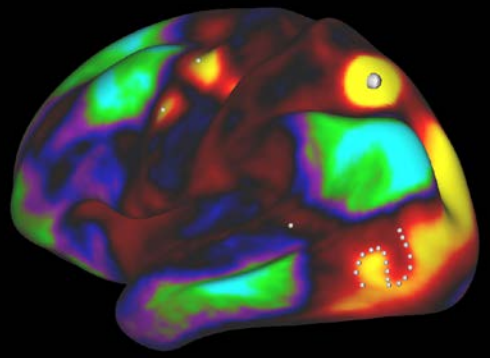
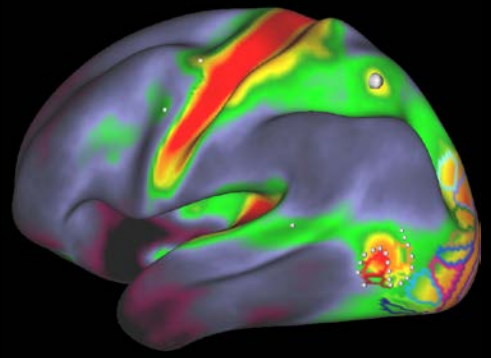
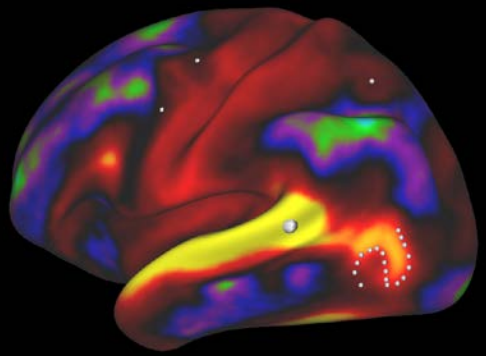


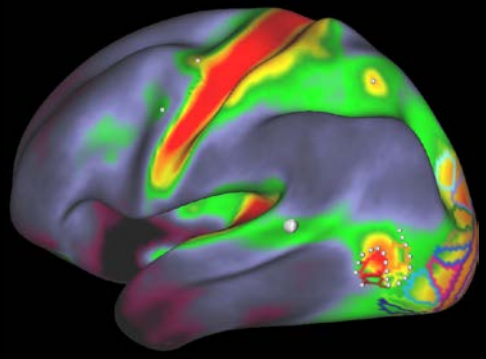


Structural MRI: Precise Neuroanatomical Localization through Careful Processing

Matt Glasser: Lecture 1 of 3



HUMAN Connectome PROJECT



Motivation

- So far you've:
  - Had basic introduction to the HCP and some neuroanatomical realities from David
  - Learned how to acquire high resolution HCP-style data from Gordon and Mike
  - Learned about surface, volume, and CIFTI files from Tim
  - Had a chance to explore our visualization tool, Connectome Workbench, with Jenn
- Now we'll focus on the careful preprocessing and registration approach that
  - Preserves the high resolution of HCP-style data
  - Allows for precise spatial localization across subjects and studies
  - We hope you'll find useful for your future work
- My lecture format: opportunities for questions after each topic

Lecture Topics

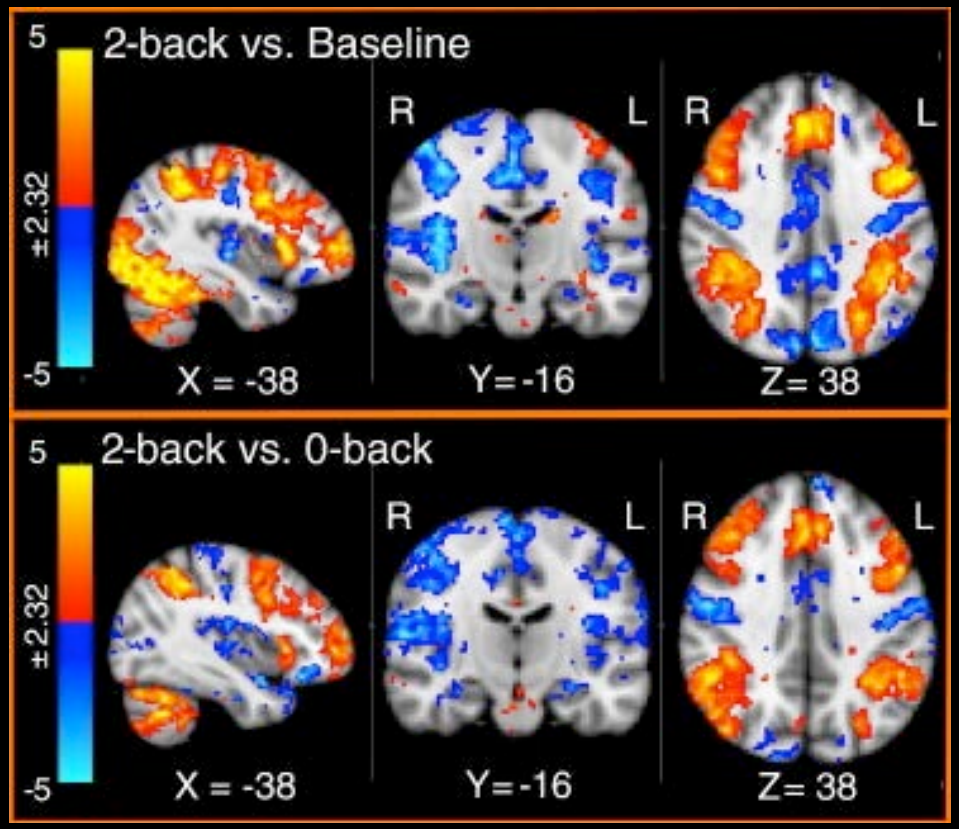
- Neuroanatomical localization in the HCP's CIFTI grayordinates-based neuroimaging analysis paradigm vs traditional volume-based analysis
- The HCP's Minimal Preprocessing Pipelines: From raw images to standard CIFTI grayordinates space
- Cross-subject surface registration based on cortical areal features vs folding patterns
- Removal of group average registration drift to for more accurate comparisons across studies
- Reproducibility of HCP data after careful preprocessing

Spatial Localization: Comparing across Subjects or Studies

- Why bother with spatial localization?
  - Is my effect of interest reproducible across people?
  - Is one group of people different from another group?
  - Did I get the same result as another study?
  - Can I see weak brain/behavior relationships when I average across people?
- These questions all assume…
  - We have aligned brain areas across subjects and studies—like with like
  - There is one to one correspondence across brains at the level we are studying
    - For the higher levels of neural hierarchy, e.g. functional systems and brain areas this is usually true
    - For the lower levels of neural hierarchy, e.g. individual neurons, this is unlikely to be true
- Data analysis methods make a big difference in spatial localization accuracy
  - And the precision/validity of the answers to the above questions
- We will now compare and contrast two methods of analyzing brain imaging data

What Has Traditionally Been Done: Volume-based Brain Imaging Analysis

- Take a bunch of brains in a study and:
  - Use volume-registration to align them to a standard average brain space (e.g. MNI space)
  - Smooth (i.e. blur) them in an attempt to reduce misalignments
  - Do some kind of voxel-wise statistical analysis, e.g.
    - Task fMRI Analysis
    - Resting State Analysis
    - Structural Image Analysis (e.g. on T1w/T2w ratio)
- Out comes a thresholded statistical map which…
  - Represents the confidence in each voxel that any positive or negative effect was not due to chance
- The thresholded statistical map has some clusters of significant voxels
  - Are these likely to represent brain areas?



Barch et al (2013)

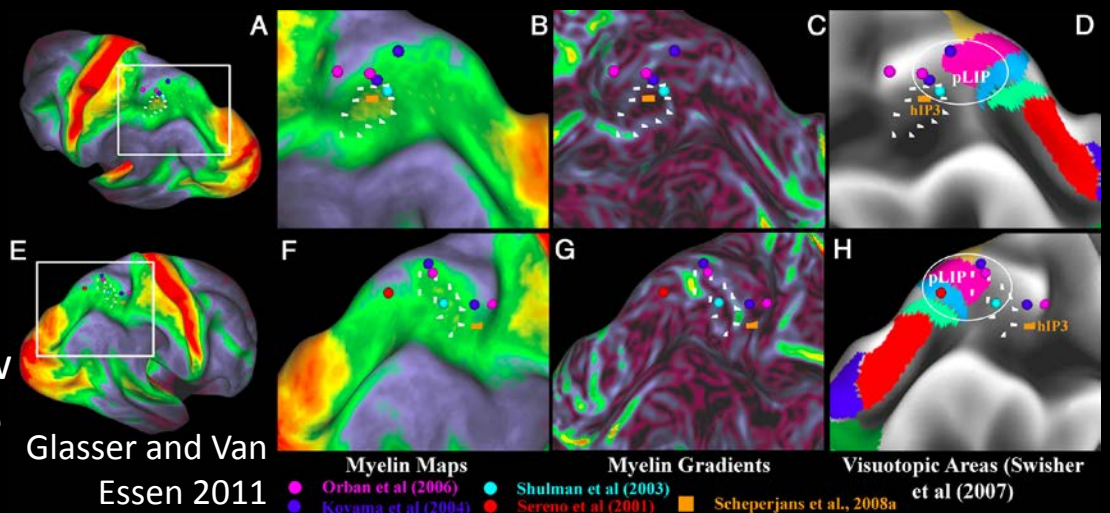
Volume-based Brain Imaging Analysis: Where Am I?

- The investigator looks at the gyral and sulcal landmarks near the cluster on the standard average brain atlas and gives the cluster a name:
  - "e.g. Left Dorso-Lateral Prefrontal Cortex (L DLPFC), Right Temporal-Parieto-Junction (R TPJ)"
- The investigator may attempt to assign each cluster to a brain area based on an interpretation of Brodmann's schematic drawing from 1909 (i.e. a Brodmann Area—BA)
- Typically each cluster will be summarized by the coordinates of its highest value (peak) or its center of gravity in the standard space
- The investigator will report these <u>standard space coordinates</u> (e.g. MNI coordinates) in a data table in their paper
  - Hoping that if everyone aligns their brains to the same standard volume space they will be able to compare results across studies

Data Table From Brain Imaging Paper

Many Papers Are Published Using This Approach

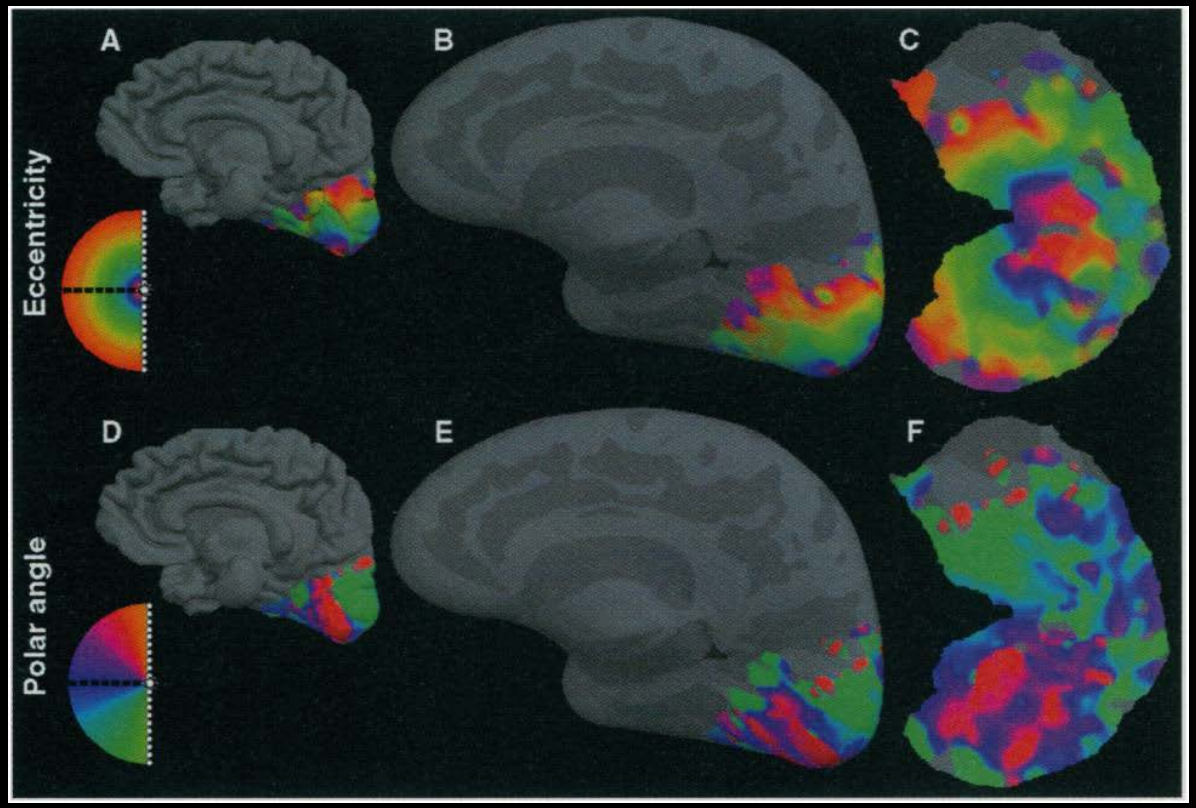
- It has a number of advantages:
  - It's better than no spatial localization at all (what mostly preceded it)
  - It's simple to implement and understand
  - The statistical approximations used are reasonably easy
  - It's what most senior investigators are used to (politics are key)
- Volume-based Neuroimaging Analysis Methods also have a number of disadvantages through their implicit assumptions
  - The brain is not a uniform volume of tissue
  - Brain areas have many widely varied shapes and sizes, not single points (or spheres)
  - To know you are in a particular brain area you need to know its borders
  - Brodmann Areas (BAs) are from a 100 year old drawing, not the brains being studied
  - Cross-subject alignment is reasonable in non-cortical regions, but quite poor in the cerebral cortex, causing substantial blurring
  - Thus, it's challenging compare results across studies and know you are talking about the same thing



Glasser and Van Essen 2011

Data from the Sheet-like Cerebral Cortex Is More Easily Analyzed and Visualized on Surface Models

- Making a surface model used to be entirely manual and very tedious (Van Essen and Maunsell 1980)
- By the time fMRI was invented computers could help (e.g. Sereno et al 1995)
- Studies of the visual system have largely followed Sereno et al's lead, analyzing and visualizing data on cortical surfaces
- As a result, we have a better understanding of the boundaries of and fine details within the brain's visual areas
- Many other parts of the brain, especially cognitive regions, have largely had to wait for such careful study
- As a result, lots of cool stuff is likely yet to be discovered!

