Surface-based parcellation and vertex-wise analysis of ultra high-resolution *ex vivo* 7 tesla MRI in neurodegenerative diseases

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Abstract. Magnetic resonance imaging (MRI) is the standard modality to understand human brain structure and function in vivo (antemortem). Decades of research in human neuroimaging has led to the widespread development of methods and tools to provide automated volume-based segmentations and surface-based parcellations which help localize brain functions to specialized anatomical regions. Recently ex vivo (postmortem) imaging of the brain has opened-up avenues to study brain structure at sub-millimeter ultra high-resolution revealing details not possible to observe with in vivo MRI. Unfortunately, there has been limited methodological development in ex vivo MRI primarily due to lack of datasets and limited centers with such imaging resources. Therefore, in this work, we present one-of-its-kind dataset of 82 ex vivo T2w wholebrain hemispheres MRI at 0.3 mm³ resolution spanning Alzheimer's disease and related dementias. We adapted and developed a fast and easy-to-use automated surface-based pipeline to parcellate, for the first time, ultra high-resolution ex vivo brain tissue at the native subjectspace resolution using the Desikan-Killiany-Tourville (DKT) brain atlas. This allows us to perform vertex-wise analysis in the template space and thereby link morphometry measures with pathology measurements derived from histology. We will open-source our dataset, docker container, Jupyter notebooks for ready-to-use out-of-the-box set of tools and command line options to advance ex vivo MRI clinical brain imaging research on the **project webpage**.

Keywords: exvivo MRI · 7 tesla · surface parcellation · segmentation

1 Introduction

Alzheimer's disease and related dementias (ADRD) are heterogeneous, with multiple neuropathological processes jointly contributing to neurodegeneration

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[34]. Currently, co-pathologies are not reliably detected with in vivo imaging, which makes it difficult for clinicians to accurately diagnose the cause of cognitive impairment in individual patients and to identify those most likely to benefit from treatment with emergent drugs that target AD pathology. The efficacy of in vivo biomarkers can be enhanced by combined analysis of regional measures of neurodegeneration, such as cortical thickness, derived from brain MRI (ex vivo or in vivo) and pathological measures obtained at autopsy. Such analysis can help identify distinct spatial patterns of disease progression linked to AD-specific pathologies (i.e. β -amyloid plaques and phosphorylated tau protein tangles) and common co-pathologies. While such studies are performed using either *in vivo* or *ex vivo* MRI, the latter offers advantages in temporal proximity to pathological markers and in spatial resolution. The ability to scan ex vivo brain tissue for many hours without motion artifacts makes it possible to achieve ultrahigh spatial resolution at which intricate neuroanatomical details of the brain can be revealed [[6], [20], [2], [1], [37], [32], [36], and [10]]. However, lack of automated tools for processing ultra high-resolution ex vivo MRI is a significant barrier to study structure-pathology association in ADRD.

Decades of neuroimaging research has yielded advanced computational frameworks for automated analysis of *in vivo* brain MRI, and tools such as FreeSurfer [13] and Statistical Parametric Mapping (SPM) [5], FSL [29] have been applied in a plethora of ADRD neuroimaging studies. However, these tools cannot be directly used on ultra-high resolution *ex vivo* MRI and there is very limited work on developing *ex vivo* MRI analysis methods for widespread use, which remains a challenge primarily due to the greater heterogeneity in scanning protocols of *ex vivo* MRI and increased complexity and imaging artifacts than *in vivo* MRI. Recent developments for *ex vivo* MRI include deep learning methods for high resolution cytoarchitectonic mapping in 2D histology [3], atlas-based segmentation of MTL and the thalamus [20], [21], and whole-brain hemispheres analysis [28], [27]. Recently, deep learning-based methods were developed to segment the granular cortical layers [25], and gray matter (GM), subcortical structures, white matter (WM) and its hyperintensities (WMH) in 7T *ex vivo* MRI. NextBrain [8] provides semi-automatic brain segmentations using histology brain atlas.

