Regional Gray Matter Atrophy in Multiple Sclerosis using Tensor Based Morphometry: A Multi-Center Study

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Introduction:

Gray matter (GM) atrophy in multiple sclerosis (MS) is well recognized and thought to represent neurodegenertion. Regional GM (RGM) atrophy appears to correlate better with clinical measures and could serve as a biomarker for objectively monitoring the disease [1, 2, 3]. RGM is most commonly estimated using voxel based morphometry (VBM). Tensor-based morphometry (TBM) is a technique for estimating disease-related changes in brain structures and has been shown to provide methodological improvements over VBM. The main advantage of TBM over VBM is that former can be applied without the need for tissue segmentation. In this study, TBM is utilized to identify RGM atrophy on a large cohort of MS subjects who participated in a multi-center clinical trial. Multi-center studies provide a rich resource for developing and testing any magnetic resonance imaging (MRI)-based measure that might be considered as an advanced biomarker of the disease and as a potential measure of disease outcome.

Methods:

In this cross-sectional study, MRI data on 250 relapsing remitting MS (RRMS) subjects (188 females, 62 males; age 38.2 ± 9 years, range 18-61 years; median extended disability status scale (EDSS) of 2, range 0-5 with disease duration of less than 3 years) were analyzed. These subjects participated in a phase 3 multi-center clinical trial and were randomly selected for this study from a total of 1008 at baseline. This sub-cohort was evaluated using images from 163 subjects acquired at 1.5 T and 87 subjects acquired at 3 T. In addition, MRI data on 125 age and gender-matched healthy controls (92 females, 33 males; age 37.3 ± 10.8 years, range 20-59 years) from the UTHouston Med center and publicly available databases were included. The MRI protocol included two-dimensional dual fast spin echo (FSE), fluid attenuated inversion recovery (FLAIR), pre- and post-contrast T1-weighted, and three-dimensional T1-weighted images were acquired on MS subjects. 3D T1-weighted images were acquired either using SPGR or MPRAGE sequences (voxel dimensions 0.94 mm x 0.94 mm x 1.5 mm).

Fourteen scans on controls from our center were randomly selected for generating an unbiased atlas. The images were skull-stripped and bias corrected using BET [4] and N4ITK [5] algorithms respectively. Unbiased atlas with voxel dimension of 1 mm^3 was generated using an iterative procedure of applying symmetric diffeomorphic non-linear registration and averaging all co-registered images [6]. An automated pipeline for the applications of BET, N4ITK, and symmetric diffeomorphic non-linear registration techniques to T1-weighted images was designed and implemented for this study. The results obtained from automated pipeline were qualitatively evaluated for poor brain extraction. Normalized logarithmic Jacobian (NLJ) was obtained for each subject using the deformation field. SPM5 statistical analysis was used for group analysis on MS cohort and controls with family-wise error (FWE) set at 0.05.

Results:

Based on qualitative evaluation, fifteen scans from MS group were discarded due to poor brain extraction. Age and gender were included as covariates in the SPM analysis for two groups of 235 MS subjects and 125 controls respectively. Figure 1 shows examples of non-linear registration of MS subject and control with the unbiased atlas. Figure 2 shows areas of significant regional atrophy as assessed by TBM with cluster size of 10 superimposed on the unbiased atlas. The atrophied structures are also labeled in this figure. As can be observed from this figure, significant atrophy is seen in a number of RGM structures.
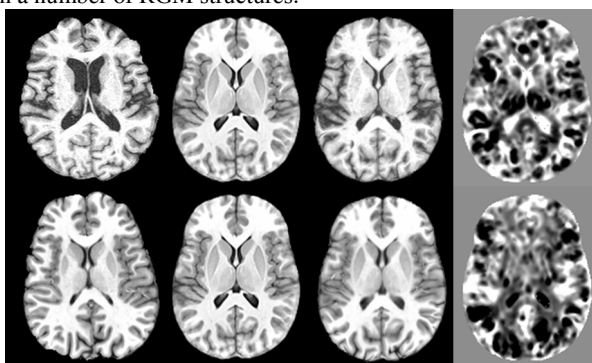

Figure 1: 1st row: T1 of MS subject, unbiased atlas, registered T1, NLJ; 2nd row: T1 of a control, unbiased atlas, registered T1,
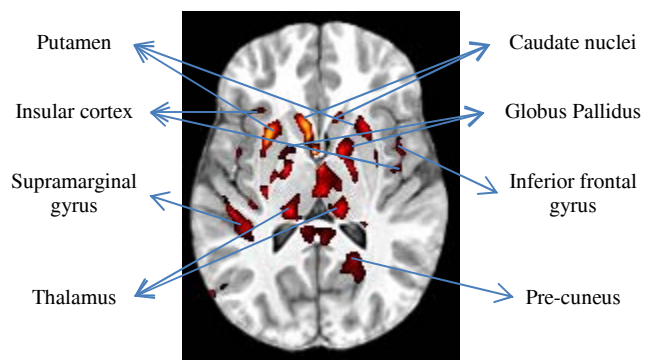

Figure 2: Significant atrophy from minimum (black red) to maximum (yellow) obtained by TBM overlaid on unbiased atlas.

Discussion and Conclusions:

We have implemented TBM to assess RGM atrophy in MS subjects compared to controls. We have detected significant atrophy in major deep GM structures including thalamus, putamen, caudate nuclei and globus pallidus. Several other GM structures also showed atrophy. These results are consistent with our previous study that was done on 88 RRMS subjects acquired on single scanner [3], suggesting that atrophy is robust measure in MS. Our future studies include the correlation analysis of the measures of atrophy in various GM structures with clinical and other MRI-derived measures including EDSS, T2 hyperintense lesions and T1 hypointense lesions, respectively. We also plan to explore the effect of field strength on regional atrophy. To the best of our knowledge, this is the first study to analyze regional atrophy in MS using TBM on data acquired on a large cohort scanned at multiple centers.

References: [1] Nocentini et al., BIB 2012 (in press), [2] Schoonheim et al., N 2012;79:1754-1761, [3] Tao et al., JNS 2009;282:39-46, [4] Smith, HBM 2002;17:143-155, [5] Tustison et al., IEEE TMI 2010;29:1310-1320, [6] Avants et al., MIA 2008;12:26-41.