Tissue Segmentation and Regional Parcellation Methods for Scan

Charles DeCarli, MD, Evan Fletcher, PhD, Pauline Maillard, PhD
Department of Neurology and Center for Neuroscience, University of California at Davis
Version 1 03/07/2023

Contents

Summary

Alzheimer's disease research has entered the era of "big data". While single-laboratory research remains a mainstay of mechanistic discovery research, large data sets are increasingly necessary in clinical and translational settings. Such datasets currently exist in the fields of genetics, epidemiology, clinical trial registries, and, to a lesser extent, imaging. Brain imaging now plays a central role in aging and dementia research. It is easy to see how a standardized database of MRI and PET images collected across the ADCs would become a major research resource. This database – openly shared amongst dementia researchers – will impressively broaden the scope of research. The methods described here were developed to address the common needs for summary variables of regional brain volumes and quantification of the extent of white matter hyperintensities.

Method

Brain volumes, cortical thickness, and surface area: UCD analyses performs standard processing of all MR images using FreeSurfer versions compatible with ADNI. FreeSurfer is a set of software tools for the study of cortical and subcortical anatomy. In the cortical surface stream, the tools construct models of the boundary between white matter and cortical gray matter as well as the pial surface. Once these surfaces are known, an array of anatomical measures becomes possible, including cortical thickness, surface area, curvature, and surface normal at each point on the cortex. The surfaces can be inflated and/or flattened for improved visualization. In addition, a cortical surface-based atlas has been defined based on average folding patterns mapped to a sphere. Surfaces from individuals can be aligned with this atlas with a high-dimensional nonlinear registration algorithm. The registration is based on aligning the cortical folding patterns and so directly aligns the anatomy instead of image intensities. The spherical atlas naturally forms a coordinate system in which point-to-point correspondence between subjects can be achieved. This coordinate system can then be used to create group maps (similar to how MNI space is used for volumetric measurements). Most of the FreeSurfer pipeline is automated, which makes it ideal for use on large data sets. Standard readouts provided by UCD to the NACC database include the parcellations of regional brain volumes, cortical thickness and surface area for 31 bilateral gray matter regions from the Desikan-Killiany atlas[1, 2].

White Matter Hyperintensity: WMH quantitation is performed on a combination of FLAIR and 3D T1 images using a modified Bayesian probability structure based on a previously published method of histogram fitting[3]. The first step in this process is to segment the image into gray, white and CSF tissues. Our segmentation algorithm is based on an Expectation-Maximization (EM) algorithm that iteratively refines its segmentation estimates to produce outputs that are most consistent with the input intensities from the native-space T1 images along with a model of image smoothness[4, 5]. At each iteration, the algorithm uses a Gaussian model of T1-weighted image intensity for each tissue class, in order to produce a segmentation. In the first iteration, these models are estimated from a standardized segmented image. The segmentation yielded by these appearance models alone is then refined using a Markov Random Field (MRF) model, a computational statistical method that efficiently produces a label map consistent with both the input intensities and image smoothness statistics. Inference in the MRF is computed using an adaptive priors model[4]. This refined segmentation from the MRF is then used to compute new Gaussian intensity models for each tissue class, and the algorithm repeats, iteratively switching between calculating Gaussian appearance models and MRF-based segmentation, until convergence. The MRF-based segmentation at the final iteration is used as the final output segmentation. Once gray, white and CSF tissues have been identified, FLAIR analysis is added to the process. WMH segmentation also is based on a Bayesian approach. Prior probability maps of WMH were created from more than 700 individuals with semi-automatic detection of WMH followed by manual editing. Likelihood estimates of the native image are calculated through histogram segmentation and thresholding. All segmentation is initially performed in standard space resulting in probability likelihood values of WMH at each voxel in the white matter. These probabilities are then thresholded at 3.5 SD above the mean to create a binary WMH mask. Further segmentation is based on a modified Bayesian approach that combines image likelihood estimates, spatial priors, and tissue class constraints. The segmented WMH masks are then back- transformed on to native space for tissue volume calculation. Standard readouts from this procedure provided to the NACC database include gray matter, cerebrum total cranial and WMH volumes.