These previous methods have several limitations as they are specialized for specific parts of the brain or specific *ex vivo* datasets mainly limited to a healthy (unremarkable) brain tissue specimens. The methods were evaluated on very small datasets of only 1 [12], 5 [8], and 17 [25] *ex vivo* brain tissue for unremarkable specimens or at low-resolution [28]. Crucially, to our knowledge, the feasibility of using existing *ex vivo* MRI analysis pipelines to perform large-scale structure-pathology association studies in ultra-high resolution *ex vivo* MRI has not been demonstrated.

Contributions. In this study, we perform structure-pathology association analysis in a large dataset of ultra high-resolution 0.3 mm^3 T2w 7T MRI scans of whole brain hemispheres from 82 brain donors with ADRD diagnoses, a first study of such scale conducted at this resolution. We present a new computational pipeline that performs automated segmentation and **whole-hemisphere**

FreeSurfer DKT atlas [11] parcellation of the cortex in native subject space at sub-millimeter 0.3 mm³ resolution, a first large-scale surface-based scheme for *ex vivo* whole-hemispheres analysis in diseased population. We achieve this by adapting the surface-based pipeline in FreeSurfer with an initial subject-space topology-corrected WM segmentation derived from a deep learning-based segmentation model as developed in [24]. We evaluate the framework by correlating cortical thickness with neuropathological markers implicated in AD (regional measures of p-tau, neuronal loss; global amyloid- β , Braak staging, and CERAD ratings) and perform vertex-wise generalized linear modeling.

2 Materials and Methods

Dataset. We acquire and analyze a dataset of **82 ex vivo whole hemisphere 0.3 mm³ 7T MRI** (See Fig. 1) at our XYZ center with left: 42 and right: 40 hemispheres, postmortem interval (PMI) of 18.48 ± 13.60 hours and fixation time of 256.70 ± 280.48 days. The cohort included patients with Alzheimer's Disease or related dementias (ADRD) [26] spectrum, such as Lewy body disease, limbic-predominant age-related TDP-43 encephalopathy, corticobasal degeneration, primary age-related tauopathy comprising of 41 female (age: 76.97 ± 9.70 years) and 41 male (age: 76.48 ± 11.67 years). Human brain specimens were obtained in accordance with local laws and regulations, and includes informed consent from next of kin at time of death. After autopsy, one hemisphere (Supp Fig. A.1) was fixed in formalin for atleast 4 weeks and then imaged at T2-w 7T using a 3D-encoded T2 SPACE sequence with 0.3 mm³ isotropic resolution, 3s repetition time (TR), echo time (TE) 383 ms, turbo factor 188, echo train duration 951 ms, bandwidth 348 Hz/px with 2-3 hours per scan.

The non-imaged hemisphere, i.e., contralateral tissue, underwent histological processing for neuropathological examination (Supp Fig. A.2). Tissue blocks were embedded in paraffin, sectioned at 6 μ m thickness, and underwent immunohistochemistry. In each region, semi-quantitative severity ratings of p-tau pathology, amyloid- β , and neuronal loss, were assigned by expert neuropathologists on a scale of 0–3 i.e. '0: None/Rare', '1: Mild', '2: Moderate' or '3: Severe'. Standardized global ratings of AD progression were also derived, including Thal stage (global amyloid- β), Braak stage (global p-tau), and CERAD stage (neuritic plaques) [4].

Methodological pipeline. We present a fast and reliable whole-hemisphere anatomical parcellation and cortical thickness quantification framework that combines deep learning-based methods developed in [24] with classical methods for topology correction [33] and surface-based cortical modeling, inflation, registration, and parcellation in FreeSurfer [[13], [14]]. Our framework processes one hemisphere in around 60 minutes. Rather than reinventing the wheel, our approach focuses on combining the strengths of these existing tools and making modifications that enable them to scale to ultra-high resolution *ex vivo* MRI.