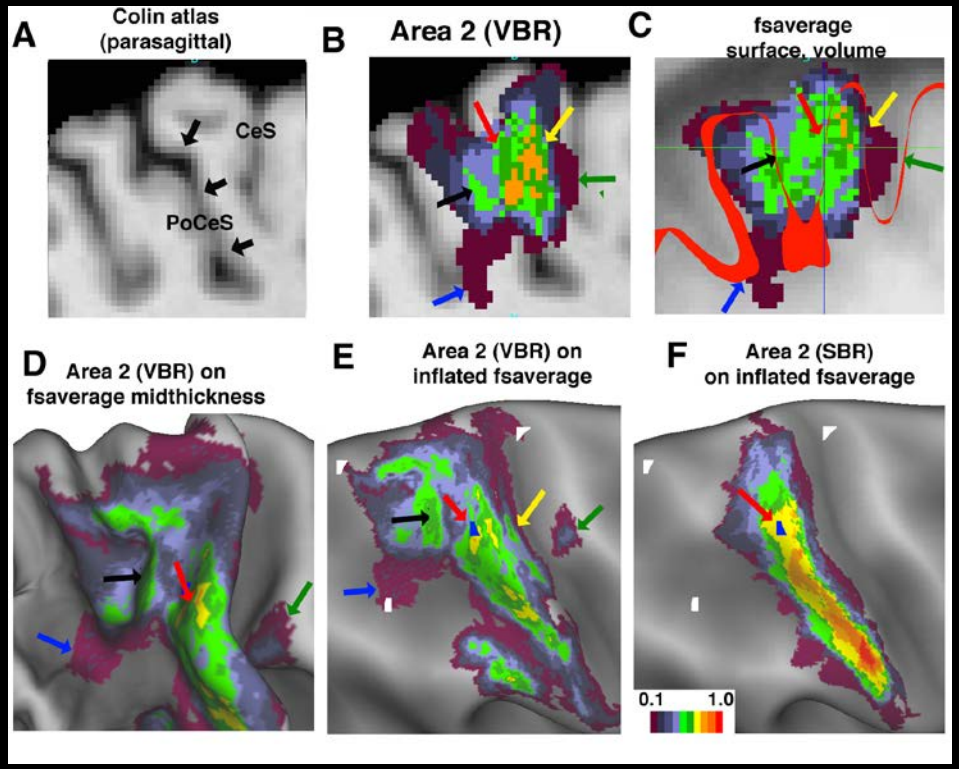


Sereno et al (1995)

Surface-based Registration Substantially Improves Spatial Localization in Cerebral Cortex

- Aligning cortical areas along the 2D cortical sheet across subjects is fundamentally easier than trying to align both the cortical areas and the folded cortical sheet itself in a 3D volumetric registration
- It's much easier to preserve the spatial relationships and borders between cortical areas on the surface
  - e.g. area 2 only on the anterior bank of the post central sulcus

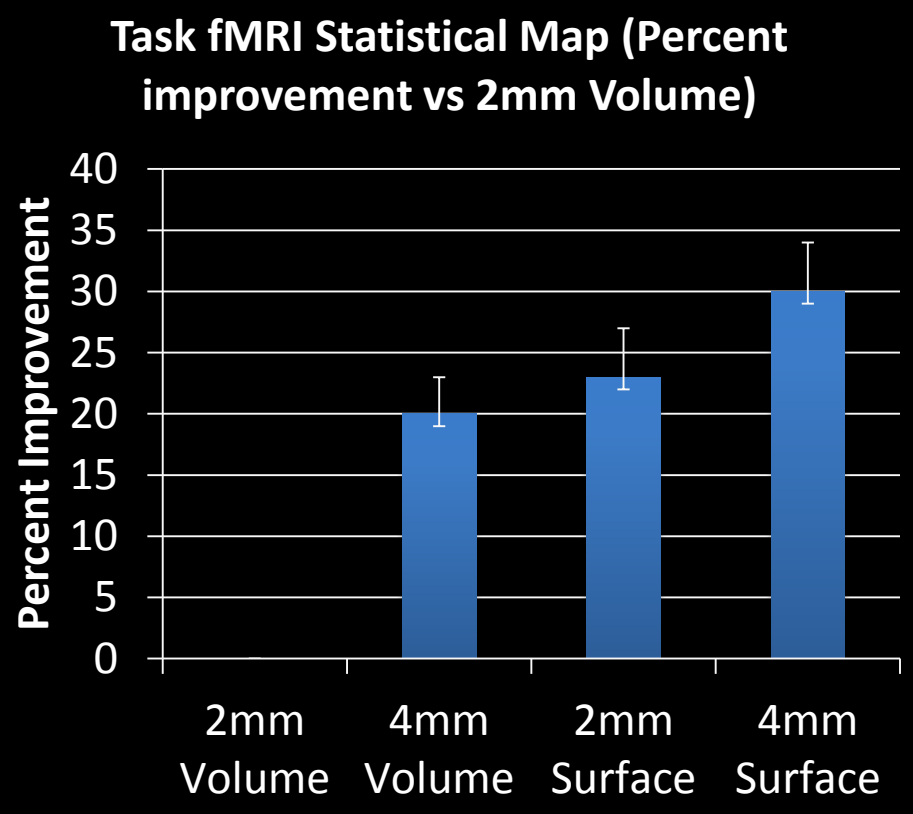
Van Essen et al 2012



Probabilistic cytoarchitectonic areas from Zilles and Amunts group registered on the surface by Fischl et al (2008)

Simply Using Folding-based Surface Registration Is a Big Improvement Over Volume-based

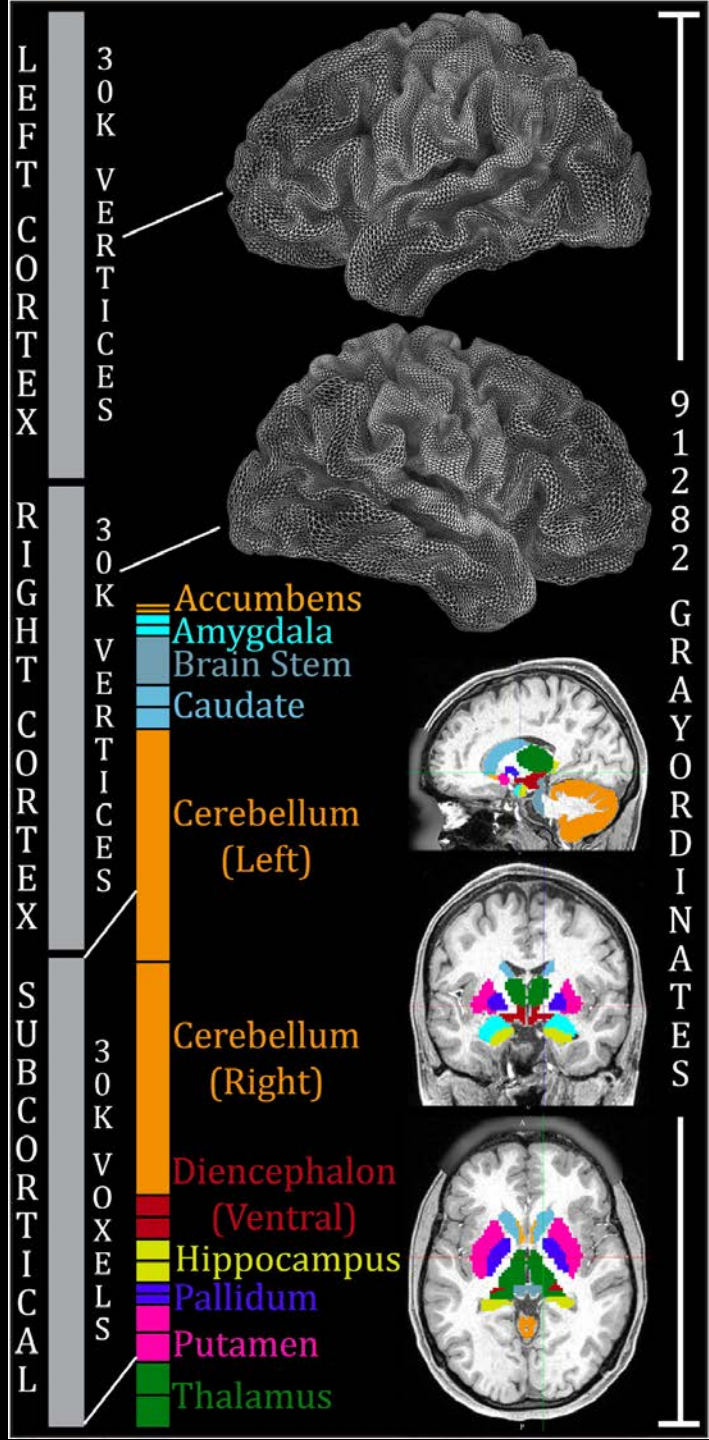
- Volume Registered:
  - 2mm FWHM volume smoothed
  - 4mm FWHM volume smoothed
- Surface Registered:
  - 2mm FWHM surface smoothed
  - 4mm FWHM surface smoothed
- Percent improvement in task fMRI statistical maps over 2mm volume registered
  - 2mm surface smoothed better than 4mm volume smoothed



Not a novel finding (across many modalities): Fischl et al 1999, Fischl 2008, Anticevic et al., 2008, D.C. Van Essen et al., 2012, Frost and Goebel, 2012, Tucholka et al., 2012, Smith et al 2013, etc…

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



Other Things to Think about When Switching to CIFTI Grayordinates

- Large amounts of spatial smoothing is often done in volume-based analyses in lieu of aligning brain areas and this approach has been brought to the surface
  - "As long as you smooth in 2D on the surface, 15mm FWHM is okay, besides smoothing makes my statistics go up"
  - Is altering your data in this way a good idea or does it make it harder to see what is really going on?
- Neuroimaging data have many thousands of datapoints, each with relatively low SNR, but most brain imagers are after a coarser level of information
  - Should one consider these noisy datapoints all independently (with post-hoc statistical approximations to deal with multiple comparisons)?
  - Alternatively could we often simplify the problem by making use of the brain's intrinsic neuroanatomical organization to increase our sensitivity and power? (lecture 2)
- In neuroimaging, maps of statistical significance are often all that is shown and data that is below the chosen threshold is often changed to zero and hidden
  - How does thresholding change the appearance of the data for effects that are just above vs just below the threshold?
  - How reproducible is the spatial pattern of this threshold across different studies or even different groups within a study?
  - Do statistical thresholds reflect areal boundaries or something else?

Volume-based vs Grayordinates-based Spatial Localization Summary

- Volume-based analysis is easy to do, but relies on a number of problematic assumptions about the brain
- Volume-based cortical spatial localization is not very good and we don't really know what cortical areas are being shown in most published results
- The outcome is a large amount of literature with substantial challenges for reconciling conflicting results or even knowing if they are conflicting or not
- Grayordinates-based analysis combines cortical surface and subcortical volume analyses in order to analyze the whole brain and offers the promise of better spatial localization
- Grayordinates-based analyses can take advantage of further registration improvements (later section)
- Questions about analysis paradigms?

