ADNI Alzheimer's Disease Neuroimaging Initiative

Tensor-Based Morphometry

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Contents

Summary (or Abstract) [200 words max]

Tensor-based morphometry (TBM) is an image analysis technique that measures brain structural differences, cross sectional differences or changes over time in repeat scans, from the gradients of deformation fields that align one image to another. TBM may be applied to cross-sectional MRI data for local volumetric comparisons, based on nonlinearly registering individual brain scans to a common anatomical template (*cross-sectional TBM*). When TBM is applied in a longitudinal MRI study, a change map is computed by nonlinearly registering a follow-up scan to a baseline scan from the same individual (*longitudinal TBM*). TBM-derived measures of brain atrophy, reflecting the rate of tissue loss, can be used as an imaging surrogate biomarker to facilitate clinical trials. Care must be taken that the analysis methods are symmetric and free from multiple sources of bias [1]. Our method has been tuned to handle poorer quality scans robustly, i.e., it does not require the throw-out of scans, as a real clinical trial would not allow the selective exclusion of data.

Method

Methods for the cross-sectional TBM [2, 3] and the *improved* longitudinal TBM [1] are summarized below. Numerical summaries of cumulative temporal lobe atrophy are only available for longitudinal TBM.

Image Download

MR scans (1.5T or 3T) were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database (http://adni.loni.ucla.edu/). Downloaded images had been processed with the standard Mayo Clinic processing pipeline, identified with the term "scaled" (ADNI-1) or "MT*" (ADNI-GO/2) in the file name.

Image pre-processing

To adjust for linear drifts in head position and scale within the same subject, the follow-up scan was linearly registered to its matching screening scan using 9-parameter (9P) registration, driven by a mutual information (MI) cost function [4]. 9P linear registration was chosen to correct for scanner voxel size variations in large longitudinal studies and any residual scaling errors after phantom-based image correction. Additionally, to account for global differences in brain scale across subjects, the mutually aligned time-series of scans was then linearly registered to the

International Consortium for Brain Mapping template (ICBM-53) [5], applying the same 9P transformation to both mutually aligned scans. Intermediate transformation matrices were concatenated into a single transformation file so that both screening and follow-up scans were resampled once during the linear registration (see [6] on the need for equivalent resampling of both images to avoid one source of bias in analyzing longitudinal data). Globally aligned images were re-sampled in an isotropic space of 220 voxels along *x*-, *y*- and *z*-dimensions with a final voxel size of 1 mm^3.

Average group template - minimal deformation target (MDT)

A minimal deformation target (MDT) was created from the scans of 40 randomly selected normal subjects to serve as an unbiased average template image [7] (**Figure 1**). To construct an MDT, we first created an initial affine average template by taking a voxel-wise average of the 9P globally aligned scans after intensity normalization. Next, a non-linear average template was built after warping individual brain scans to the affine template [8, 9]. The above steps were repeated until a full-resolution image registration was achieved. Lastly, the MDT was generated by applying inverse geometric centering of the displacement fields to the non-linear average [10, 11].

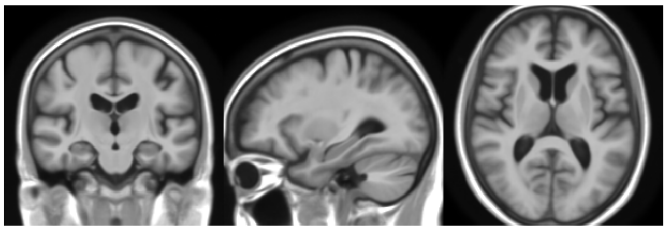

Figure 1: High-resolution average group template – the 'minimal deformation' target (MDT). The MDT is shown here using the radiological convention (with slices at x=140, y=110, z=110, in a coordinate system whose image centroid is at (110,110,110)).

Cross-sectional TBM

To quantify 3D patterns of volumetric brain differences, all individual screening images (*N*=817) were aligned to the MDT, using a non-linear inverse consistent elastic intensity-based registration algorithm [12], which optimized a joint cost function based on mutual information (MI) and the elastic energy of the deformation. A Jacobian matrix field was derived from the gradients of the deformation field that aligned an individual brain to the MDT template. The determinant of the local Jacobian matrix was derived from the forward deformation field to characterize local volume differences, with a Fast Fourier Transform (FFT) resolution of 32x32x32; this corresponds to an effective size of 6.875 mm (220 mm / 32 = 6.875 mm) in each of the x-, y-, and z- dimensions. Color-coded Jacobian determinants were used to illustrate regions of volume expansion, i.e. those with $\det J(r) > 1$, or contraction, i.e., $\det J(r) < 1$ [13-18] relative to the normal group template. As all images were registered to the same template, these *Jacobian* maps share a common anatomical coordinate defined by the MDT template.