Volume-based segmentation: First, we train a deep learning segmentation model nnU-Net [23] as explained in [24] to obtain whole-hemisphere volumebased segmentations of 8 regions namely: cortical gray matter (GM), white matter (WM), white matter hyperintensities (WMH), ventricles and four subcortical structures: caudate, putamen, globus pallidus and thalamus. The model was trained on Nvidia Quadro RTX 5000 GPU using manual-labeled images and extensively validated, as detailed in the work by Khandelwal et al. [24]. The inference time for each hemisphere is around 15 minutes on a CPU. We merge the WM, WMH, ventricles and subcortical labels in a single label and employ the post-hoc topology correction method [[16] and [7]] based on fast-marching algorithm implemented in 'Nighres/CRUISE' [18] to solve the *buried sulcus* problem, i.e., clearly separating the adjoining gyri in the opposite banks of a buried sulcus. This correction step takes around 5 minutes on a conventional Intel CPU.

Surface-based parcellation: Next, we modify the surface-based scheme in FreeSurfer to obtain DKT atlas-based surface parcellations in *ex vivo* native subject space. Of note is that this step does not require the raw MRI intensity image and is purely based on the voxel-level segmentation of cortical GM from above. First, a 'filled' segmentation (Supp Fig. A.3) with WM, WMH, ventricles and the four subcortical structures as the foreground; and the cortical GM along with the CSF as the background, is created from the initial volume-based segmentation. This 'filled' segmentation is then tessellated and corrected for any topological errors such as holes and handles based on [33], termed as the 'WM surface'. The 'WM surface' is smoothed and inflated to a sphere which is then registered to the spherical representation of the Buckner40 spherical atlas [22] provided in FreeSurfer using the curvature map of the WM surface. The labels of the DKT-atlas is then warped from the spherical-atlas to the spherical-representation of the ex vivo subject.

Next, the 'WM surface' is deformed and re-positioned to find the GM-CSF pial surface using the method described in [13] [14] which employs three energy functionals: spring-like term, decomposed into tangential and normal components, to smooth and for regularization of the surface. The third term in the energy functional is dependent on the gradient of the intensity image. This term is the classic stopping criteria (inverse of the image gradient) used in deformable models based on level sets and fast marching methods. FreeSurfer uses raw in vivo T1w (or where applicable T2w) MRI intensity values for this energy term. For the current study, the T2w ex vivo MRI has a varying intensity profile within the GM which causes the deformable surface to prematurely stop in the GM cortical ribbon and does not reach the pial surface. Therefore, we use the segmentation derived from the above volume-based step (Supp Fig. A.3) in place of the T2w ex vivo MRI intensity image. This has a clear advantage as the intensity is constant in the GM cortical ribbon with a zero gradient everywhere. The evolving surface then stops at the pial surface as expected. Finally, the DKT-atlas labels are projected onto the pial surface and the parcellations are mapped to the voxel-space to get the region-wise segmentation in the volume. This surface-based scheme takes around 40 minutes on a CPU with 64 threads.

3 Experiments and Results

Segmentation and parcellation. We deployed the deep-learning model to produce the initial segmentation of GM, WM, WMH, ventricles and the sub-



Fig. 1. Ex vivo MRI and parcellations. Sagittal, axial and coronal viewing planes of ex vivo MRI at 0.3mm³ resolution for two subjects (A and B) with corresponding DKT volumetric segmentations and surface-based parcellations on pial and inflated surfaces for the medial and lateral views in subject space resolution. Our method is able to correctly delineate the brain even in regions where the MR signal contrast is low in the anterior and the posterior brain MRI due to artifacts in acquisition protocol. Bottom row: the segmentations and parcellations on the corresponding 3T in vivo MRI of subject B which shows that the developed pipeline correctly map the labels to similar brain locations in ex vivo MRI. Legend: See Fig. 2 for the brain region labels.

cortical structures. Note that validation of this deep learning-based pipeline was done extensively in a previous work [24] as explained in Sec. 2 and is out of scope of the current paper. The surface-based scheme was then used to jointly obtain the cortical parcellations and volumetric segmentations as shown in Fig. 1 in the native subject space. Due to the immense manual labelling efforts involved in *ex vivo* MRI, in the order of 3-4 weeks per subject, the reliability of these parcellations are evaluated using the following two correlation studies.

