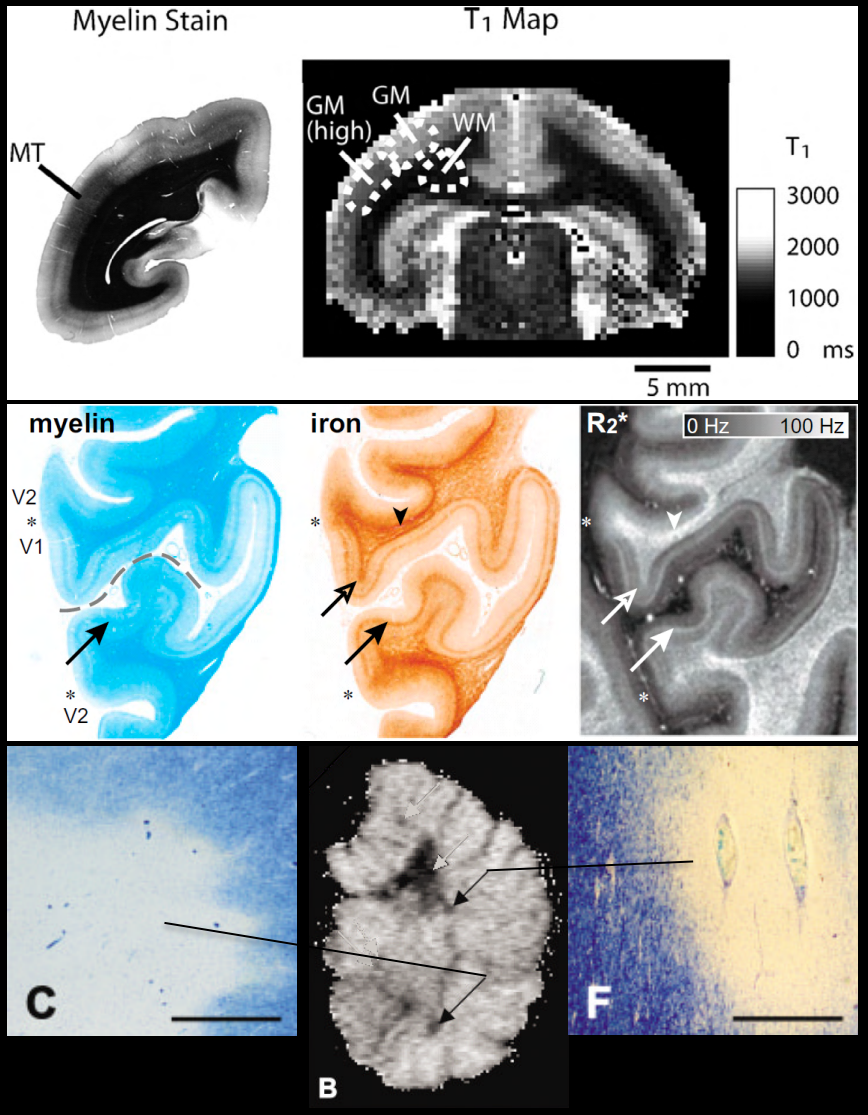


http://www.cytochemistry.net/cell-biology/myelin.jpg

- 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

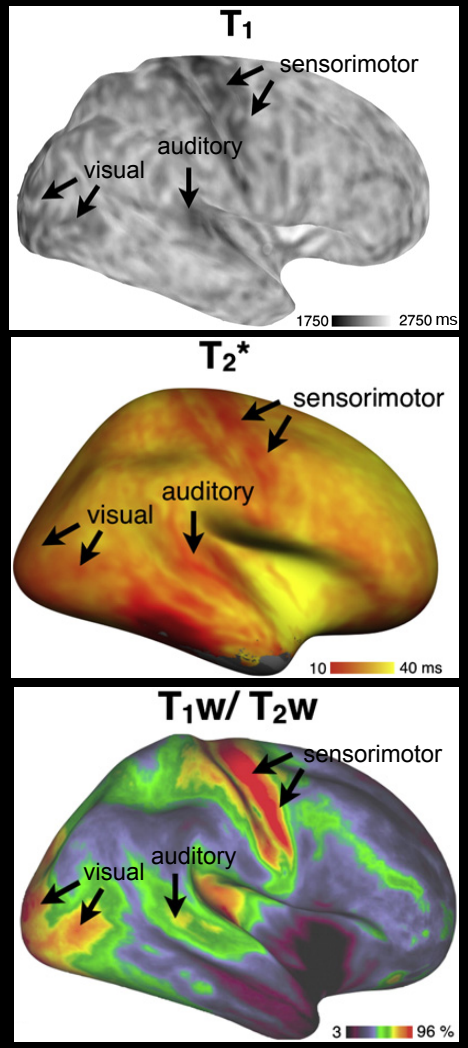
- Bock et al 2009 compared T1 maps and T1w images to myelin stained sections of the same animal, showing similar patterns in both
- Fukunaga et al 2010 compared myelin and iron stained sections to R2* (1/T2*) maps showing close correspondence of all three modalities
- Schmierer et al 2004 compared myelin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



# MRI Techniques for Cortical Myelin Mapping for Localizing Cortical Areas

- Three general approaches have been used:
  - T1 mapping (e.g. Sigalovsky et al 2006, Geyer et al 2011, Sereno et al 2012)
  - T2* mapping (e.g. Sánchez-Panchuelo et al 2011, Cohen-Adad et al 2012)
  - T1w/T2w ratio images (e.g. Glasser and Van Essen 2011)

Cohen-Adad (2013)

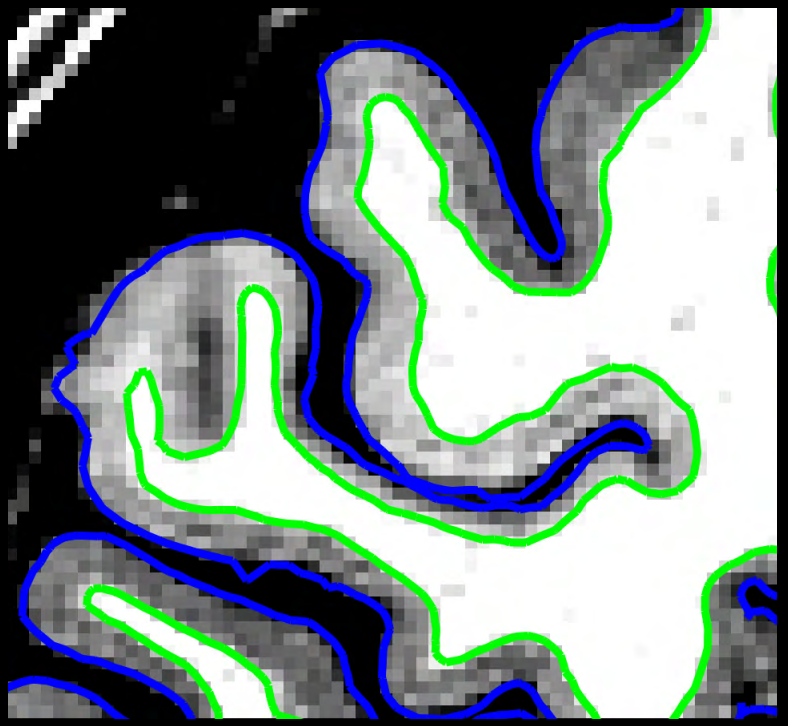


# MRI Techniques for Cortical Myelin Mapping for Localizing Cortical Areas

- These method produce similar overall patterns, but have unique strengths and limitations:
  - The quantitative methods—if you get the details right—reflect intrinsic tissue properties and thereby should be directly comparable across different scanners
  - T2* maps suffer some from MR susceptibility and fiber orientation effects
  - The T1w/T2w ratio method is a relative measure, and must be normalized to compare across different scanners or displayed on a percentile scale
  - The quantitative methods generally require longer acquisitions or higher field strengths to achieve comparable spatial resolution and CNR to the T1w/T2w ratio method (e.g. 0.7mm isotropic for the Human Connectome Project at 3T in ~16 minutes)
  - Most people already acquire T1w images and many people acquire T2w images, or can easily add them (1mm isotropic or ideally higher)
  - Standard tools (e.g. FreeSurfer) use T1w and T2w images to generate cortical surfaces