Lecture Topics

- Contrast neuroanatomical localization in the HCP's CIFTI grayordinates-based neuroimaging analysis paradigm vs traditional volume-based analysis
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- Reproducibility of HCP data after careful preprocessing

Getting to Grayordinates: Goals of (Spatial) Minimal Preprocessing Pipelines in the HCP

- Remove spatial artifacts like distortions to get back to the subject's physical space
- Align data within each subject to remove the effects of motion/get all modalities into spatial correspondence
- Make the geometric models that underlie all of the other analyses
- Begin the process of getting brain areas aligned across subjects
- The HCP Pipelines are publicly released (see https://github.com/Washington-University/Pipelines/releases) and described in a publication (Glasser et al 2013)
- We will just scratch the surface here, for more detail, read the paper/code ;)

Pipeline Architecture (Order of Operations)

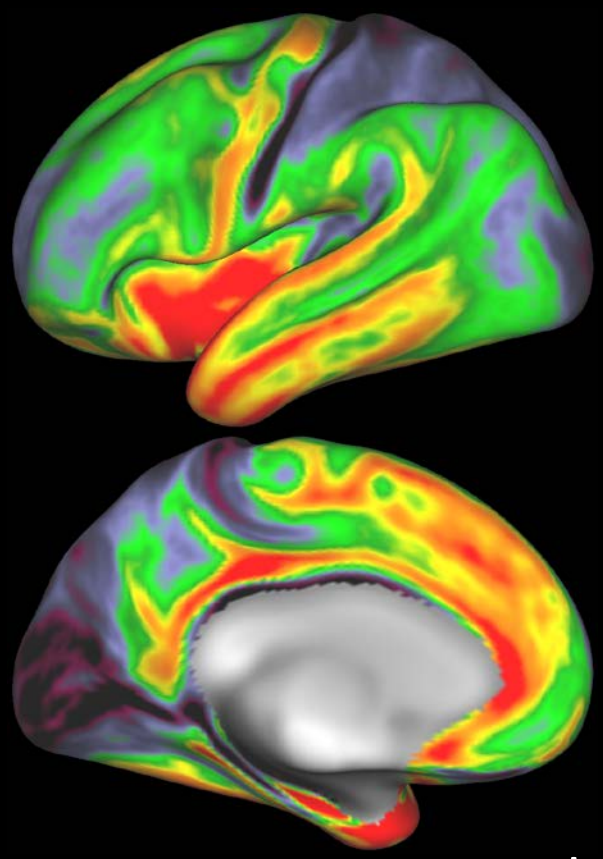
HCP Minimal Preprocessing Pipelines

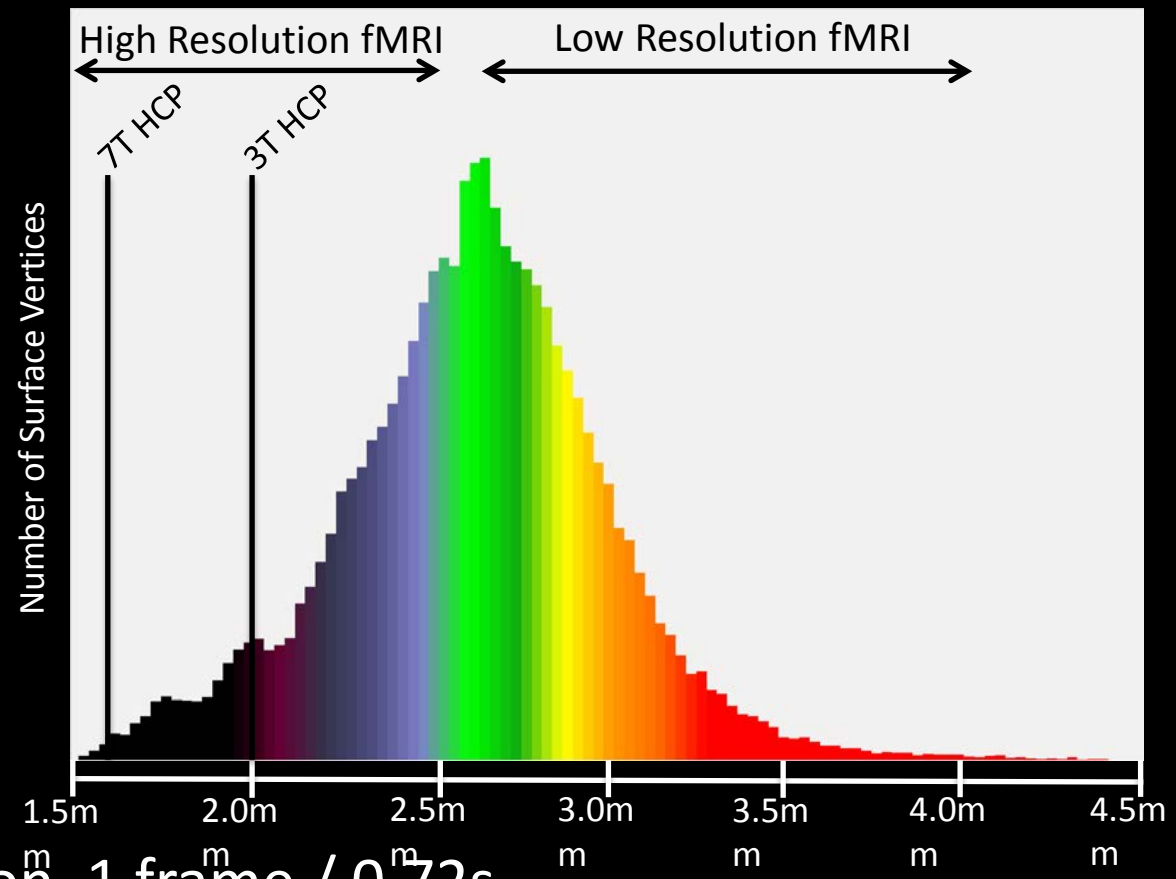
- Files organized in the “Connectome In a Box” format:
  - ${StudyFolder}/${Subject}/…

Minimum Image Acquisition Requirements for the HCP Pipelines

- Structural
  - T1w MPRAGE (at least 1mm isotropic, ideally 0.8mm or better)
  - T2w SPACE (at least 1mm isotropic, ideally 0.8mm or better, FLAIR also works but is not optimal)
- Functional
  - fMRI (preferably high spatial and temporal resolution)
  - SBRef if using multi-band
  - Field Map (preferably of the spin echo variety, matched to fMRI geometry)
- Diffusion
  - DWI (preferably high spatial and angular resolution, reversed phase encoding directions)

What is High Resolution fMRI? Cerebral Cortical Thickness vs Imaging Resolution





- 3T: 2.0mm resolution, 1 frame / 0.72s
- 7T: 1.6mm resolution, 1 frame / 1.0s
- High temporal resolution is ~1.0s or less

The PreFreeSurfer Pipeline

- Correct gradient and b0 (readout) distortion and rigidly align to MNI (subject's physical space in a standard orientation)
- Initial robust brain extraction (*FreeSurfer needs help here)
- Register T1w and T2w images
- Bias field correction (*FreeSurfer needs help here)
- Nonlinear volume registration to MNI (for subcortical alignment)
- Creates the subject's folder structure and gets the data ready for FreeSurfer:
  - ${StudyFolder}/${Subject}/T1w – Native Volume Space
  - ${StudyFolder}/${Subject}/MNINonLinear – Atlas Volume Space

The FreeSurfer Pipeline

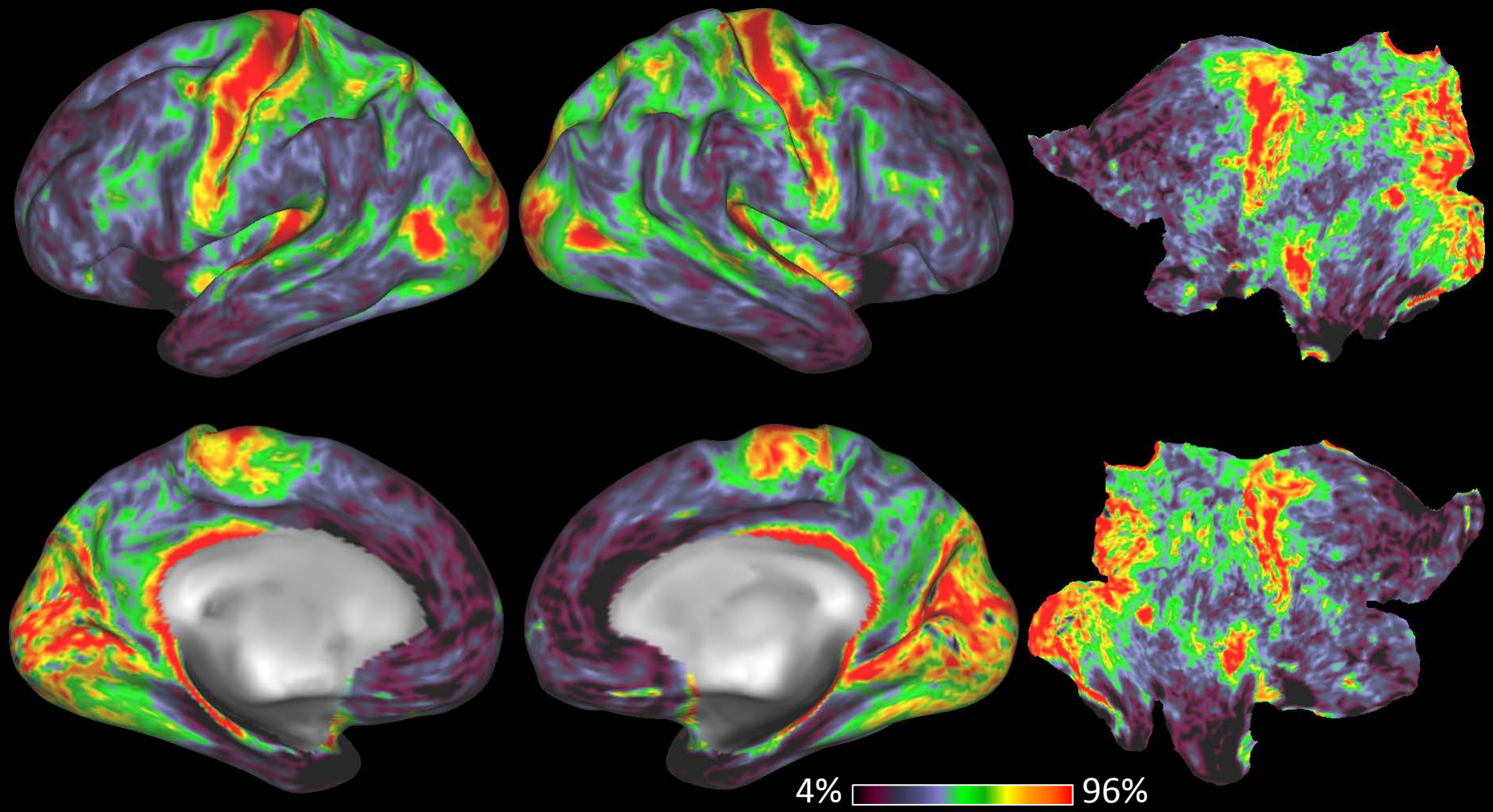
- Automatically generates surfaces and subcortical segmentation
- Runs FreeSurfer's recon-all pipeline with a few modifications
  - Help for brain extraction and intensity normalization
  - Use high resolution T1w for more accurate white matter surface placement
  - Use high resolution T2w for more accurate pial surface placement
- A modified pipeline, FreeSurferNHP automatically generates macaque and chimpanzee surfaces and subcortical segmentations
  - Will hopefully be released in the future
  - Otherwise the HCP pipelines will run on other species with appropriate templates/settings

The PostFreeSurfer Pipeline

- Performs initial folding-based surface registration (MSMSulc)
- Gets data into standard NIFTI/GIFTI/CIFTI formats and gets it ready for easy visualization in Connectome Workbench (makes the spec files)
- Creates the rest of the subject's folder structure:
  - ${StudyFolder}/${Subject}/${VolumeSpace}/Native – Native surface mesh
  - ${StudyFolder}/${Subject}/${VolumeSpace}/fsaverage_LR32k/ – 2mm standard surface mesh
- Computes myelin maps…

What is a Myelin Map?