Region-based cortical thickness vs neuropathology correlations. Fig. 2 shows the Spearman's ρ -value between the mean cortical thickness (mm) in each brain region (computed in subject space at native resolution) and five pathology measures: global ratings of amyloid- β , Braak staging, CERAD, and regional ratings of p-tau pathology and neuronal loss in the MTL, the region first



Fig. 2. Spearman's correlation plots between mean ROI thickness (mm) and neuropathological ratings in native subject-space. We observe significant negative correlation with global ratings of amyloid- β , Braak staging, CERAD, and the semi-quantitative ratings of the medial temporal lobe (MTL) tau pathology and neuronal loss. All the analysis were covaried for age, sex and postmortem interval (PMI) for the entire cohort of 82 subjects. See legend for the regional brain labels.

implicated in AD. The analysis were covaried for age, sex and postmortem interval (PMI) and corrected for multiple comparisons using Bonferroni method. Significant negative correlation were found in entorhinal, parahippocampal, medialorbitofrontal, temporal pole, inferior temporal and parietal lobes which are consistent with literature on progressive loss of cortical gray matter in AD [35].

Surface-based vertex-wise cortical thickness vs neuropathology correlations. The thickness maps for each individual subject were warped to the Buckner40 template-space for vertex-wise correlation analysis between cortical thickness (mm) and the five neuropathological ratings. The parcellations and thickness maps of two subjects in the Buckner40 *fsaverage* space are shown in Fig. 3. Vertex-wise correlation between thickness and the neuropathology ratings was performed by fitting a GLM at each vertex across the entire cohort of 82 subjects with age, sex and PMI as the covariates and corrected for multiple comparisons using family-wise error rate (FWER) correction. Fig. 4 shows the t-statistics map on the pial and the inflated surfaces with the clusters outlined in white indicating regions where the significant strongest associations were observed (p<0.05) surviving FDR correction. We observe that the strongest correlations were observed in MTL, the region associated with AD.

4 Discussion

Using both recent advances in deep learning based segmentation models and classic deformable and spherical registration methods, we developed a pipeline that enables surface-based modeling and group-wise registration of the corti-



Fig. 3. Desikan-Killiany-Tourville (DKT) surface-based parcellations and thickness maps shown for two subjects (A and B) in Fig. 1 in FreeSurfer Buckner40 [22] template space on pial and inflated surfaces for the medial and the lateral views. Note there is no segmentation in the regions with missing MRI signal (Fig. 1 and that is correctly reflected in the missing parcellation in the anterior surface for subject B. The thickness maps (smoothed with a 5mm FWHM Gaussian kernel) is used for the vertex-wise GLM analysis.

cal gray matter in ultra high-resolution ex vivo MRI. In addition to its higher resolution, ex vivo MRI poses multiple challenges for computational analysis, including deformation during brain removal and fixation (particularly collapse of the ventricles), and distinct artifacts, such as intensity inhomogeneity both across the whole image domain and across cortical layers. Hence our ability to successfully combine nnU-Net, Nighres/CRUISE and FreeSurfer pipelines to achieve the same type of parcellation as is ubiquitous in *in vivo* MRI studies is a non-trivial accomplishment. Crucially, the Nighres/CRUISE and FreeSurfer components used in our pipeline operate only on segmentation maps, rather than MRI intensity. Thus, to generalize our approach to other scanners and ultra-high resolution MRI protocols, one only needs to focus on the segmentation aspect. There are imperfections in our existing segmentation that propagate to the hemisphere parcellations. We observe that there is missing cortical GM segmentation in the anterior and posterior regions due to lack of MRI intensity contrast, an imaging artifact introduced due to a limitation of our magnetic coil. On the inflated white matter surface (Fig. 3), we can observe the missing portion of the frontal-brain areas for subject B.