# 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



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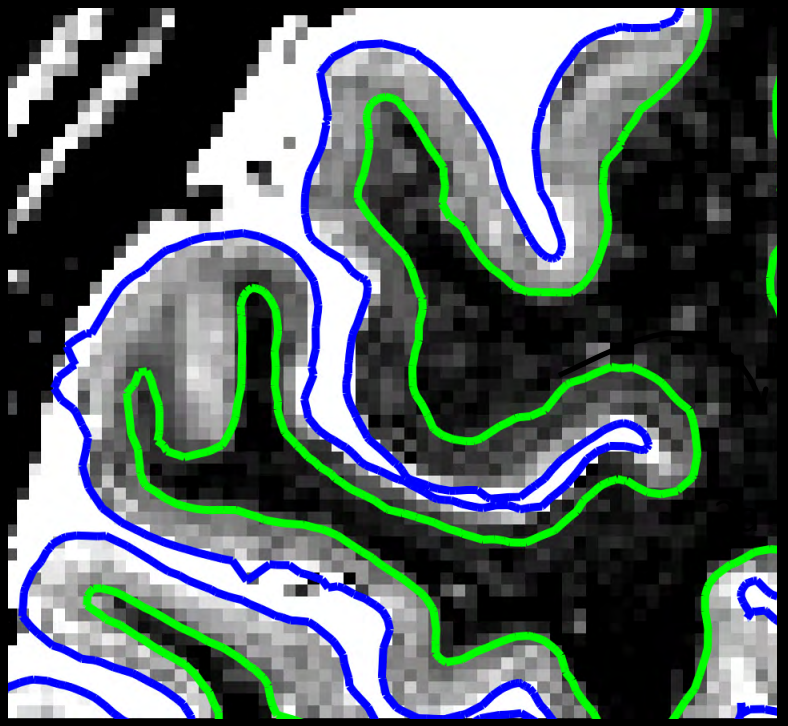

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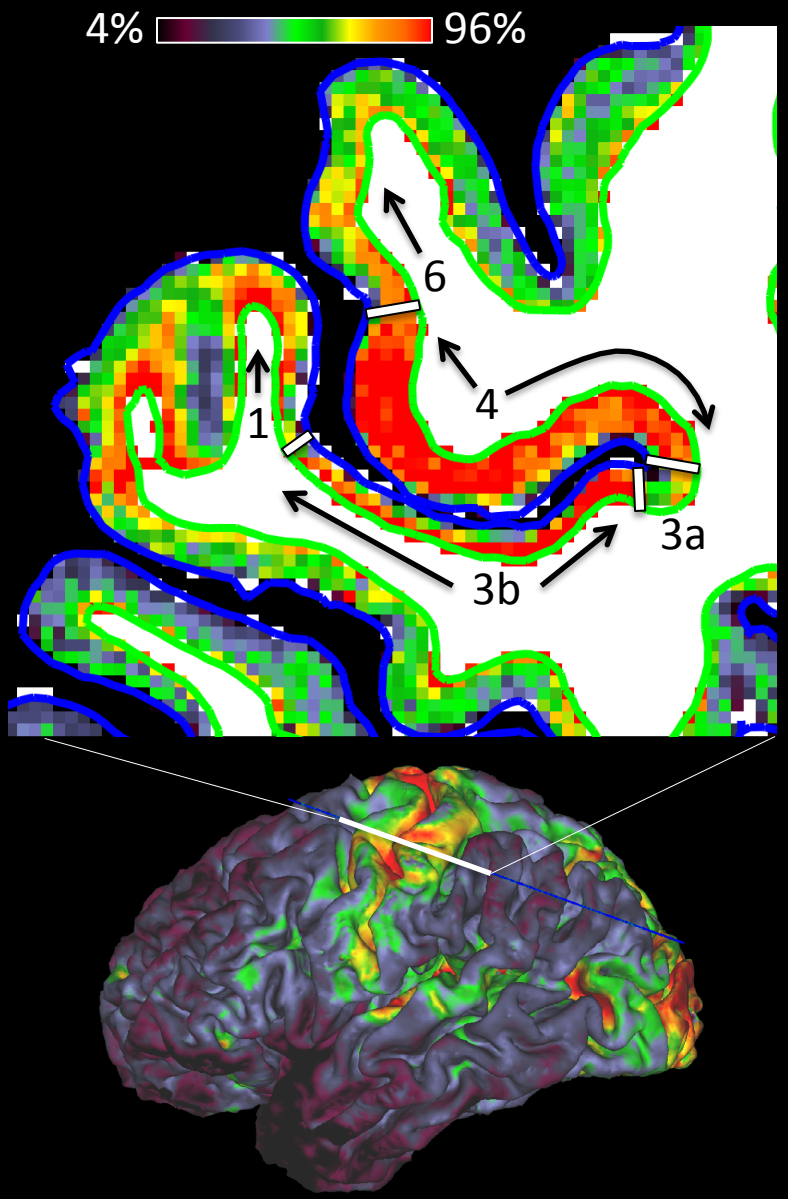
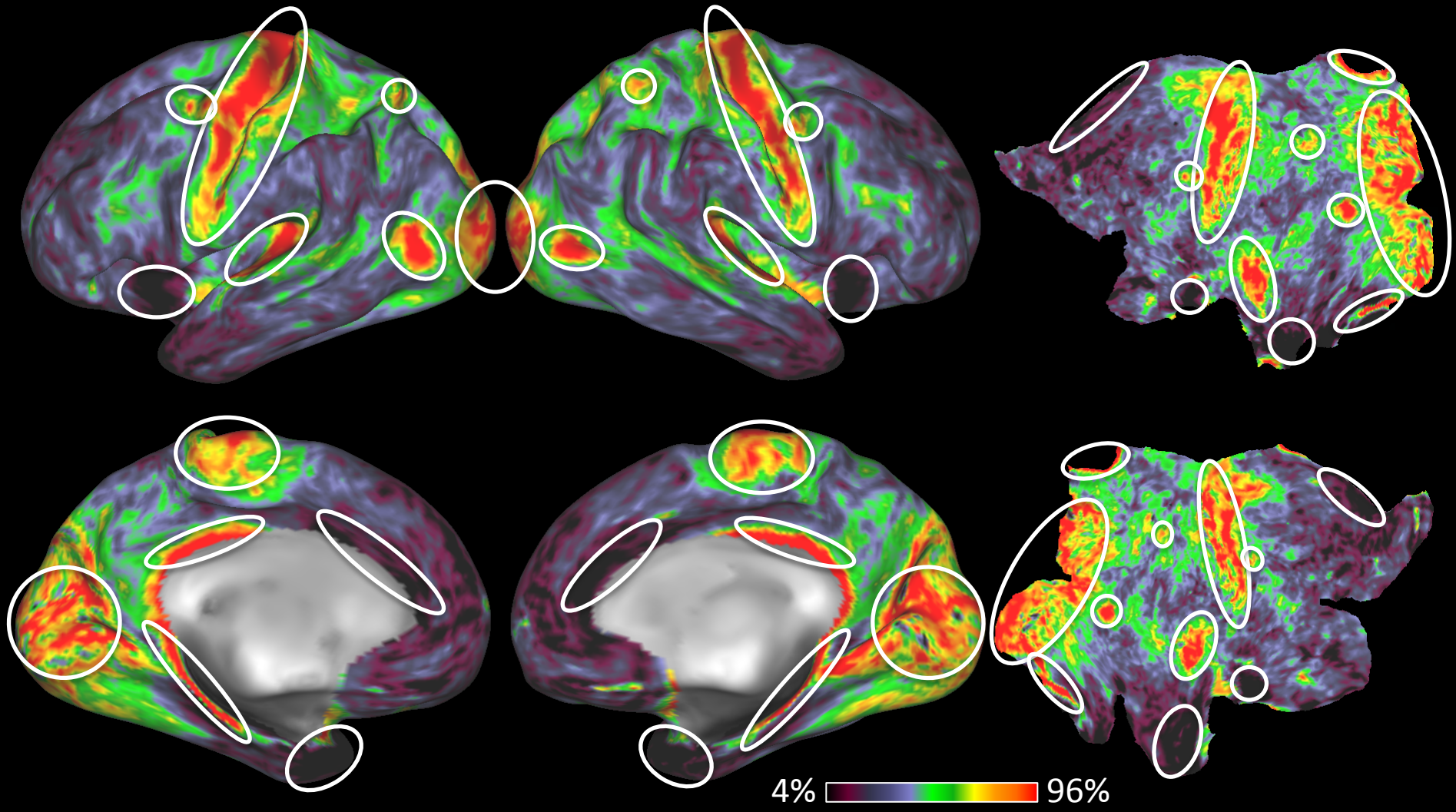
- Myelin is dark in the T2w image
- Because the contrast is inverted between the T1w and T2w images dividing them enhances contrast for myelin while attenuating MR intensity bias fields
- Visualization and comparison across subjects is greatly aided by mapping to the cortical surface
  - Usually average myelin content across the cortical layers, but some attempts at laminar myeloarchitecture for some areas

