

TBM-SyN Based Scores

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Data Information	
Mar. 18, 2013	Image collection formed from all ADNI-GO/2 3 Tesla T1 images available on LONI
Oct. 31, 2013	Results uploaded

1. Summary

Longitudinal MRI measurements are highly sensitive to detecting relevant neurodegenerative changes in Alzheimer's disease (AD) and are used as an outcome measure for clinical trials. We set out to develop a robust MRI metric for longitudinal studies with the following features: i) the longitudinal change measurement between scans is free of bias due to asymmetric image registration between the serial scans and ii) the measurement is relative to change in cognitively normal subjects (CN) who do not have AD pathology. To address the issue of symmetric image registration we employed Symmetric Diffeomorphic Image Normalization method (SyN) [4] for normalization of the serial scans to obtain Tensor Based Morphometry (TBM) maps which indicate the structural changes between pairs of scans. To form a summary measure for each scan pair, we log transformed and annualized the Jacobian determinant maps, and computed the mean over 31 unique regions of interest (ROIs) which we identified by analyzing Jacobian maps and cross sectional gray matter maps in an independent training set of 51 late-onset AD subjects and 51 PiB-negative (global PiB SUVR<1.4), age, gender and education matched CN subjects.

We processed all available ADNI-2 and ADNI-GO subjects with serial MRI scans through the TBM-SyN pipeline, and obtained TBM-SyN summary scores for each subject, at each follow-up time point. The TBM-SyN Scores represent annualized atrophy rates computed from the subject's baseline scan to each follow-up and summarized by averaging over the 31 ROIs.

2. Method

2.1. Data Processed

We processed all ADNI-2 and ADNI-GO subjects with available and usable (passed quality control) serial scans as of March 18th 2013, through the Mayo TBM-SyN pipeline. Additionally each subject processed through pipeline was required to have at least two usable serial scans available. All accelerated and unaccelerated scans were processed independently.

2.2. Image Preprocessing for Each Individual Image

For each subject, we begin with the “N3m” preprocessed datasets. For each image set we have created masks of the brain and the third and lateral ventricles. We begin by forming an initial mean image of all N3m images and using SPM5 based mutual information co-registration without reslicing, we iteratively register each N3m image to the mean, applying the transformations to the brain and ventricle masks, and forming a new mean after each iteration, allowing it to continue until the mean image has not changed from one iteration to the next, or until a preset maximum of 10 iterations is reached. After the final iteration, the set of all images are co-registered one last time to the base image, to ensure no registration failures. Using dilation, hole filling, and subtraction on the co-registered brain and ventricle masks, we form collections of voxels dominated by WM and CSF, and fit Gaussian functions to the intensity spectra. We scale image intensities, mapping the WM and CSF spectrum peaks to constant arbitrary values of 20,000 and 5,000, respectively.

Next, using Aladin (<http://sourceforge.net/projects/niftyreg/>, Ourselin et.al.), we rigid-body (6DOF) co-register each image to the subject's known baseline image, restricting the cost function with an approximate intracranial mask to eliminate variability in neck positioning. We average the transformations within subject in quaternion space and resample the grey scale image and masks into this average space with 1mm isotropic resolution using cubic spline, and linear interpolation, respectively. We form a new registration target by averaging the resampled images, and a new intracranial mask by applying dilation and hole filling to the union of the resampled brain and ventricle masks. We then perform affine (9DOF) registration between unregistered images and the average image, and finally resample all images and masks into the target space at 1mm isotropic resolution.

We next balance intensities and perform differential bias correction (DBC). We determine the WM and CSF peak intensities for the mean image and each resampled image from a fit of Gaussians, and a GM-enhanced intensity spectrum from voxels that are spatially between the WM and CSF samples. We fit the GM-enhanced spectra with the sum of two Gaussians, to allow for WM “contamination” – one Gaussian has center and width fixed at the values determined by the WM fit with arbitrary amplitude. We employ a spline-based intensity re-mapping to bring each image's GM, WM and CSF peak intensity into agreement with the mean image. The DBC is carried out using the collection of voxels that is consistently near CSF peak intensity or consistently near WM peak intensity and inside a hole-filled brain mask. Using only points inside the collection, we create a log transformed ratio image of R_i to the mean image. Since the point collection is sparse in space, we use a tri-linear 3D interpolation to create a dense field, requiring it go to zero at the edges of the image. We then smooth the dense field with a 20mm

isotropic Gaussian kernel, exponentiate the resulting field and finally apply the result to image R_i to arrive at the final preprocessed image.

