ADNI Alzheimer's Disease Neuroimaging Initiative

TBM-SyN Based Scores

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Sept 1	All data downloaded from LONI
Oct 31	Results uploaded

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) [1] 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.

1. Method

1.1 Data Processed

We processed all ADNI-2 and ADNI-GO subjects with available serial scans as of September 1st 2012, through the Mayo TBM-SyN pipeline. We only processed the un-accelerated T1 scans.

1.2 Image Preprocessing for each individual image

For each image, we begin with the "N3m" preprocessed datasets. For each image set we have created masks of the brain and the third and lateral ventricles. Using dilation, hole filling, and subtraction, 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.

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 intra-cranial 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 trilinear 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.

1.3 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 [2]. In this work we used the Symmetric

Normalization algorithm (SyN) developed by Avants et al. [1] 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 [3]. 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 intra-scan 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.

1.4 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 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.

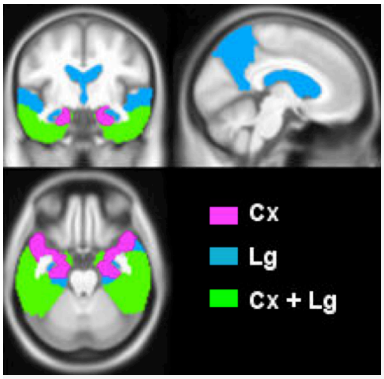

Figure 1: The top 20 features selected based on t-test differences between the 51 AD and 51 PIB –ve CN. Colors indicate the regions selected in the cross-sectional (Cx) and longitudinal (Lg) array of values. Magenta: Cx only; Blue: Lg Only and Green: Cx and Lg.

1.5 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.

2. 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).

3. Version Information v 1.1

This is the first document that is being submitted from the Mayo Clinic Rochester for the longitudinal measures of structural MRI scans.

Dataset Information

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

Dataset Name	**Date Submitted**
Jack Lab – TBM-SyN Scores Version 1.1	31 October 2012
Jack Lab – TBM-SyN Scores Version 1.1	06 February 2013

References

1. ***Avants, B.B., et al., Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Medical image analysis, 2008. 12(1): p. 26-41.***

2. ***Fox, N.C., G.R. Ridgway, and J.M. Schott, Algorithms, atrophy and Alzheimer's disease: cautionary tales for clinical trials. Neuroimage, 2011. 57(1): p. 15-8.***

3. ***Klein, A., et al., Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. Neuroimage, 2009. 46(3): p. 786-802.***

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