# 3D MAPPING OF BRAIN ATROPHY IN ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT & HEALTHY ELDERLY SUBJECTS USING TENSOR-BASED MORPHOMETRY

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**Summary:** Tensor-based morphometry (TBM) is an image analysis technique that computes the locations and rates of tissue atrophy in the brain from the gradients of the deformation fields used to align one image to another. TBM may be applied to cross-sectional MRI data for local volumetric comparisons between two or more groups of subjects, based on nonlinearly registering individual brain scans to a common anatomical template. Moreover, when TBM is applied to a longitudinal MRI study, the derived Jacobian maps reflect the percentage of tissue change over time. We use two separate classes of registration methods that we developed at UCLA, both driven by a mutual information (MI) cost function. Different regularizing functions are used, which affect the spatial covariance of the deformations. For our cross-sectional studies [1, 2], we use a method we developed, termed "3DMI" [3], which utilized a regularizing term based on the Cauchy-Navier linear elasticity operator. In our longitudinal studies [4, 5], we use a related algorithm that we developed, termed "sKL-MI", using the symmetrized Kullback-Leibler (sKL-MI) distance to regularize the deformation [6, 7].

**Methods:**

*Image Download*

Brain MRI scans were downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) public database (http://www.loni.ucla.edu/ADNI/Data/). All downloaded images were processed with a processing pipeline at the Mayo Clinic, consisting of *GradWarp* [8], "B1-correction" [9], "N3" bias field correction [10], and geometrical scaling [9].

*Image Pre-processing*

To adjust for global differences in position and scale across subjects (cross-sectional), individual scans were linearly registered to the International Consortium for Brain Mapping template (ICBM-53) [11] using 9-parameter (9P) registration, driven by a mutual information (MI) cost function [12].

To adjust for linear drifts within the same subject (longitudinal), the follow-up scan was linearly registered to its matching baseline scan using 9P registration. Both mutually aligned scans were then linearly registered to the ICBM-53 by applying the same 9P transformation.

Globally aligned images were re-sampled into an isotropic space of 220 voxels along *x*-, *y*- and *z*-dimensions with a final voxel size of 1 $mm^3$.

*Unbiased Group Average Template - Minimal Deformation Target (MDT)*
A minimal deformation target (MDT) was created based on 40 randomly selected normal subjects to serve as an unbiased average template image. To construct an MDT, the first step was to create an initial affine average template, by taking a voxel-wise average of the 9P globally aligned scans after intensity normalization. In the second step, a non-linear average template was built after warping individual brain scans to the affine template using 3DMI. A non-linear average intensity template was then derived from the mean of the 40 deformed scans that had been non-linearly registered toward the affine average template. In a final step, the MDT was generated for the normal group by applying inverse geometric centering of the displacement fields to the non-linear average.

*TBM and three-dimensional Jacobian Maps*
To quantify 3D patterns of volumetric tissue differences in cross-sectional data, all individual brain images were non-linearly aligned to the MDT for the normal group, using 3DMI. For each subject, a separate Jacobian matrix field was derived from the gradients of the deformation field that aligned that 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. 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 normal template.

To quantify 3D patterns of atrophic rates in longitudinal data, individual Jacobian maps were derived from the deformation field warping the follow-up scan to match the baseline scan of the same subject, using sKL-MI. The inter-subject displacement vector field, obtained from the above step, was then applied to transform the Jacobian (i.e., local expansion or contraction) map of each subject to the brain coordinates defined by the MDT. Spatial normalizations among different brains enable regional comparisons and group analyses to be performed.

3DMI and sKL-MI interpolate the deformation into white matter regions in slightly different ways. Please refer to our recent publications for detailed comparisons of the two TBM algorithms [5, 6, 19-23].

*Regions of interest (ROIs) and mean atrophy rate*

Both anatomically and statistically-defined ROIs are used in our studies. First, a temporal lobe ROI, including the temporal lobes of both brain hemispheres, was manually delineated on the MDT template by a trained anatomist using the Brainsuite software program [24]. Secondly, a *statistically-defined* ROI (stat-ROI) was defined based on voxels with significant atrophic rates over time ($p < 0.001$) within the temporal lobes, in an independent training set of 22 AD patients [5]. A separate stat-ROI was generated and applied for each TBM design with different algorithms, 3DMI versus sKL-MI.

A numeric summary – the mean atrophy rate for all voxels with in the ROI – was computed for each person, to summarize annual change within the ROI.

Image processing steps were submitted to a computing cluster using the LONI Pipeline Processing Environment which allows parallelization of multiple tasks [25].

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