2.3. Longitudinal Measure Free of Bias

High accuracy is the main metric that is often considered in the development of the warping algorithms; however recently it has been shown that asymmetric registration between serial scans will introduce bias in longitudinal measurements [3]. In this work, we used the Symmetric Normalization algorithm (SyN) developed by Avants et al. [4] which provides symmetric normalization between serial scans and has a high degree of accuracy when compared to manual measurements and in comparison to other nonlinear deformation algorithms [5]. Starting with the preprocessed scans for each subject, we compute the SyN deformations between each pair of images, in both directions explicitly, saving an image of the log transformed Jacobian determinants for each. We form an “annualized” log Jacobian map by dividing each log Jacobian voxel by the intrascan time interval, measured in years. We then apply each deformation to the corresponding moving image, and create a “soft-mean” of the “fixed” and the “moved” image. We then apply SPM5 unified segmentation to each soft-mean image, and propagate ROI masks from the template space to the soft-mean space, to obtain mean annualized log Jacobian measurements in the various ROIs.

2.4. Mayo Clinic Patients for Region Selection

In the development of longitudinal measurements, statistically significant ROIs are often determined by analyzing a training set consisting of both patients and matched controls, in order to get a more accurate picture of neurodegenerative changes in patients relative to matched controls. In this work, we identified a training set of AD and CN subjects with longitudinal MRI scans, drawn from the Mayo Clinic Alzheimer's Disease Research Center (ADRC) and the Mayo Clinic Study of Aging (MCSA). In total, there were 51 AD subjects, and 51 PiB-negative CN patients that were matched on age, gender and education. The PiB-negative status of the CN subjects was defined as global PiB SUVR < 1.4. We applied this PiB-negative criterion in order to exclude CN subjects who have indication of early AD pathology. Each subject had two serial MRI scans and in order to maintain a clean training dataset we took the following additional steps: all subjects were required to maintain the same clinical primary diagnosis at both the serial scans; the baseline age of all subjects was restricted to ≥ 64 years, in order to filter out possible early onset AD subjects. We used a two-sample t-test to select the top 20 regions (with right and left information combined) that were significantly different when both cross-sectional GM volumes as well as longitudinal annualized log Jacobian data were all compared together. This led to the selection of the 31 unique ROIs that are shown in Figure 1. Since 30 of the regions were gray matter (GM) ROIs, which show volume shrinkage, and one of the ROIs is the ventricle, which shows expansion, we inverted the sign of the ventricle log Jacobian determinant before combining it with the values from the cortical GM ROIs.

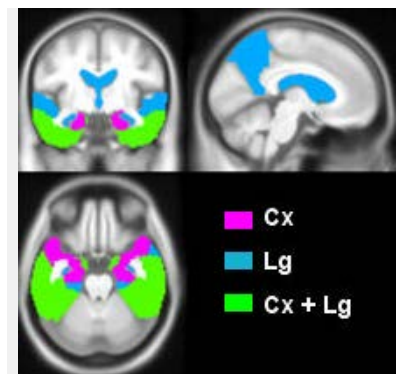


Figure 1: The top 20 features selected based on t-test differences between the 51 AD and 51 PiB -ve CN. Colors indicate the regions selected in the cross-sectional (Cx) and longitudinal (Lg) array of values. Magenta: Cx only; Blue: Lg Only and Green: Cx and Lg.

2.5. TBM-SyN Scores

We computed summary TBM-SyN Scores between pairs of scans, by forming the average of the annualized log Jacobians determinants from the TBM-SyN pipeline, in the 31 regions described above.

3. Results

The TBM-SyN scores were computed for all subjects with serial scans by computing the SyN deformations between each follow-up scan and the subject's baseline scan. The software packages that were used for the development of the tool were - MATLAB (Mathworks, Natwick, MA), ANTs 1.9.x (Penn Image Computing and Science Lab, University of Pennsylvania, PA), SPM5 (Wellcome Trust Center for Neuroimaging, UCL, UK).

4. Version Information v 1.2

This document includes a minor revision to the original TBM-SyN methods document submitted from the Mayo Clinic ADIR lab. Version 1.2 includes additional co-registration in the algorithm as described in Section 2.2, Paragraph 1.

5. Dataset Information

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

Dataset Name	Date Submitted
Mayo (Jack Lab) – TBM-SyN Scores, Version 1.2	31 October 2013

References

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