- Measure of cortical graymatter myelin content based on T1w and T2w images – more in lecture 2 on brain parcellation
- Red/orange/yellow – high myelin
- Black/purple/blue – low myelin



The fMRIVolume Pipeline

- Removes gradient and b0 distortions
- Corrects for motion with spatial realignment
- Registers fMRI to T1w data with BBR (especially accurate cross-modal registration algorithm)
- Combines all transforms and resamples data into MNI space in a single spline interpolation
- Creates the volume fMRI timeseries
  - ${StudyFolder}/${Subject}/MNINonLinear/Results/${fMRIName}/${fMRIName}.nii.gz

The fMRI Surface Pipeline

- Cortical ribbon-based volume to surface mapping using the individual's white and pial surfaces together with a mask to remove locally noisy voxels (veins, etc)
- Resampling to standard grayordinates space on the surface and within the subcortical volume structures
- Minimal smoothing (2mm FWHM) to regularize the mapping to the 2mm standard grayordinates space
- Creates the CIFTI fMRI dense timeseries
  - ${StudyFolder}/${Subject}/MNINonLinear/Results/${fMRIName}/${fMRIName}_Atlas.dtseries.nii
- Steve will talk about clean up of temporal artifacts from fMRI data later today

The Diffusion Pipeline

- Remove distortions from gradients, b0, and eddy currents
- Corrects for motion with spatial realignment
- Register DWI to T1w data with BBR
- Rotate diffusion gradient vectors into structural space, and compute gradient nonlinearity correction of these vectors in that space
- Creates the diffusion data files
  - ${StudyFolder}/${Subject}/T1w/Diffusion/data.nii.gz, bvals, bvecs, nodif_brain_mask.nii.gz, grad_dev.nii.gz
- Much more about this pipeline and image distortion correction from Jesper on Wednesday

HCP Minimal Preprocessing Pipelines Summary

- HCP Pipelines were written to take advantage of high spatial and temporal resolution data
  - Also to set a reasonable “minimum” standard of HCP data preprocessing
- Have tried to remove all image distortions, subject motion, and use very accurate registration methods
- Generate data ready for analysis in the HCP’s CIFTI grayordinates analysis paradigm
- HCP Pipelines have minimum data acquisition requirements
  - If you don’t want to have to do major hacking to achieve something that may not be as good
  - T1w, T2w, fMRI, field map will also be sufficient for additional pipelines to be discussed below
- HCP Pipelines are based on the open source development model and we want to see them improve as the field needs, so patches are welcome!
- Question about HCP Pipelines?

Lecture Topics

- Contrast neuroanatomical localization in the HCP's CIFTI grayordinates-based neuroimaging analysis paradigm vs traditional volume-based analysis
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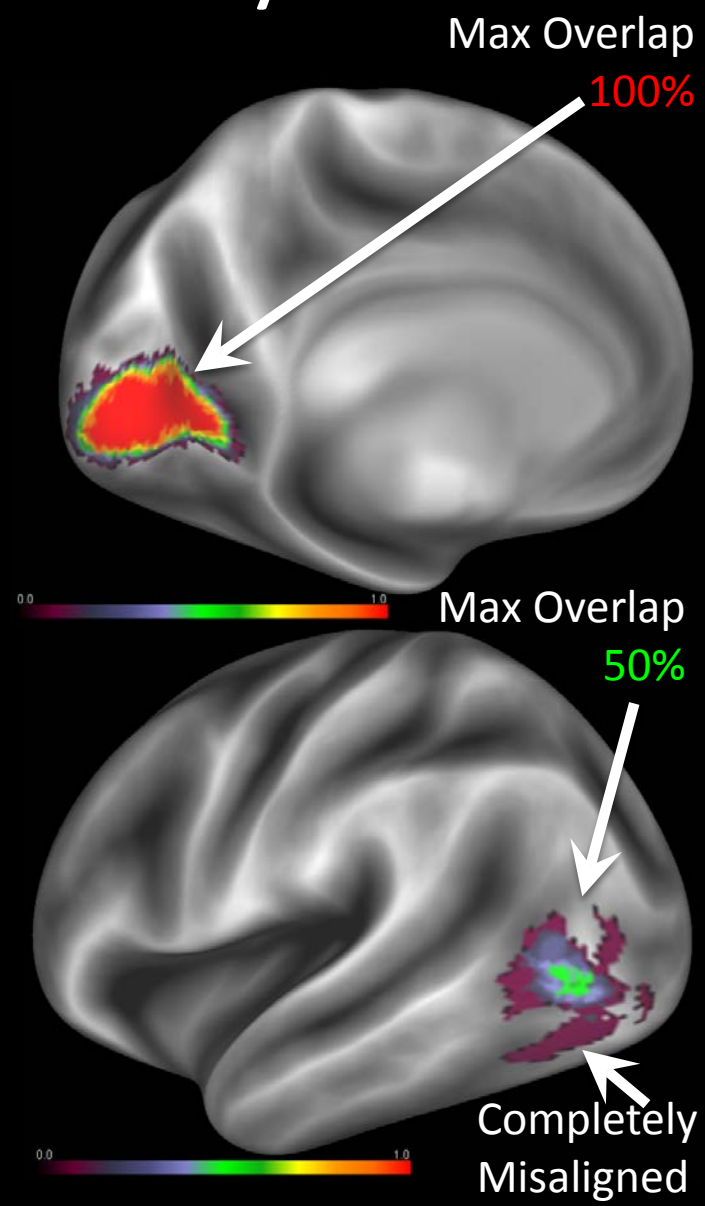
Cortical Folding-based Surface Alignment Is Often Blurry

- Registration using folding patterns alone does not accurately align cortical areas across subjects in many parts of cortex
- When folding patterns are consistent across subjects and areas are consistently located relative to folds, areas may be well aligned by folding-based registration
  - e.g. V1 or early somatosensory and motor areas
- Many other regions areas may still have significant misalignment, even after folding-based registration
  - e.g. around MT+, FEFs, putative VIP/LIP complex, etc

From Fischl et al 2008

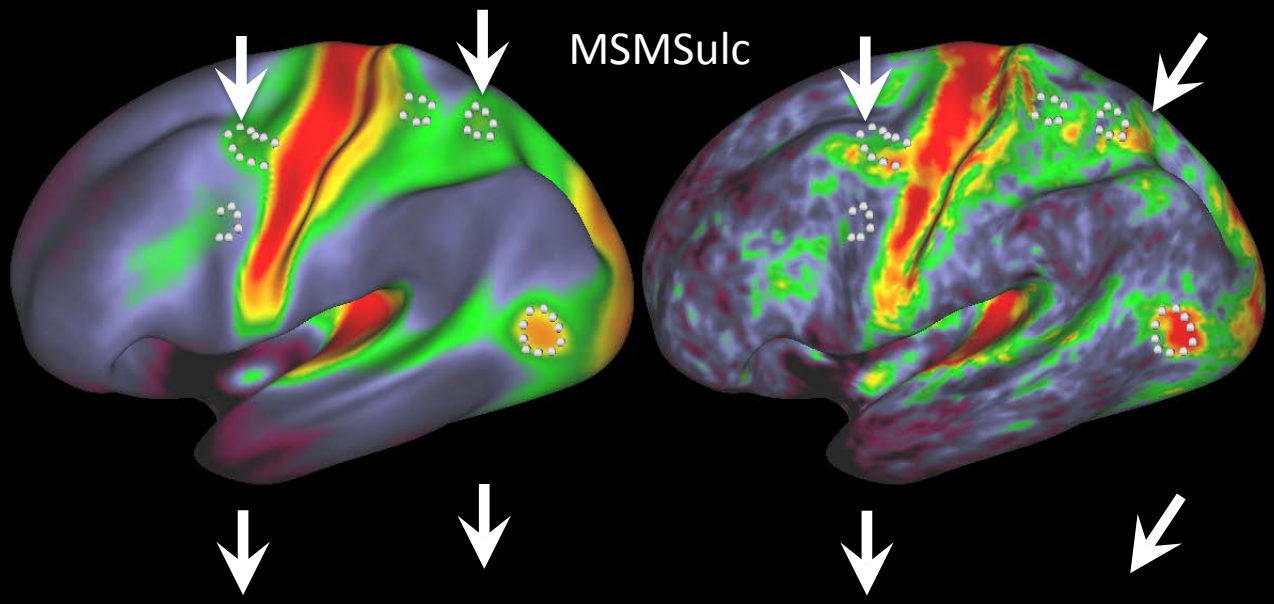


How Do We Do Better?

- Align subjects based on features more closely related to their cortical areas than folding is, e.g.
  - Myelin maps
  - Resting state functional connectivity
  - Topographic maps
  - Even the cortical area definitions themselves
- New surface registration algorithms like Multi-modal Surface Matching (MSM) (Robinson et al 2014) offer improved areal alignment with <u>cortical areal feature-based surface registration</u>
  - Of course MSM starts by registering cortical folds