Longitudinal TBM

In the improved TBM [1], we added a step to generate brain masks and remove the image background before longitudinal nonlinear registrations. Image background removal or skull stripping improves the precision of longitudinal TBM, where subtle changes are detected as

subject's brain degenerates over time; it is however unnecessary for cross-sectional TBM, where large changes inside the brain are expected when aligning individual brains across the subjects.

Brain masks that exclude skull, other non-brain tissues, and the image background were generated automatically using a parameter-less robust brain extraction tool (ROBEX) [19]. Separate ROBEX masks were created for mutually aligned screening and follow-up scans in the ICBM space. A joint mask was then created using the union of two masks, followed by 2 iterations of morphological dilation using the mean dilation tool in FSLMATHS (http://www.fmrib.ox.ac.uk/fsl/avwutils/index.html), to ensure that all brain tissues were included. Finally, we applied the dilated joint mask to uniformly "skull-strip" the screening and 9P registered follow-up scans, which were later used to compute the longitudinal change maps, or *Jacobian* maps.

Individual Jacobian maps were created to estimate 3D patterns of structural brain change over time by warping the 9P-registered and 'skull-stripped' follow-up scan to match the corresponding screening scan, using the same non-linear inverse consistent elastic intensity-based registration algorithm [12]. The deformation field was computed using a FFT resolution of 64x64x64. This corresponds to an effective voxel size of 3.4 mm in the x, y, and z dimensions (220 mm / 64 = 3.4 mm). These longitudinal maps of tissue change were also spatially normalized across subjects by nonlinearly aligning all individual Jacobian maps to a MDT, for regional comparisons and group statistical analyses.

Numerical summaries of cumulative temporal lobe atrophy

To derive a single-number summary of the 3D map of brain atrophy for each subject, a single numerical measure was derived by computing an average within a region-of-interest (ROI). Both anatomically and statistically-defined ROIs were used. First, a temporal lobe ROI (temp-ROI), including the temporal lobes of both brain hemispheres, was manually delineated on the MDT template by a trained anatomist using the Brainsuite software (version 2.11) [20]. Secondly, a *statistically-defined* ROI (stat-ROI) was defined based on voxels with significant atrophic rates over time ($p < 0.00001$) within the temporal lobes, in a non-overlapping training set of 20 AD patients (age at baseline: 74.8±6.3 years; 7 men and 13 women) scanned at baseline and 12-month.

We computed numerical summaries of the 3D *Jacobian* map to estimate the amount of cumulative temporal lobe atrophy, by taking an average within the stat-ROI or temp-ROI. For the 20 AD patients selected to create the stat-ROI, we used a leave-one-out strategy so that they could all be included in the final analysis (i.e., 19 AD patients were used for creating a stat-ROI, which was used to derive a numerical summary for the left-out subject, and this process was repeated by leaving out each of the other subjects). The numeric summaries represent the overall amount of cumulative temporal lobe atrophy during an observation time of 6, 12, 18, 24, and 36 months respectively.

Version Information

This document supersedes our previous document dated [June 03, 2009]. Specific changes in our methods are summarized in this section. In addition to adding more subjects, we implemented two major changes in the recent longitudinal TBM analyses: (1) brain masks were generated and used to exclude non-brain tissues and the image background, prior to nonlinear registration; (2) prior versions used a nonlinear registration algorithm using the symmetrized Kullback-Leibler distance to regularize the deformation, also known as "sKL-MI". In the current version, sKL-MI was replaced with the non-linear inverse consistent elastic intensity-based registration algorithm [12], also known as "3DMI". Therefore, both cross-sectional and longitudinal TBM were processed with 3DMI, at different FFT resolutions, in the new uploads.

Dataset Information

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

Dataset Name	Date Submitted
Thompson Lab – Cross-sectional and longitudinal tensor-based morphometry Version 2.0	1 October 2012

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For data analyses using the Jacobian maps and/or numerical summaries of cumulative temporal lobe atrophy, please reference the following paper:

[1] Hua, X., et al., Unbiased Tensor-Based Morphometry: Improved Robustness and Sample Size Estimates for Alzheimer's Disease Clinical Trials. Submitted, 2012.