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



# Myelin Maps of an Individual HCP Subject

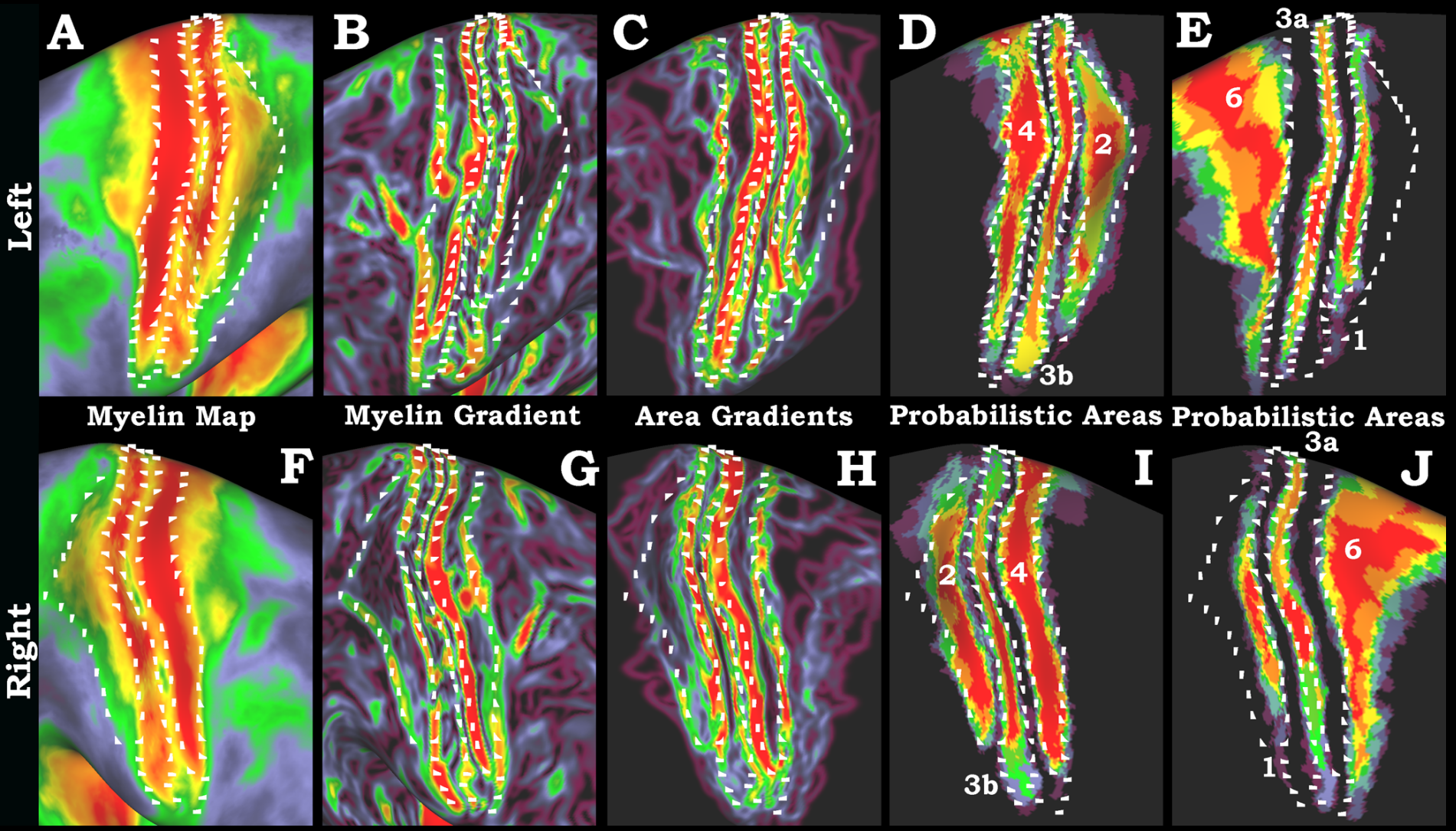
- Many areal features are visible, including:



# Neuroanatomical Validation of Myelin Maps

Glasser and Van Essen 2011
(69 In Vivo Humans)

Fischl et al 2008
(10 Post Mortem Humans)