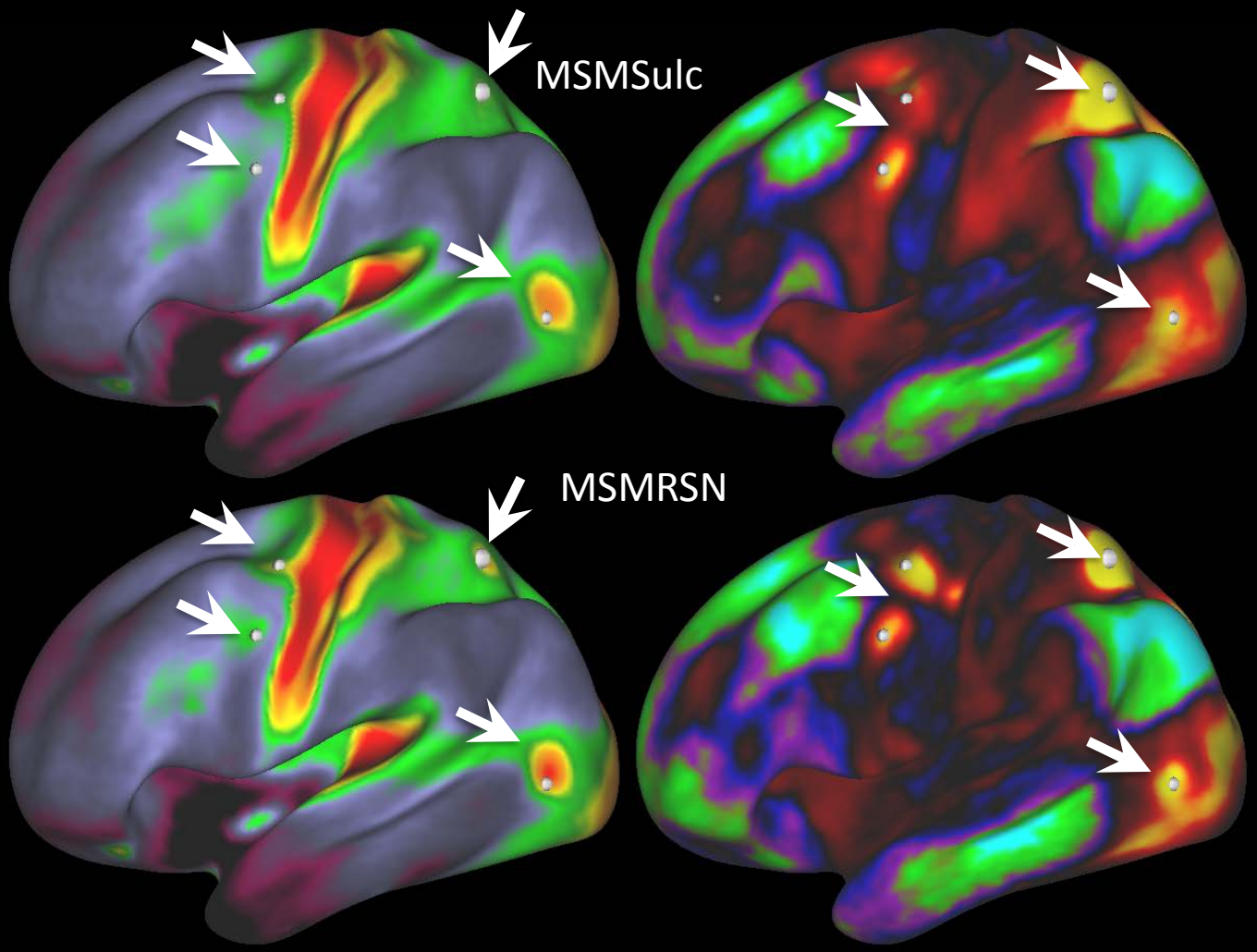
MSM with Myelin Maps

- 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

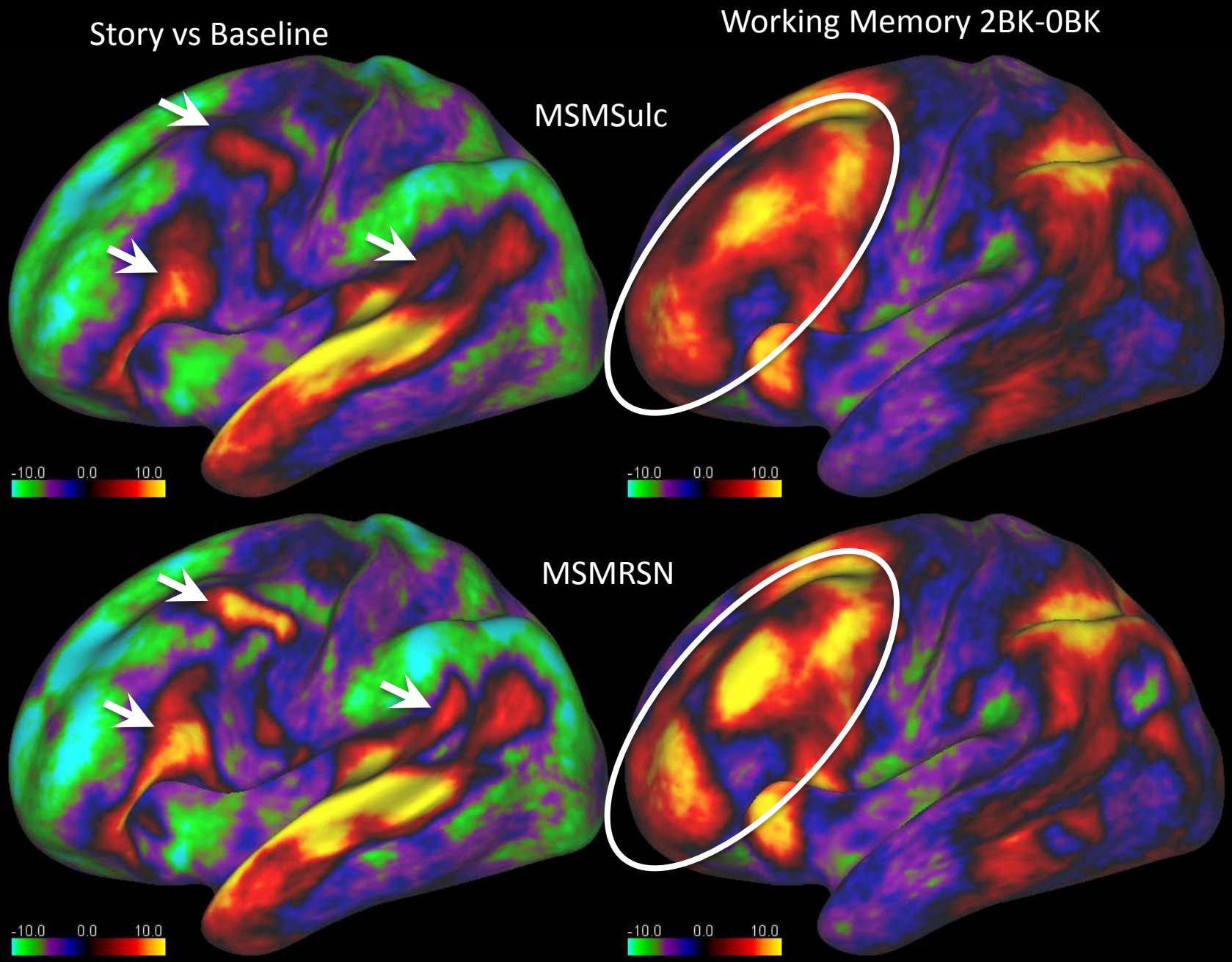


Resting State Networks Can Also Be Used with MSM for Cross-subject Registration

- 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

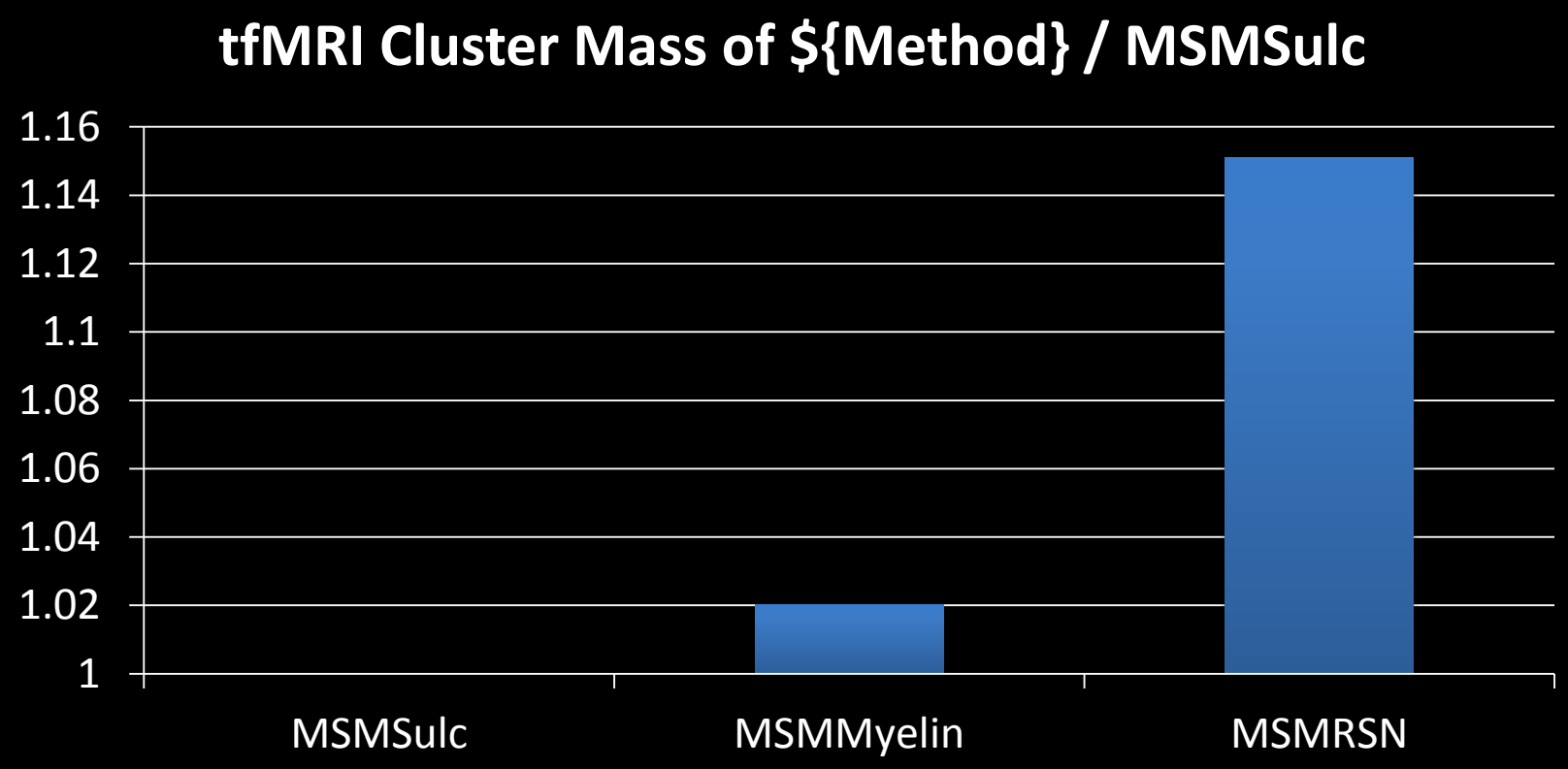


MSMRSN: Sharper Task fMRI Contrast Maps



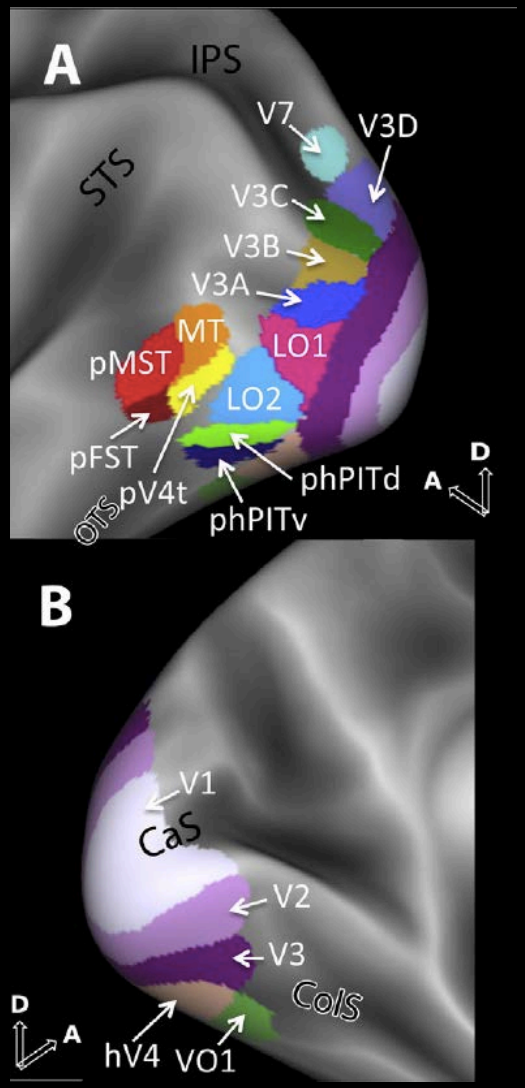
Quantitative Evaluation of MSM Registration

- MSM is really helpful for sharpening spatial patterns in group maps
- Also Really helpful for increasing cross-subject statistics

