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?

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
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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.
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

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

- 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)
MRI Techniques for Cortical Myelin Mapping for Localizing Cortical Areas

• These methods 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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- 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

\[
\frac{T1w}{T2w} \approx \frac{x \times b}{(1/x) \times b} = x^2
\]
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

- **n=196 Humans**
  - Vol = 1364cc ± 131cc

- **n=29 Chimpanzees**
  - Vol = 404cc ± 33cc

- **n=19 Macaques**
  - Vol = 92cc ± 7cc

Vol = 4% [4%] 96%
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

Story vs Baseline

Working Memory 2BK-0BK

MSMSulc

MSMRSN
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

![tfMRI Cluster Mass of ${Method} / MSMSulc](attachment:image.png)
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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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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Cross-study, Cross-modal Comparisons: Myelin and Resting State vs Retinotopy
Cross-study, Cross-modal Comparisons: Myelin and Resting State vs Retinotopy
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
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HUMAN Connectome Project

NIMH National Institute of Mental Health