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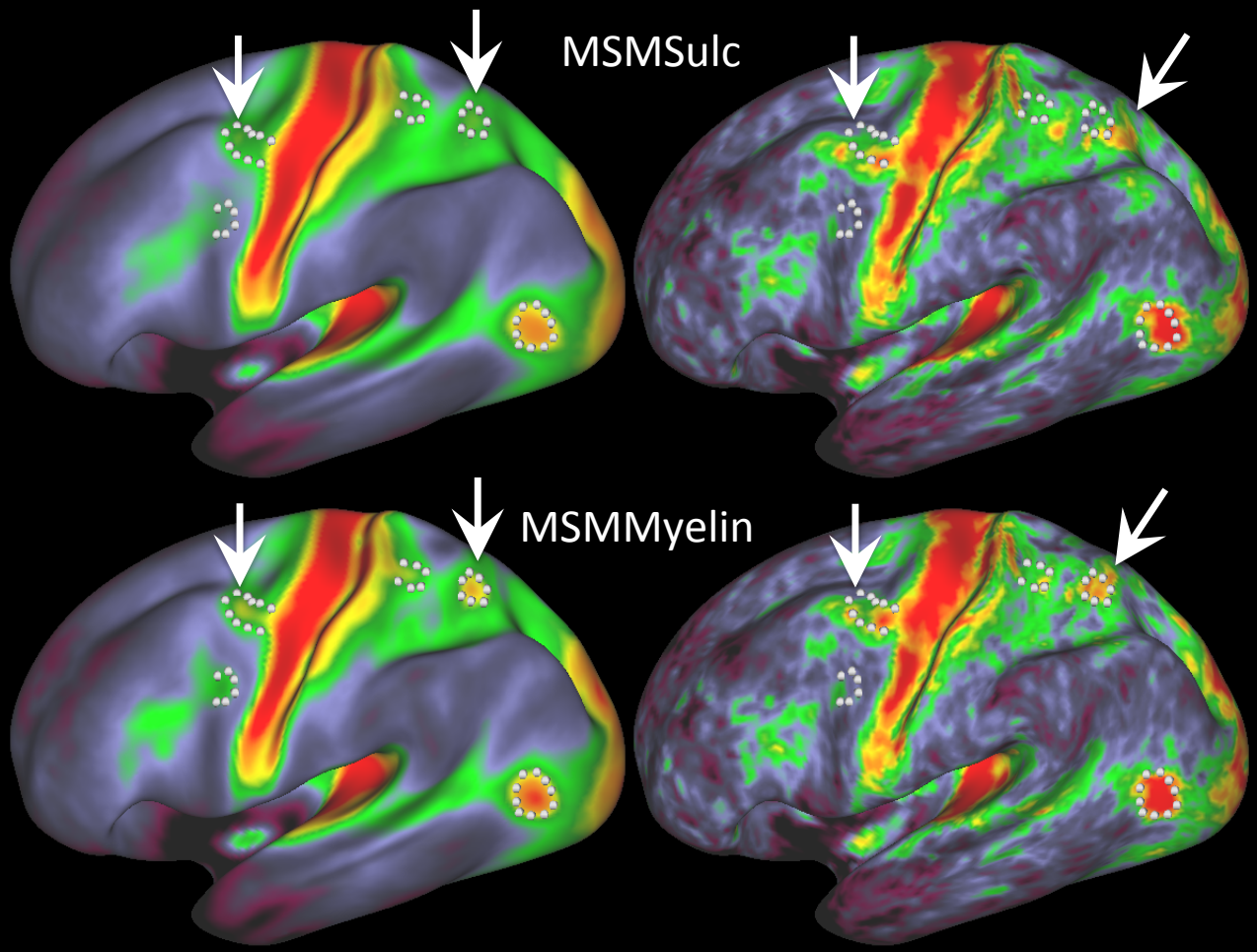
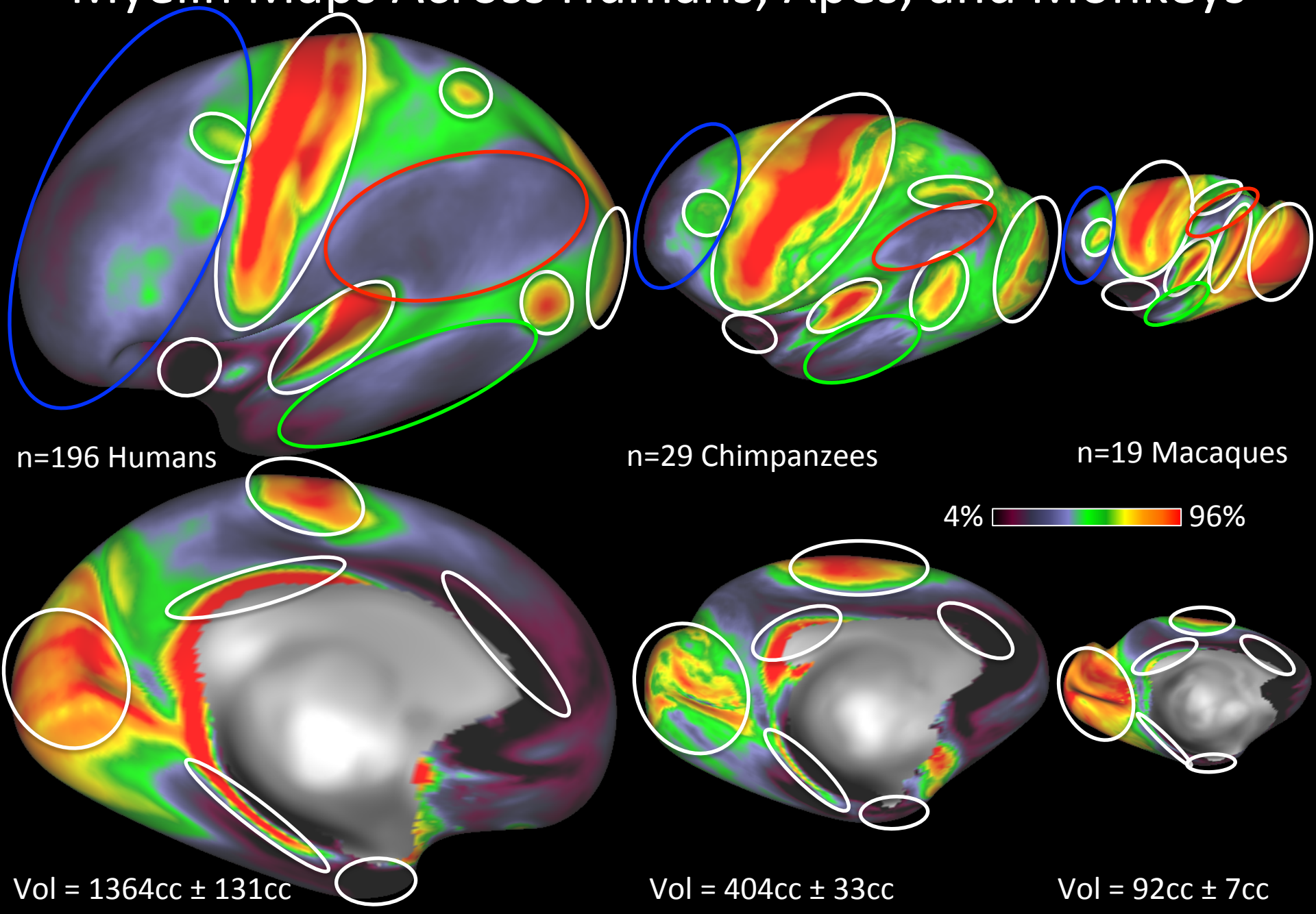
# Improving Intersubject Registration Is Important

- For cortical areas, register on the surface, of course
- It's also important to register using features more closely tied to cortical areas than folding (sulc)
- MSM (Multi-modal Surface Matching) is a general surface registration algorithm that can register many kinds of data, including myelin maps (Robinson et al In Press)