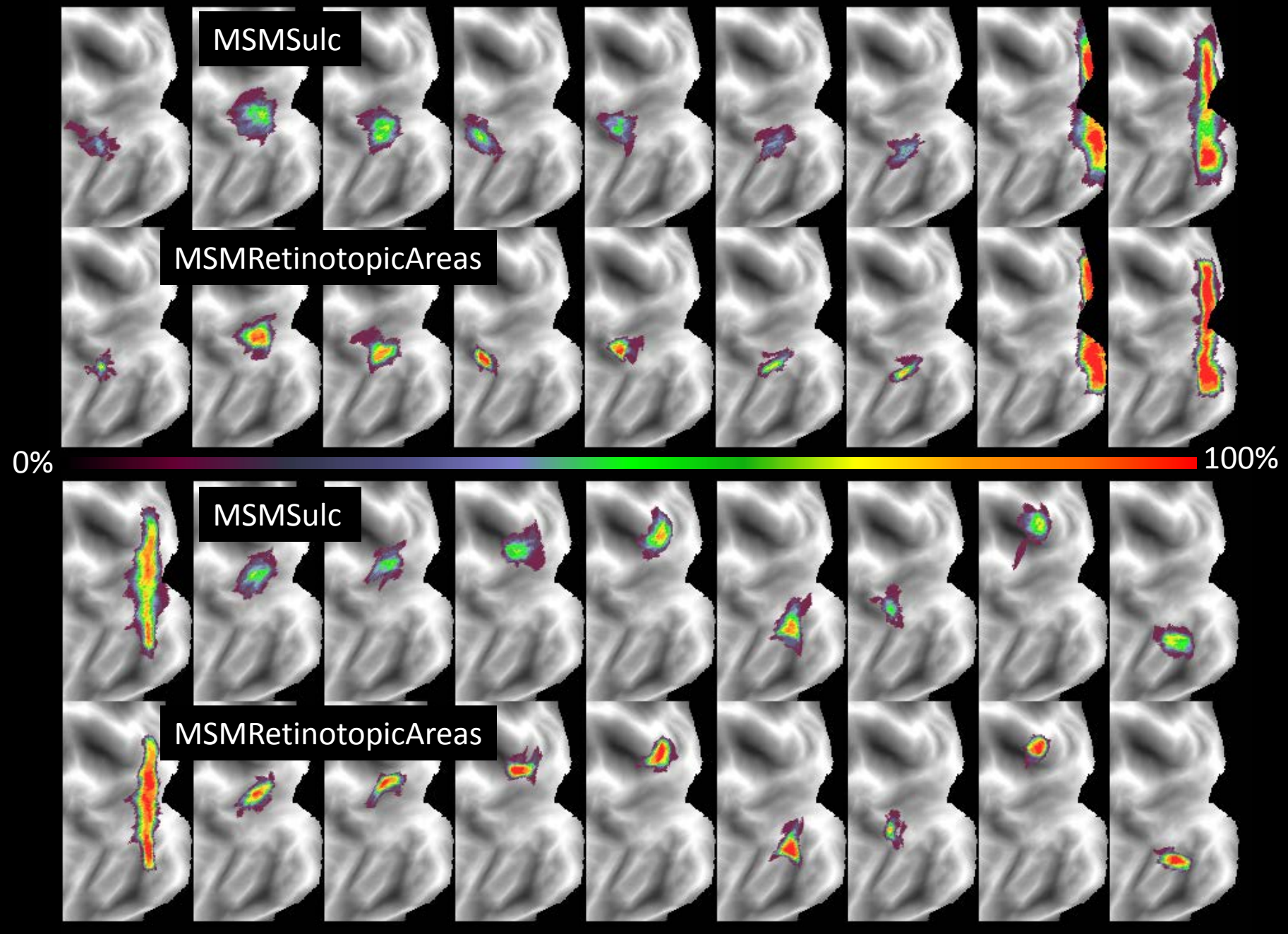


MSM Can Also Be Used to Register Binary ROIs of Cortical Areas

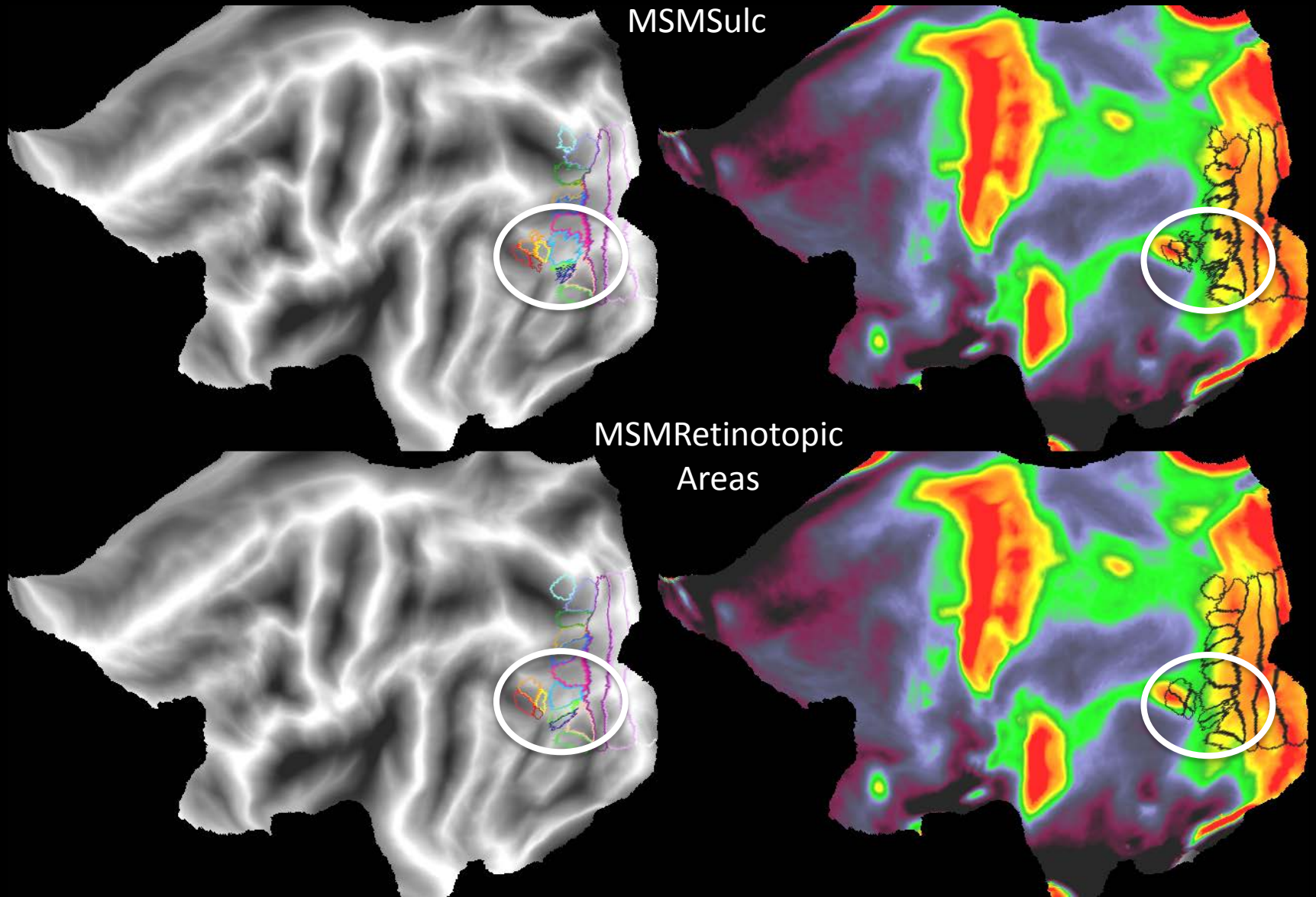
- 18 Area retinotopic fMRI parcellation of 12 individuals by Guy Orban's group (Abdollahi et al 2014).
- We compared the probabilistic maps and maximum probability map (MPM) across several registration techniques including MSMSulc (folding) and MSMRetinotopicAreas



MSMRetinotopicAreas: Areal Probability Maps



MSMRetinotopicAreas: Maximum Probability Maps



The Next HCP Data Release Will Output Grayordinate-wise Data Aligned with Areal-features

- Current data are aligned with folding-based registration (MSMSulc)
- Next release will provide data aligned with myelin + resting state networks + visual topography (MSMAll)
- Going forward, most cortical areas will be aligned across most subjects
- However, lecture 3 tomorrow will cover what to do when the topological organization of areas in a particular subject doesn’t match the group

Areal Feature-based Registration Summary

- Folding-based surface alignment alone is only good enough for some cortical areas where folding patterns are consistent
- Area-feature-based alignment offers substantial improvements in group map sharpness and group statistics
- MSM is a highly tunable algorithm that can register many kinds of cortical data (e.g. myelin maps, RSNs, and even binary ROIs)
- The next HCP data release will include cortical data registered with areal feature-based registration (MSMAll)
- Questions about surface registration?

Lecture Topics

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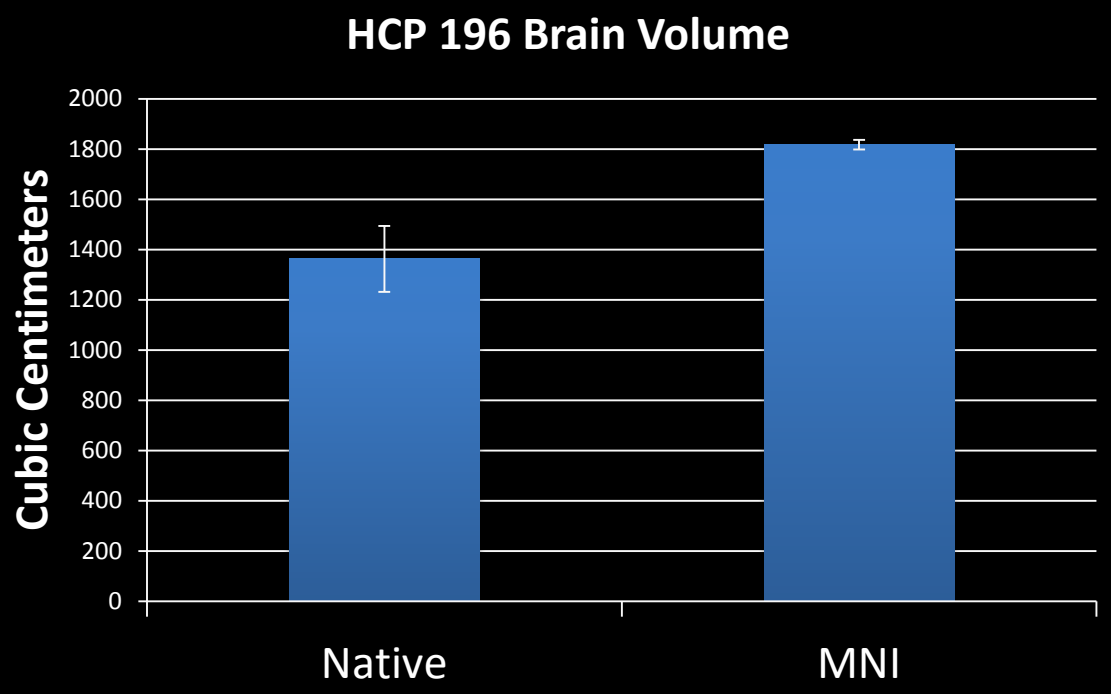
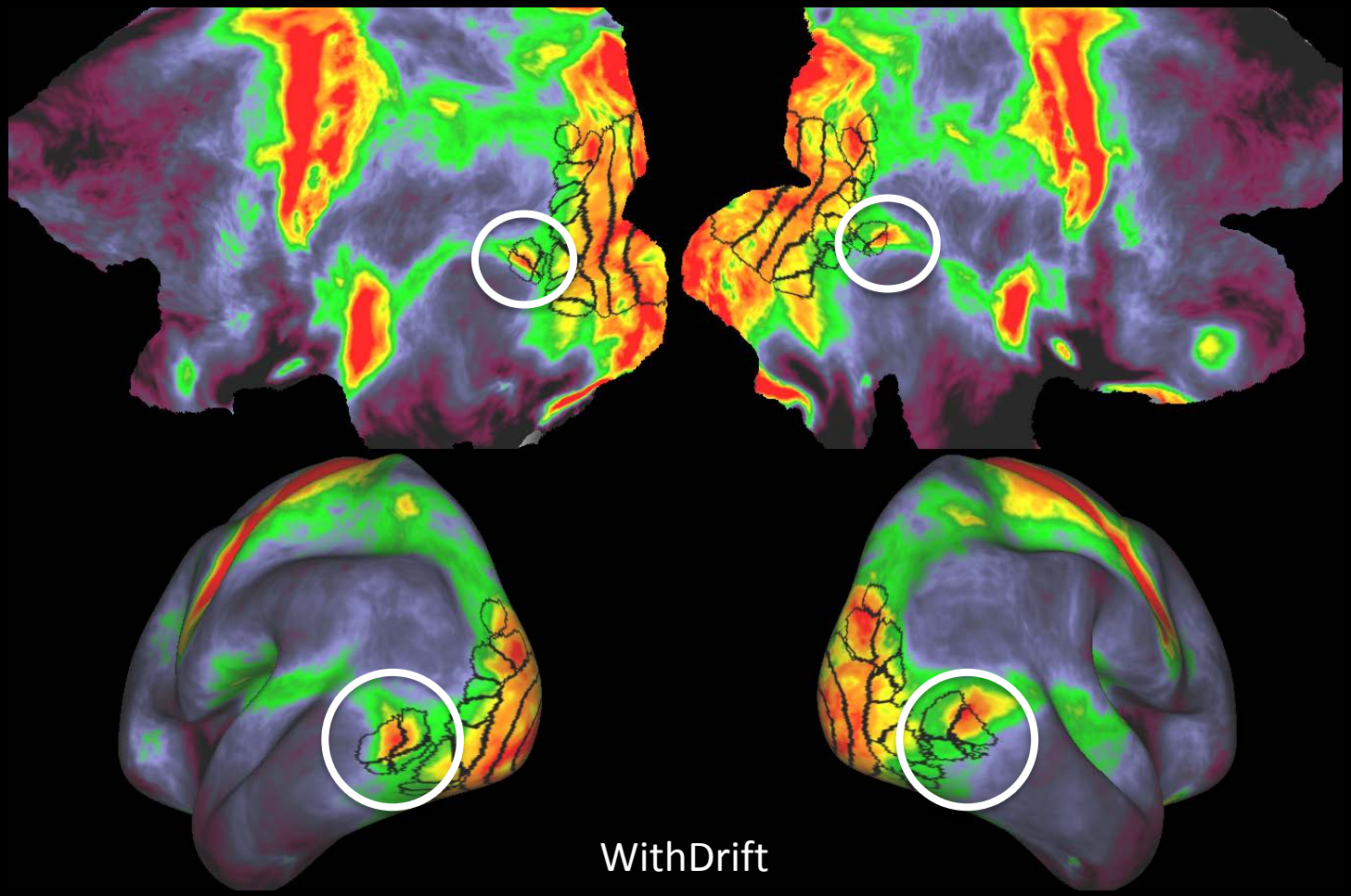
Group Registration Drift: Mismatch between the Group Average and the Typical Subject



- Example: volume-based alignment of an individual to the standard MNI volume space increases their brain volume an average of 37%
- Volume-based registration reduces individual variability in brain volume (what we want), but increases brain volume on average by 37% (we don't want this)
- When MNI space was created using iterations of registration and averaging, it "drifted" to a 37% larger brain size than the typical individual's brain volume
- This group registration drift is now "baked into" the standard MNI space (the current standard in the field of neuroimaging)
  - Let's not make that mistake again in grayordinates analyses, at least on the surface
- Remove drift by computing the group average registration and concatenating its inverse onto each subject's registration