A key contribution of this work is that it performs, for the first time, a surface-based structure-pathology correlation analysis using ultra-high resolution *ex vivo* MRI in a large cohort of brain donors with ADRD diagnoses. By



Fig. 4. Template-space vertex-wise morphometry-pathology correlations. Vertex-wise group analysis was performed to fit a generalized linear model (GLM). Shown are the statistical map (t-statistics) of the correlation between cortical thickness (mm) and with global ratings of amyloid- β , Braak staging, CERAD, and semiquantitative ratings of the medial temporal lobe (MTL) tau pathology and neuronal loss, the with age, sex and postmortem interval (PMI) as covariates across all 82 subjects. The clusters outlined in white indicate regions significant correlations (p<0.05) were observed after FWER correction for multiple comparisons.

doing so, it demonstrates the analysis approach that is ubiquitous in *in vivo* brain MRI research, and has been previously adopted to 1mm^3 resolution exvivo MRI by some groups [28] and [27], can also be applied to ex vivo studies at ultra-high resolution. To demonstrate analysis modes common in *in vivo* research, we performed both region of interest (ROI)-level correlation analysis and vertex-wise template-space analysis to study patterns of neurodegeneration within the AD continuum. Prior works [[31], [15]] shows how amyloid- β and p-tau etc have differential influences on cortical atrophy. Tau pathology is concurrent with neuronal loss in AD leading to cortical atrophy [17]. Negative correlations between MTL p-tau and neuronal loss with cortical thickness were found to be significant in the entorhinal cortex and the MTL, regions first implicated in AD [9], [30]] both in *in vivo* and *ex vivo* studies. Crucially, the ability to map data from subject space to the DKT-template space based on surface correspondence is not limited to cortical thickness measures, and in future, our pipeline can be used to analyze features that take advantage of ultra-high resolution ex vivo MRI, such as mapping iron and myelin in cortex [36].

Conclusion. We developed a fast and easy-to-use pipeline to parcellate the whole-brain hemispheres into the FreeSurfer DKT-atlas defined regions at the native subject space sub-millimeter 0.3 mm^3 isotropic resolution, and applied it to a large-scale dataset of ultra high-resolution $ex \ vivo$ 7T structural MRI. We demonstrated the feasibility and utility of this approach by performing a structure-pathology association study that is the first of its kind at this level of $ex \ vivo$ MRI resolution and one of the largest ever conducted at any $ex \ vivo$ MRI resolution. In future, we will perform an exhaustive study by delineating the brain regions with different anatomical atlases based on a surface-based

population template derived from the *ex vivo* hemispheres. This will enable us to understand the region-wise local intensity profiles to study the structural relationships with the underlying histology-derived markers. We believe that the present study will enable scientific advancements in *ex vivo* imaging and thereby inform better *in vivo* computational biomarkers.

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A Supplementary Figures



Fig. A.1. Postmortem tissue blockface photograph of a donor.



Fig. A.2. Pathological assessment for each regional pathology derived from histology. The columns are severity ratings (left to right): 0-3. The shown pathologies are: amyloid- β plaques (NAB228 antibody), p-tau pathology (PHF-1 antibody), and neuron loss (Hematoxylin and Eosin staining).



Fig. A.3. Some key components in the computational pipeline. Shown is the MRI (A) and the corresponding *filled* segmentation (B) which includes everything except the cortical gray matter (GM). This *filled* segmentation is then tessellated (D) which is the starting point for the parcellation scheme. An important remark is that instead of the MRI intensity values typically used the intensity-term in the surface-evolution step in FreeSurfer. Instead, we use the segmentation (C) as the *'intensity image'*.



Fig. A.3. Continued. Some key components in the computational pipeline. The main advantage is that the surface does not stop incorrectly in the GM due to varying granularity and sudden intensity changes in GM layers. But instead the surface correctly evolves from the WM-GM surface to the GM-CSF boundary as there is the gradient is zero everywhere in the GM segmentation and the surface-evolution term is satisfied at the boundary where there is sudden change in the gradient. The segmentation image consists of the four subcortical structures (caudate, putamen, globus pallidus, and thalamus), white matter hyperintensities (WMH), and the normal appearing white matter (WM), ventricles and the cerebrospinal fluid (CSF).