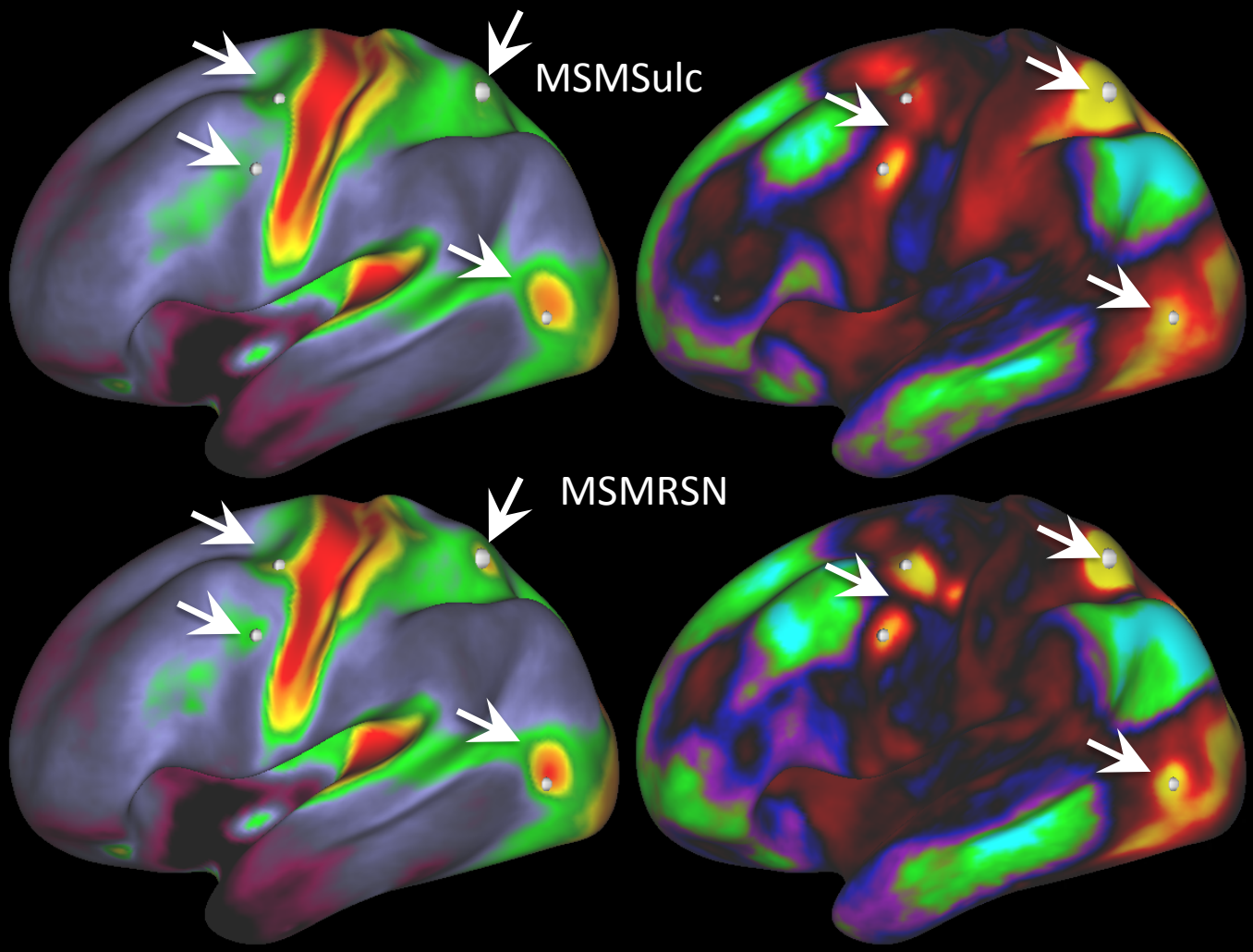


# Myelin Maps Across Humans, Apes, and Monkeys

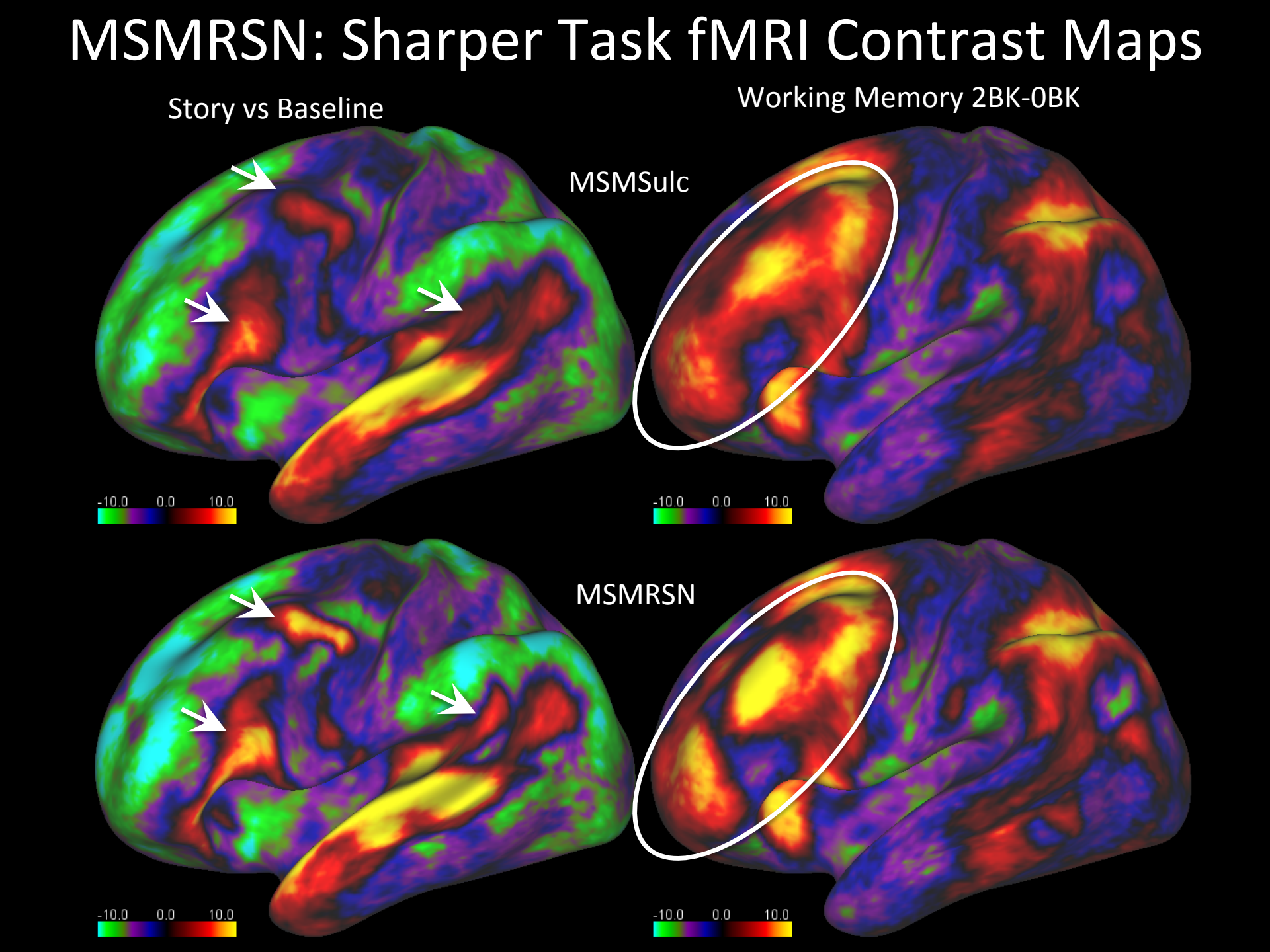


# Resting State Networks Can Also Be Used with MSM for Cross-subject Registration

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

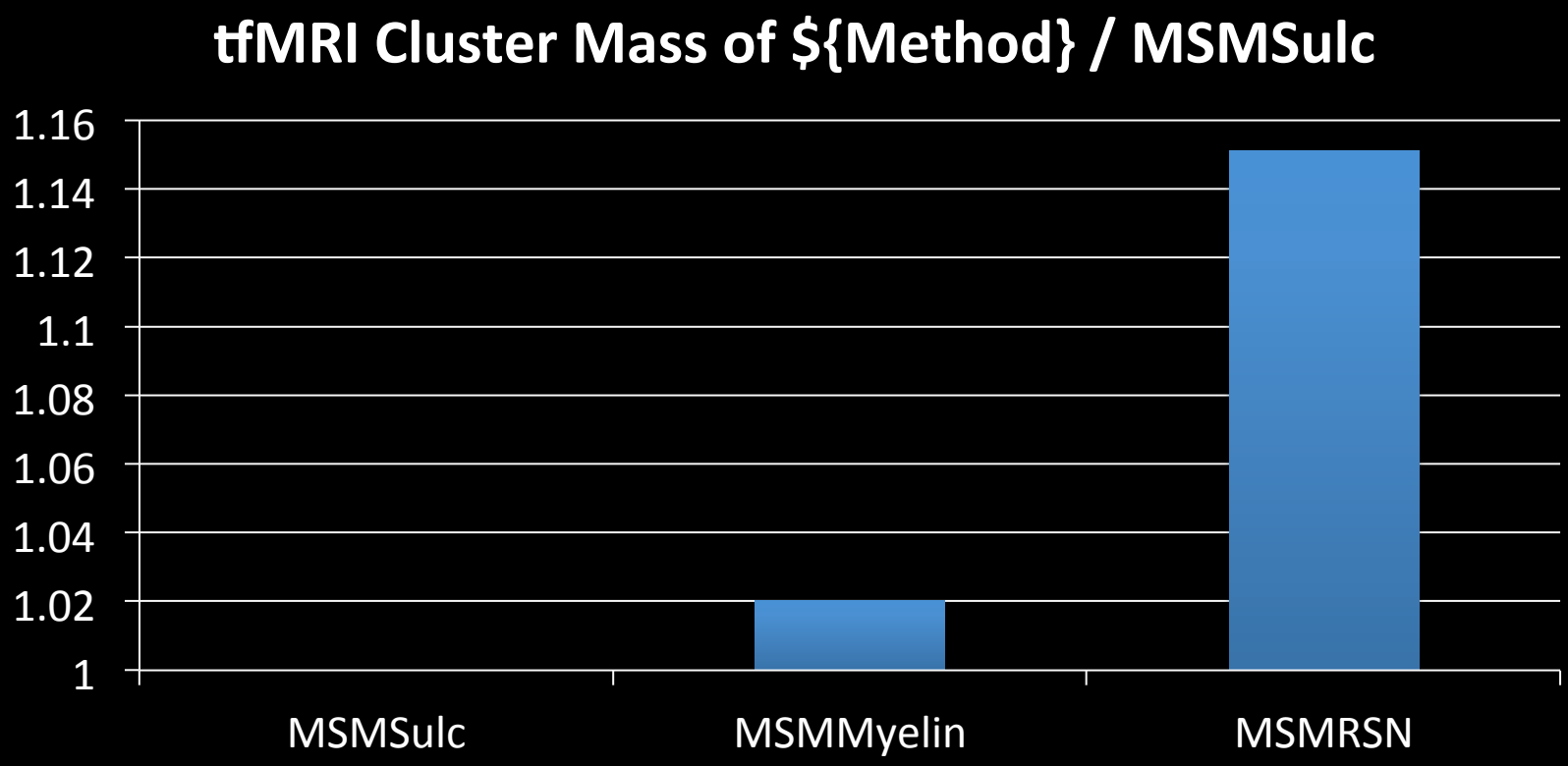


# MSMRSN: Sharper Task fMRI Contrast Maps

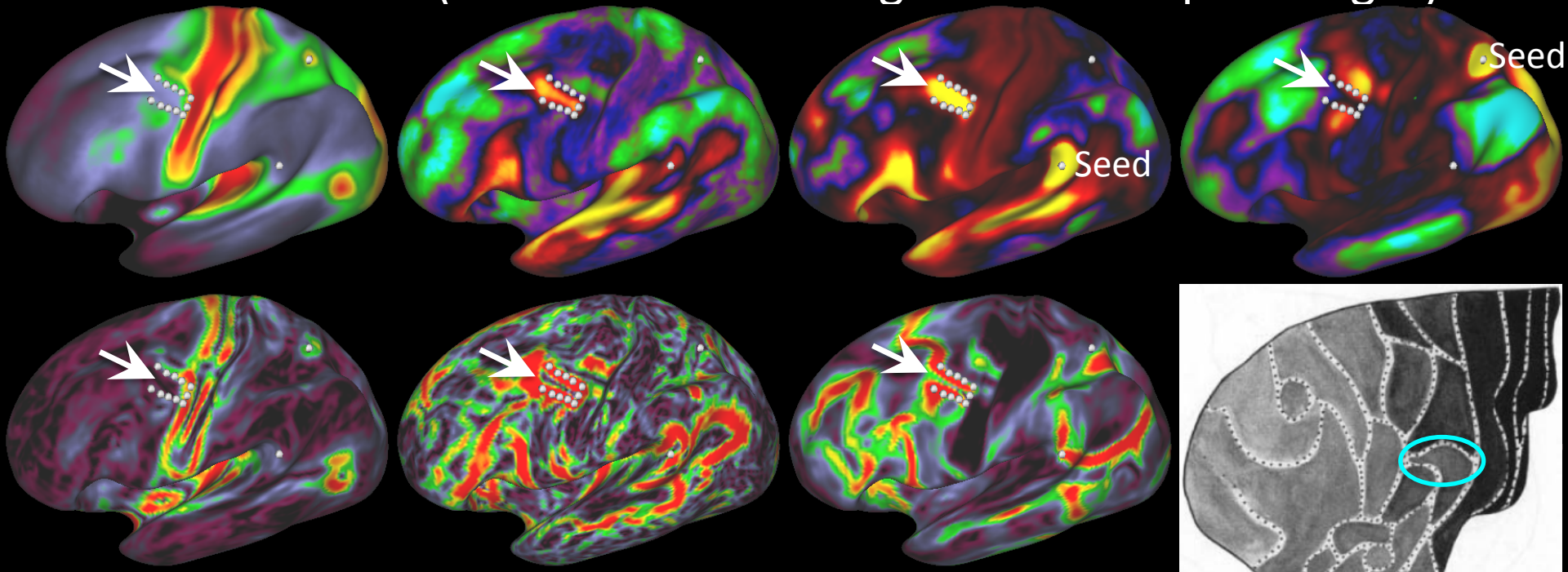


# Quantitative Evaluation of MSM Registration

- MSM is really helpful for sharpening spatial patterns in group maps (e.g. areal borders)
- Also Really helpful for increasing cross-subject statistics in dense analyses