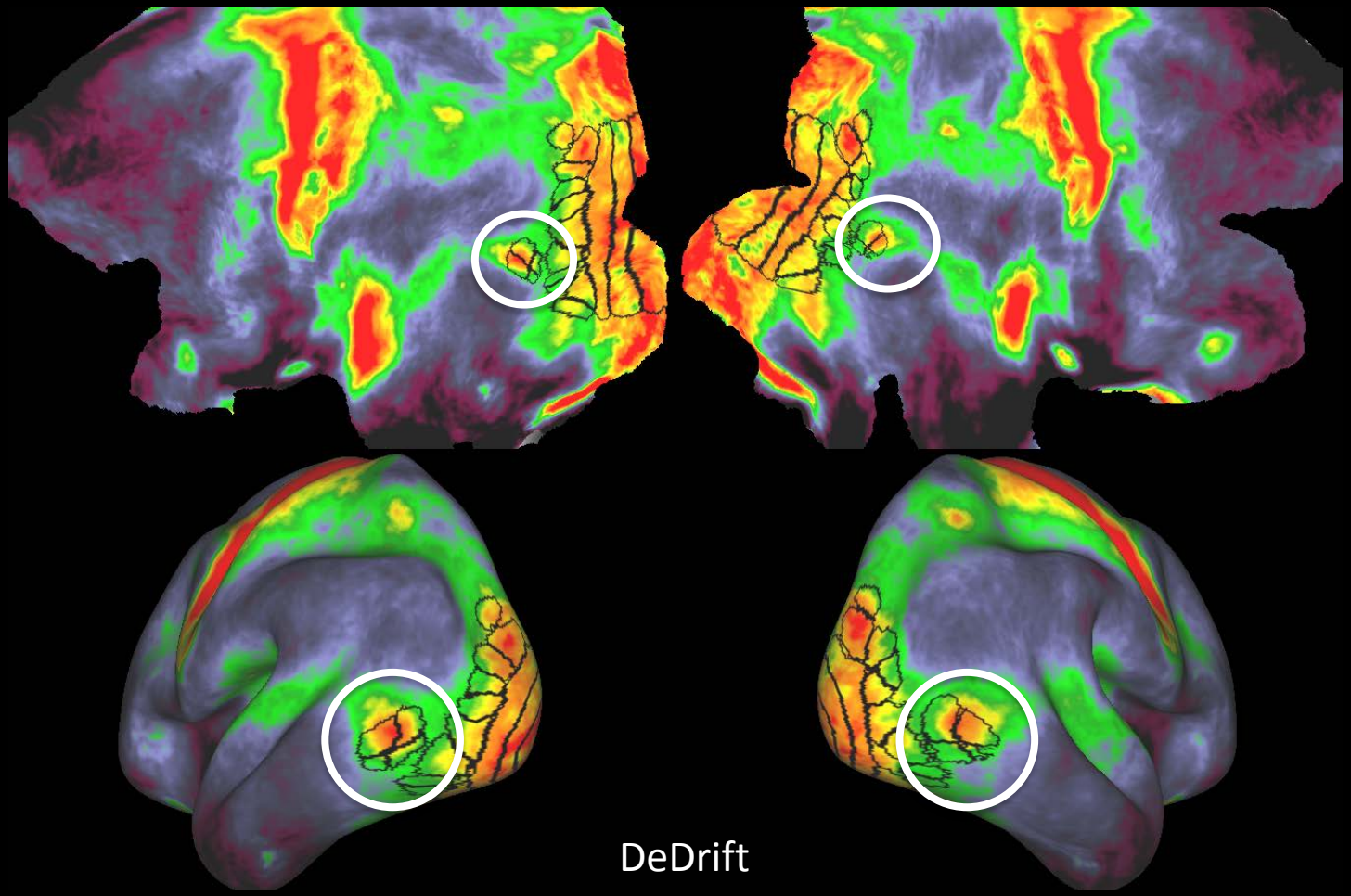
Effect of Removing Group Registration Drift on Comparison Between Two Separate Studies

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

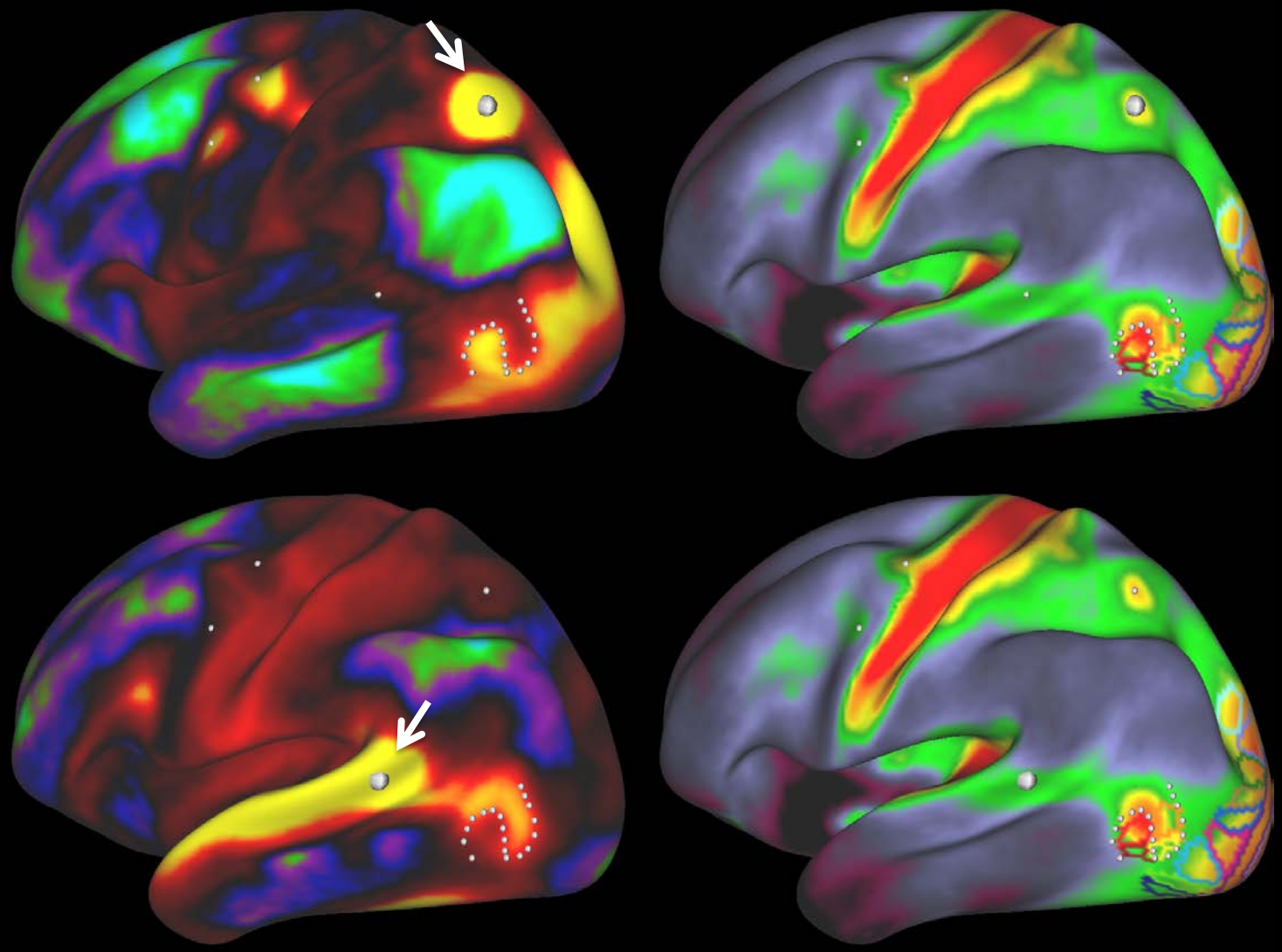


Effect of Removing Group Registration Drift on Comparison Between Two Separate Studies

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



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



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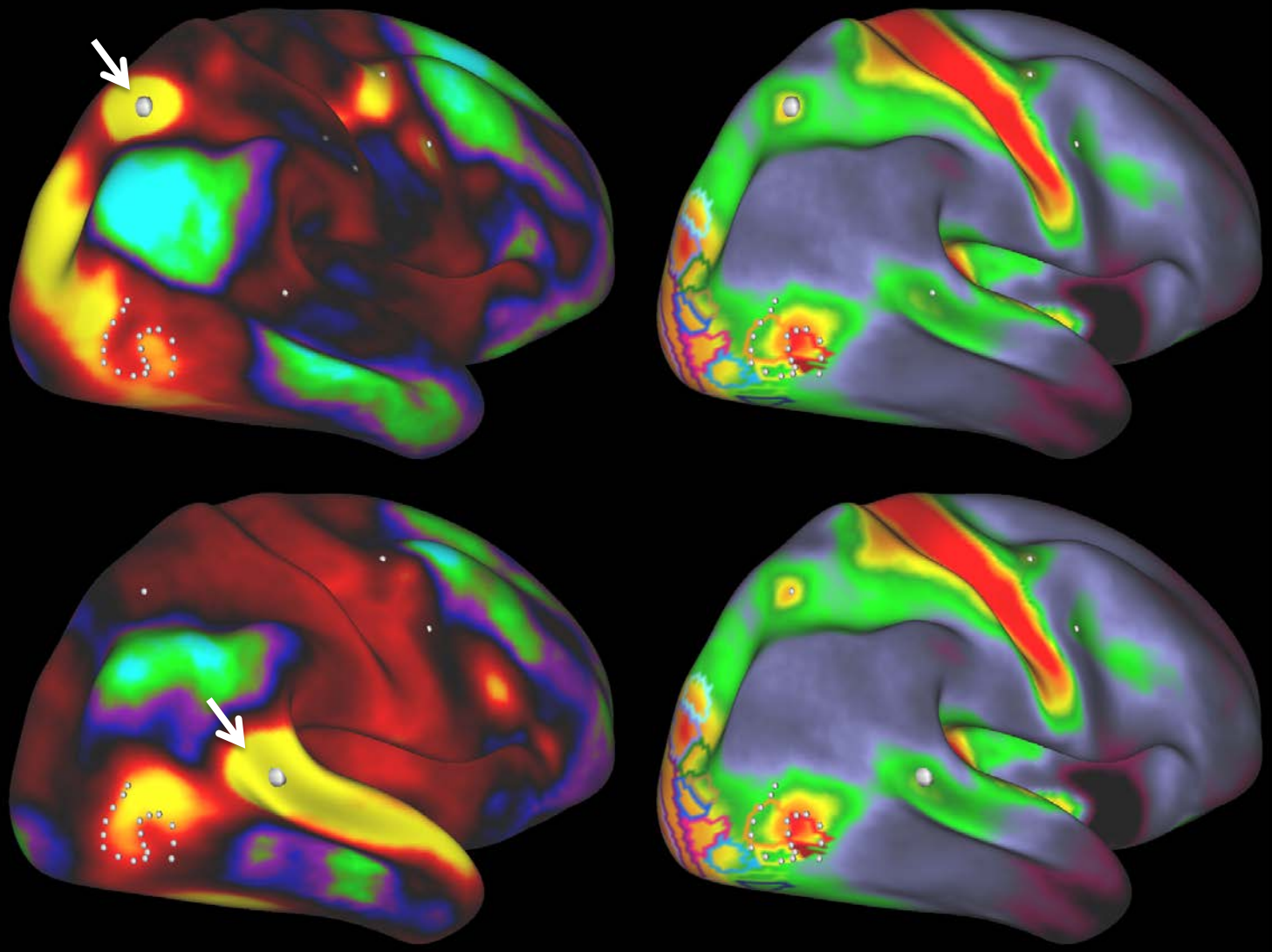


Group Average Registration Drift Summary

- Group average registration drift is when the group average dataset does not match the typical individual subject
  - Often arises from iterative template generation
  - The MNI template is an example
- Drift can be removed by computing the average registration effect and concatinating its inverse onto each subject's registration
  - This keeps the individual registration improvements
- Dedrifting enables precise cross-study comparisons using areal boundaries and overlap
  - If one provides the actual results instead of 3D coordinates
- Questions about dedrifting?

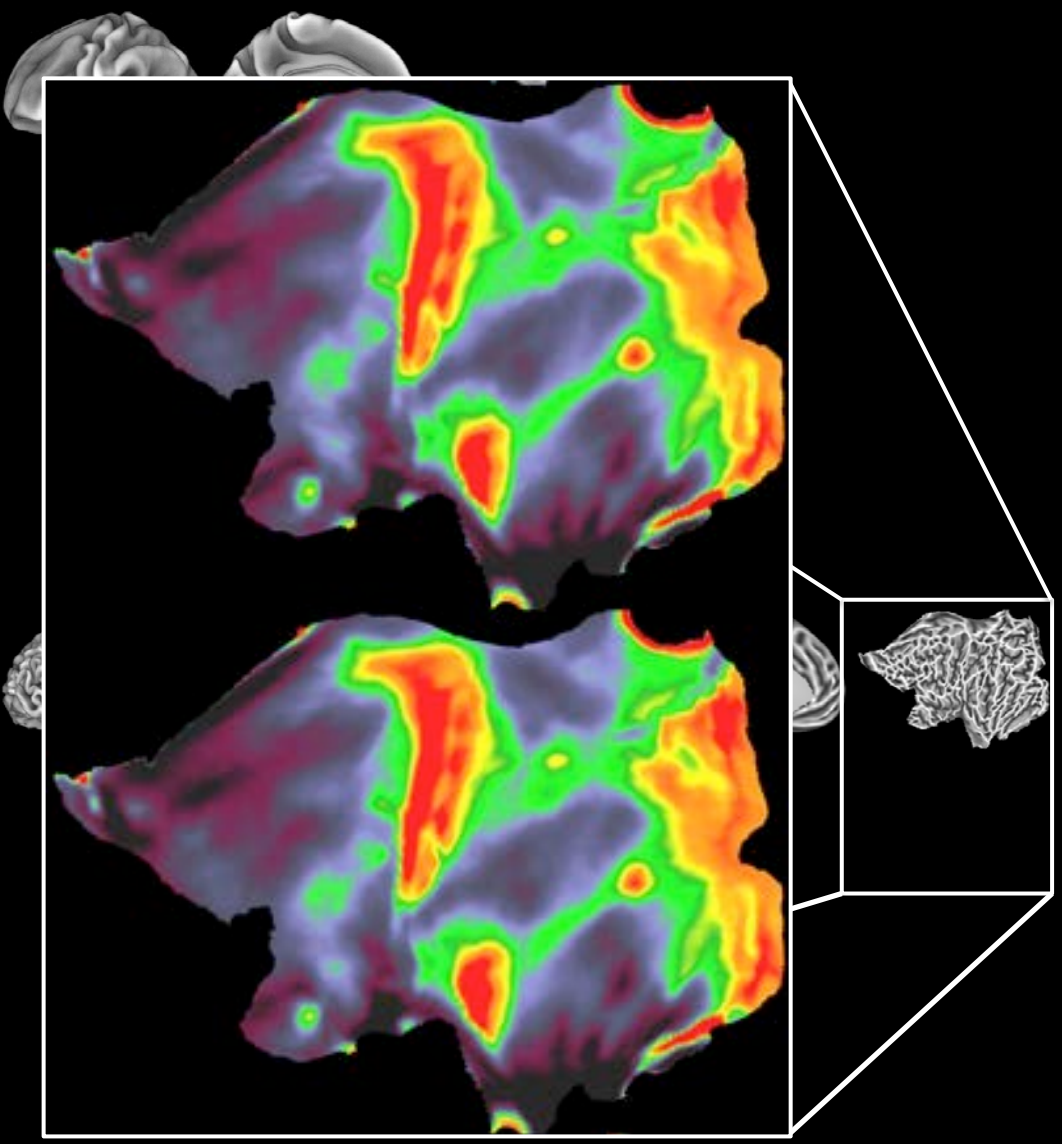
Lecture Topics

- Contrast neuroanatomical localization in the HCP's CIFTI grayordinates-based neuroimaging analysis paradigm vs traditional volume-based analysis
- The HCP's Minimal Preprocessing Pipelines: Getting from raw images to standard CIFTI grayordinates space
- Cross-subject surface registration based on cortical areal features vs folding patterns
- Removing group average registration drift to allow unbiased spatial comparisons across studies using areal overlap instead of 3D peak activation coordinates
- Reproducibility of HCP data after careful preprocessing