Hippocampal Segmentation: MRI-derived hippocampal volumetry has been a widely used biomarker in AD and dementia research to improve early diagnosis[6], enrich subject selection[7] and monitor treatment efficacy[8, 9], but harmonized anatomical borders are lacking. To address this need, the EADC-ADNI Working Group established a Delphi panel to determine the optimum protocol[10], selected orientation parameters[11], and developed the final, rigorously tested protocol along with making publicly available labels from over 100 ADNI subjects[12]. Our hippocampal segmentation method employs a standard atlas based diffeomorphic approach[13] with the minor modification of label refinement. We further modified this approach to include the EADC-ADNI harmonized hippocampal masks to assure standardization across cohorts. Therefore we have adopted the following approach: 1) Subject image pre-processing with extraction of intracranial cavity, non-uniformity correction, tissue classification as discussed above; 2) Atlas Registration of all EADC-ADNI hippocampal masks[6, 10, 12, 14, 15] to each subject; 3) Atlas Fusion utilizing MALF[16, 17]; and 4) Intensity-based label refinement. Hippocampal volumes from this approach will be an output to the NACC database.

Version Information [Heading 1]

This is the 1st version of our methods. Specific changes to our methods will be summarized in this section.

Dataset Information

This methods document applies to the following dataset(s) available from the SCAN repository:

Dataset Name	Date Submitted
UCD SCAN Methods V1	07 March 2023

About the Authors

This document was prepared by Charles DeCarli, MD and Pauline Maillard, PhD. For more information, please contact Dr. Pauline Maillard at by email at <**pmaillard@ucdavis.edu** >.

Notice: This document is presented by the author(s) as a service to SCAN data users. However, users should be aware that no formal review process has vetted this document and that SCAN cannot guarantee the accuracy or utility of this document.

References

1. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968-980.
2. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341-355.
3. DeCarli C, Miller BL, Swan GE, et al. Predictors of brain morphology for the men of the NHLBI twin study. Stroke 1999;30:529-536.
4. Fletcher E, Singh B, Harvey D, Carmichael O, DeCarli C. Adaptive image segmentation for robust measurement of longitudinal brain tissue change. Annu Int Conf IEEE Eng Med Biol Soc 2012;2012:5319-5322.
5. Rajapakse JC, Giedd JN, DeCarli C, et al. A technique for single-channel MR brain tissue segmentation: application to a pediatric sample. Magn Reson Imaging 1996;14:1053-1065.
6. Frisoni GB, Bocchetta M, Chetelat G, et al. Imaging markers for Alzheimer disease: which vs how. Neurology 2013;81:487-500.
7. Lorenzi M, Donohue M, Paternico D, et al. Enrichment through biomarkers in clinical trials of Alzheimer's drugs in patients with mild cognitive impairment. Neurobiol Aging 2010;31:1443-1451, 1451 e1441.
8. Hampel H, Wilcock G, Andrieu S, et al. Biomarkers for Alzheimer's disease therapeutic trials. Prog Neurobiol 2011;95:579-593.
9. Hampel H, Frank R, Broich K, et al. Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives. Nat Rev Drug Discov 2010;9:560-574.
10. Boccardi M, Bocchetta M, Apostolova LG, et al. Delphi definition of the EADC-ADNI Harmonized Protocol for hippocampal segmentation on magnetic resonance. Alzheimers Dement 2015;11:126-138.
11. Boccardi M, Bocchetta M, Apostolova LG, et al. Establishing magnetic resonance images orientation for the EADC-ADNI manual hippocampal segmentation protocol. J Neuroimaging 2014;24:509-514.

12. Bocchetta M, Boccardi M, Ganzola R, et al. Harmonized benchmark labels of the hippocampus on magnetic resonance: the EADC-ADNI project. Alzheimers Dement 2015;11:151-160 e155.
13. Vercauteren T, Pennec X, Perchant A, Ayache N. Non-parametric diffeomorphic image registration with the demons algorithm. Med Image Comput Comput Assist Interv 2007;10:319-326.
14. Boccardi M, Bocchetta M, Ganzola R, et al. Operationalizing protocol differences for EADC-ADNI manual hippocampal segmentation. Alzheimers Dement 2015;11:184-194.
15. Frisoni GB, Jack CR, Jr., Bocchetta M, et al. The EADC-ADNI Harmonized Protocol for manual hippocampal segmentation on magnetic resonance: evidence of validity. Alzheimers Dement 2015;11:111-125.
16. Wang H, Yushkevich PA. Dependency Prior for Multi-Atlas Label Fusion. Proc IEEE Int Symp Biomed Imaging 2012;2012:892-895.
17. Wang H, Yushkevich PA. Multi-atlas segmentation with joint label fusion and corrective learning-an open source implementation. Front Neuroinform 2013;7:27.