# Cross-modal Comparisons for Multi-modal Parcellation: An Example Cortical Area (n=196 MSMRSN Registered Group Averages)






- 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 Baseline contrast
  - Task zstat 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 (architectonics, 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…

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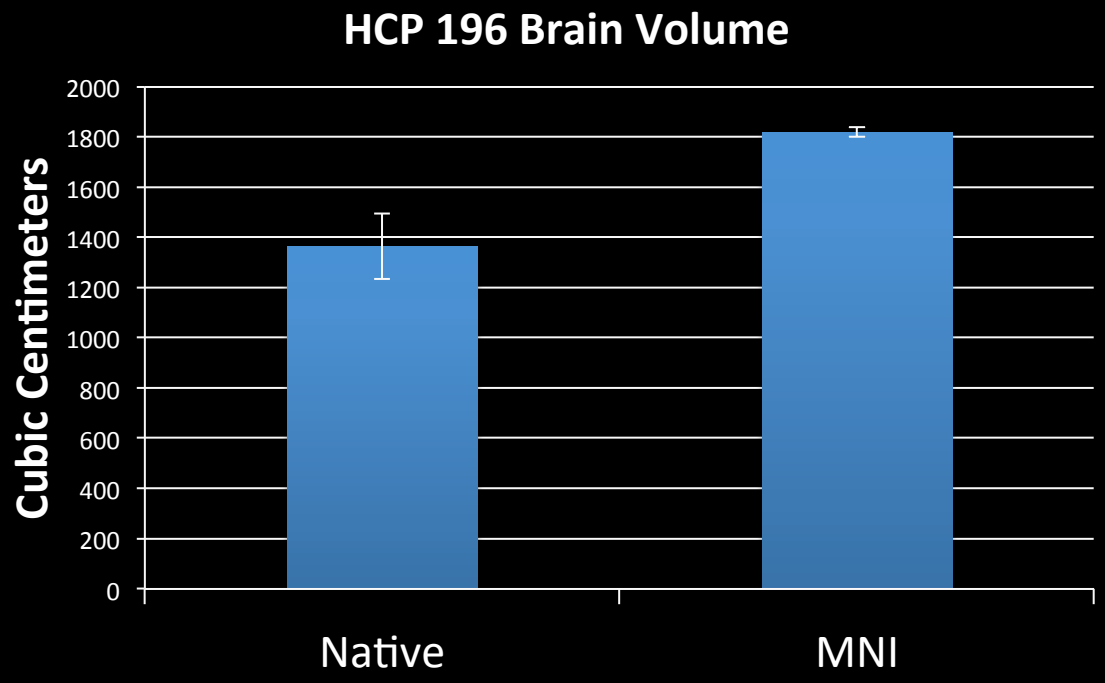
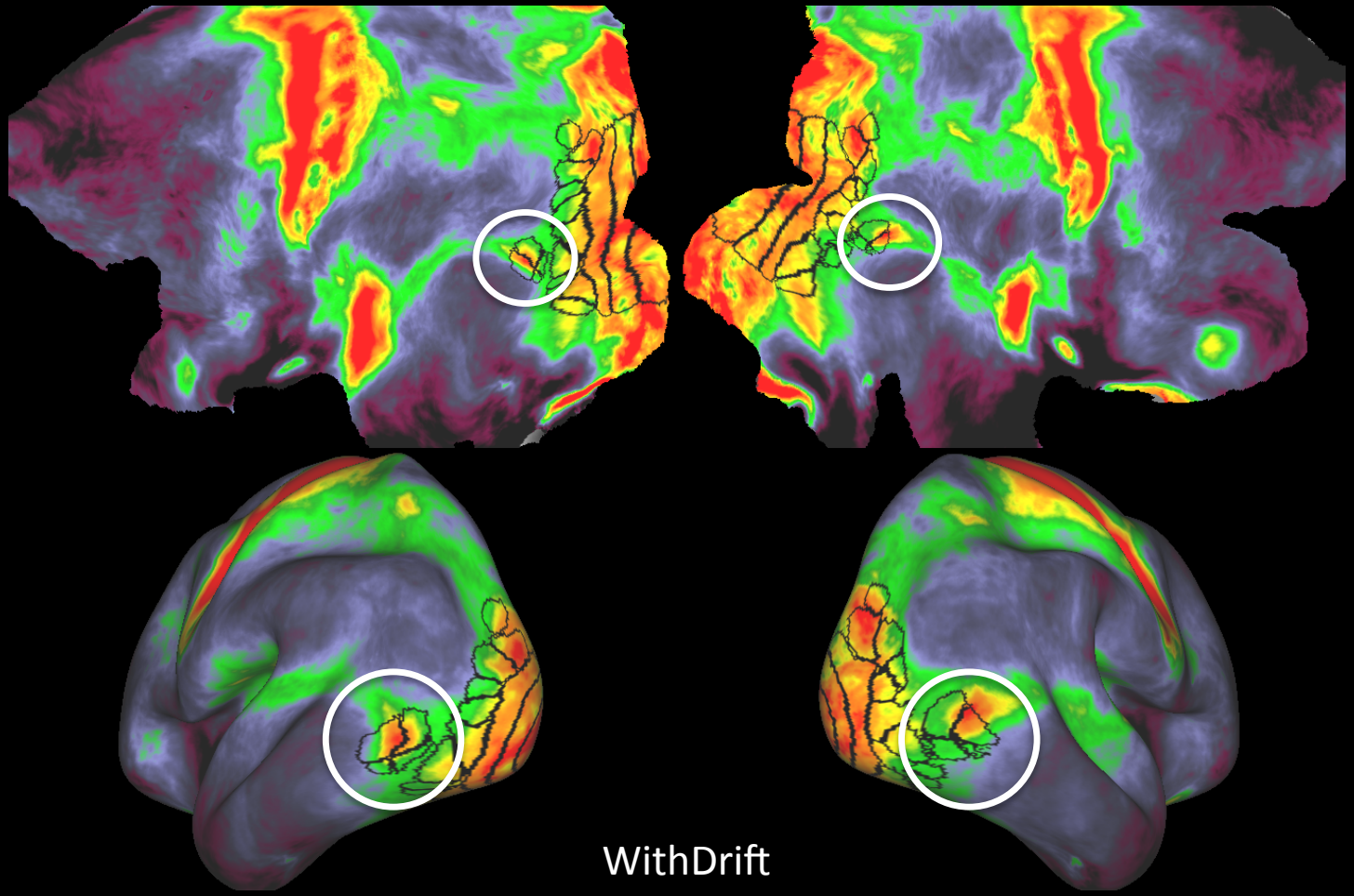
# Group Registration Drift: The MNI Template Brain Volume Expansion