Reproducibility of HCP data after careful preprocessing: Study Design

- Two groups of 210 subjects (named 210P and 210V) that share no family members
  - We'll use these groups later for parcellation (P) and statistical validation (V)
- Compare three major categories of information:
  - Architectural (myelin map, thickness map, folding maps)
  - Functional (task fMRI contrast maps)
  - Connectivity (resting state network and dense connectome maps)
- For each measure we'll compute the Pearson correlation coefficient between the dense spatial maps of the two groups
- We'll use minimally smoothed or unsmoothed data processed with the HCP minimal preprocessing pipelines, registered with area feature-based registration, and dedrifted

Structural Reproducibility: Group Surfaces, Folding, and Architectural Measures

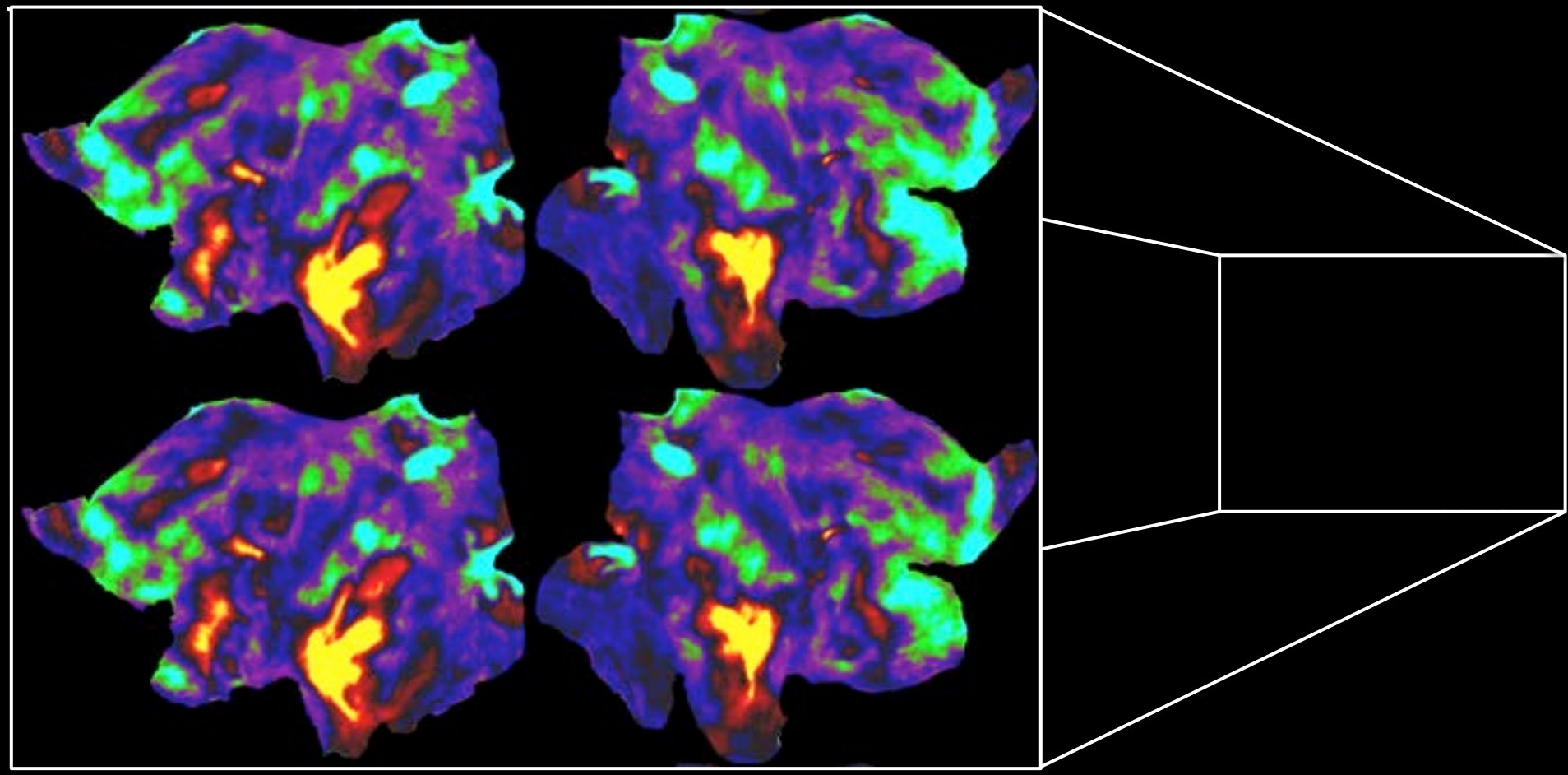


- 210P Group Surface + Folding
  - Left Midthickness
  - Left Inflated
  - Left Flat
- 210V Group Surface + Folding
- Folding Quantitative Comparison
  - Sulc Folding Map r=0.996
  - Curvature Folding Map r=0.979
- Notice how the folding patterns in many regions are blurry after MSMAll registration relative to an individual
  - Comes from poor correlation between folds and cortical areas (e.g. cognitive areas)
  - Remaining sharp folding patterns indicate regions where folds and areas are well correlated (e.g. early sensory areas)
- Architectural Quantitative Comparison
  - Myelin (r=0.998)
  - Thickness (r=0.994)
- Zooming in on the group myelin maps you can see how reproducible the fine spatial detail is

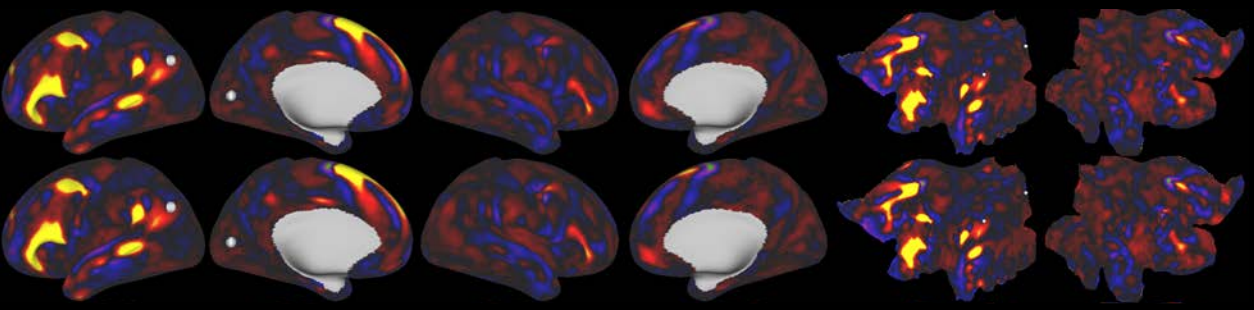
Functional Reproducibility: tfMRI

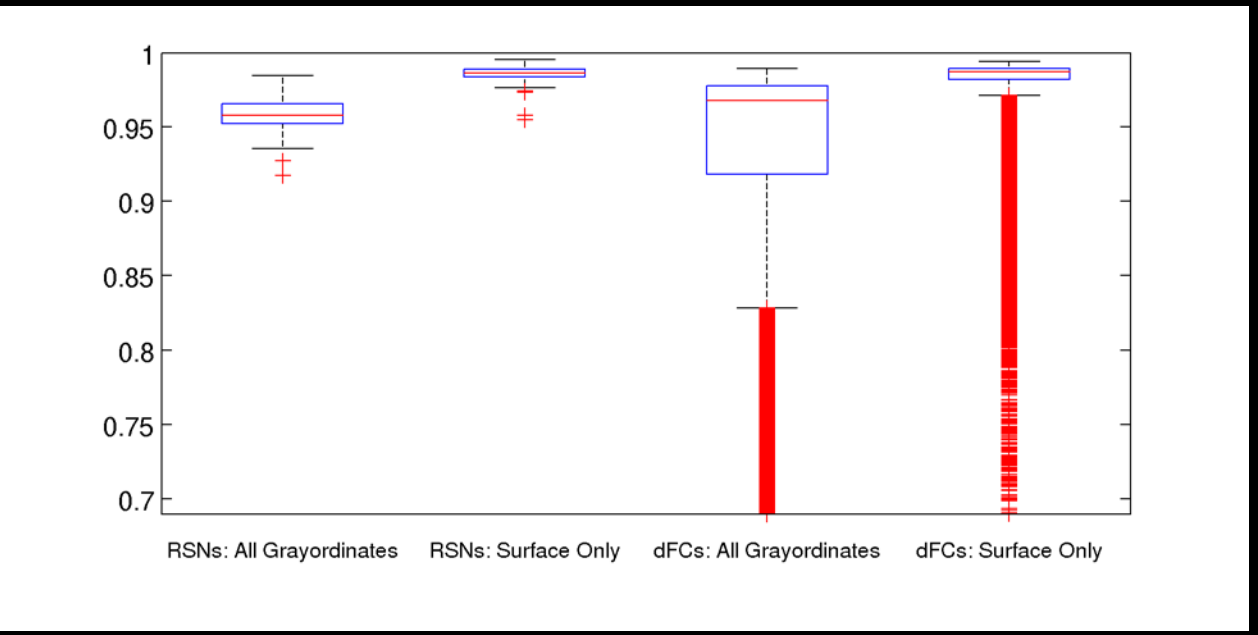
- Contrast Beta Maps Scaled from 0.75% to -0.75% BOLD from 210P for Left Inflated,

- And 210V, most Reproducible Contrast (Relational vs Baseline, r=0.995)
- Median Reproducible Contrast (Story vs Baseline, r=0.984)
- Least reproducible contrast (Tools category – Average categories, r=0.944), excluding outlier
- Overall reproducibility of all task contrasts for surface only and all grayordinates (little bit lower)
- Again, zooming in we can see how reproducible the fine spatial detail is



Connectivity Reproducibility: rfMRI





- Resting State Network (RSN) maps are highly reproducible (group ICA d=137, weighted regression in individuals, averaged across subjects)
  - Language Network
  - Its right hemisphere homologue
- Dense functional connectivity maps (dFCs) are also highly reproducible despite their low CNR
  - Task negative network (yellow) anti-correlated with task positive network (blue)
  - Globally positively correlated visual network
- Across all RSNs and most dFC seed grayordinates reproducibility is high
- Seeds in signal dropout regions are the outliers

Reproducibility of Carefully Processed Dense HCP Data Summary

- Despite minimal smoothing, the HCP data are highly reproducible across independent groups
  - This is true for structural, tfMRI, and rfMRI modalities
- Fine spatial detail remains group averages of these modalities
- This detail is removed from most regions of the folding data
  - Because we have aligned cortical areas instead of aligning folding patterns
  - Those regions where folds and areas have a consistent relationship continue to have sharp folding patterns
- Again, folding alone is not enough to align cortical areas in most brain regions
- Questions about reproducibility of HCP data?

One Last Slide

- Process your data carefully (surface for the cortex, volume for subcortical) using the HCP Pipelines and the CIFTI neuroimaging analysis paradigm
- Align subjects using areal features instead of cortical folds
- Remove group average registration drift to enable precise cross-study comparisons
- Provide the whole study results in standard grayordinates space, not just coordinates, so that overlap and areal boundaries can be compared across studies
- Limit spatial smoothing to avoid mixing across tissue types and brain areas and to preserve the available spatial detail
- Next lecture will be all about multi-modal brain parcellation
  - An application of the above preprocessing refinements to do interesting science
  - Any last questions?