- During template creation, MNI group average volume registration "drifted" to a 37% larger brain size from non-rigid registration degrees of freedom
- This means that the group average brain is 37% larger than the typical subject's brain, though individual variability is also reduced
- This can also occur in surface registration, leading to differences in areal size, shape, and position across studies using different templates and registration algorithms
- To remove drift, calculate the group average registration effect and concatenate its inverse onto each individual subject's registration
- This removes any registration induced biases in the group average so that areal size, shape, and position matches that in the typical subject across studies

# Effect of Removing Group Registration Drift on Comparison Between Two Separate Studies

- Orban retinotopic areas and HCP Myelin maps (both registered with MSM, but using different modalities)



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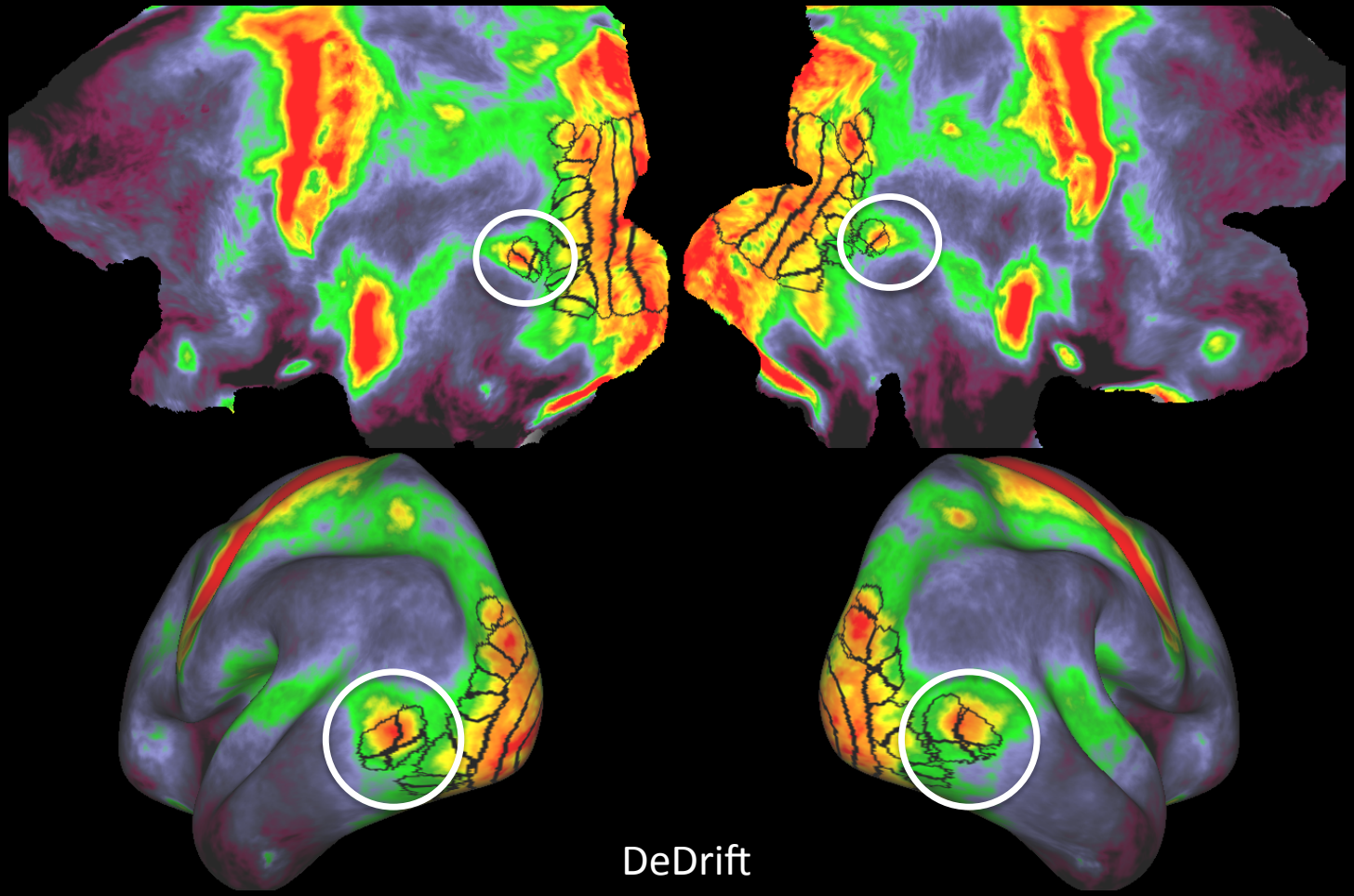
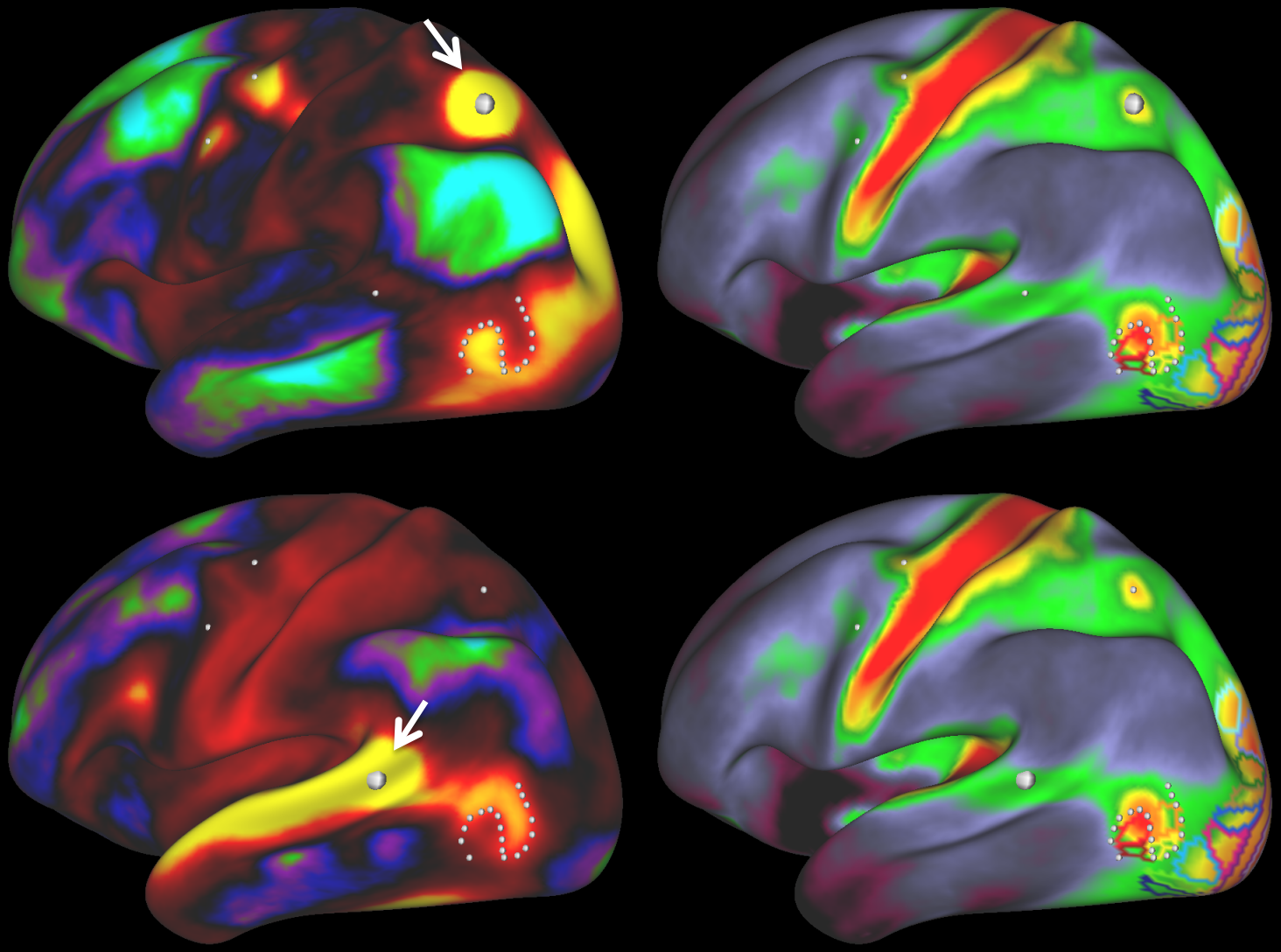


DeDrift

# Cross-study, Cross-modal Comparisons: Myelin and Resting State vs Retinotopy



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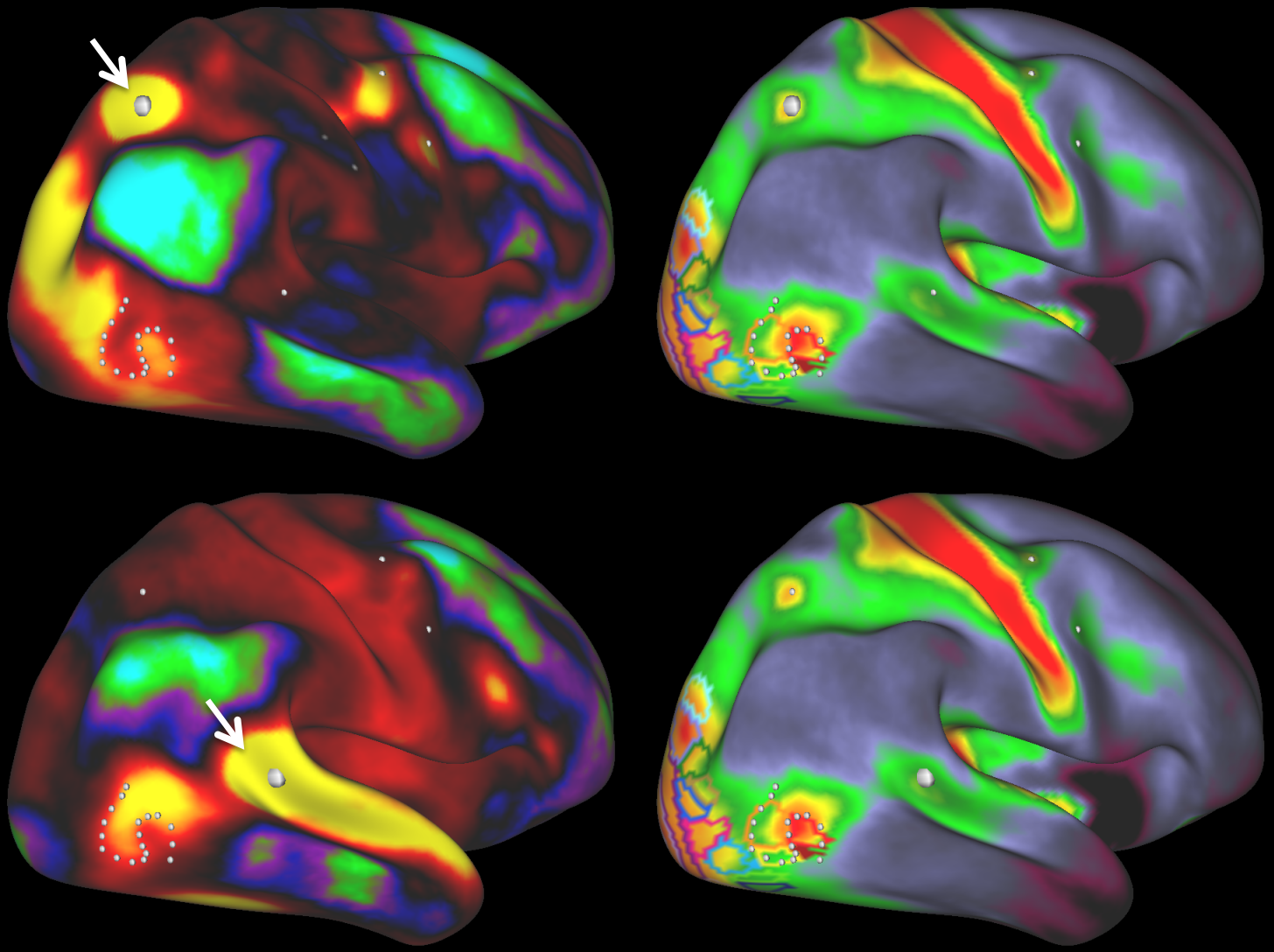

# Key Points

- Analyze and register data with methods that allow you to compare corresponding brain areas across subjects and studies
- Acquire myelin maps routinely—they are very helpful in neuroanatomically interpreting functional data
  - Most studies would just need to add a 3D T2w scan, 1mm = ~4mins
  - If you have T1w, T2w, field map, and fMRI, HCP preprocessing pipelines will work out of the box for you
- If you have a functionally relevant parcellation, use it (better SNR, fewer statistical comparisons, aid to communication)
- Comparing areas based on whether they have the same boundaries/extent is a more stringent and definitive test
- Multi-modal methods are particularly powerful for registering areal features and parcellating the brain

# Acknowledgements


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