Atrophy and Shape Changes in Deep Gray Matter in Multiple Sclerosis: A Tensor Based Morphometry

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Introduction:

We have applied tensor based morphometry (TBM) method to study the atrophy and shape changes of deep gray matter (DGM) structures in 88 Relapsing-Remitting Multiple Sclerosis (RRMS) patients. To improve the accuracy and robustness of morphometry measurement, an unbiased template was constructed from 20 normal brains for group comparison. A symmetric inverse consistent nonlinear registration method was used to co-align T1-weighted images with unbiased template. The strain tensor was then extracted from the deformation field. In addition to quantifying atrophy of DGM structures with Jacobian Determinant (JD), *tanh* of Geodesic Anisotropy (GA) was calculated to study the shape differences of these structures. Both atrophy and shape changes in several DGM structures were found to be significantly correlated with the extended disability status scale (EDSS).

Patients and MR Image Acquisition:

A total of 88 RRMS patients, 68 females and 20 males with median age 41.2 yrs (range: 20-64 yrs) and median EDSS of 1.5 (range: 0-6.5) were recruited for this study and were scanned on a 3T Philips Intera scanner. The EDSS for each patient was assessed by neurologists prior to MRI. T1-weighted images, either using fast field echo sequence (TE/TR = 4.6 ms/9.9 ms; 77 patients) or magnetization prepared rapid gradient echo (MPRAGE) sequence (TE/TR = 3.7 ms/8.1 ms; 11 patients) were acquired with the following parameters: field-of-view: 240 mm x 240 mm; image matrix: 256 x 256 with 1mm slice thickness. High resolution T1-weighted brain images from normal volunteers (45.2 ± 9.0 yrs) were obtained from the OASIS database to create unbiased template [1]. The individual T1 image volume (MNI template, Colin 27) and associated anatomical labels were obtained from the UCLA website: http://www.loni.ucla.edu/Atlases.

Methods:

The randomly selected 20 high-resolution T1 images of normal brains from the OASIS database [1] were registered to the MNI template using nonlinear registration algorithm [2]. These registered images were used to generate unbiased template by mapping the intensity average of deformed images through inversion of the geometric average transformation [3]. A symmetric inverse consistent nonlinear registration algorithm based on mutual information as similarity measure [2] was used to co-register the 88 3D images of MS subject to the unbiased template described above. For each MS brain, the strain tensor $S = (J^T J)^{\wedge 0.5}$ defined in the unbiased template space were calculated [4], where J is the Jacobian matrix obtained from the deformation field of nonlinear registration. The Jacobian determinants were normalized to compensate for the brain size differences among the all MS brains. The logarithmic of JD (LJD) was used for the TBM analysis to calculate the volume atrophy. The *tanh(GA)* was calculated from strain tensor to quantify the shape change among different groups [4].

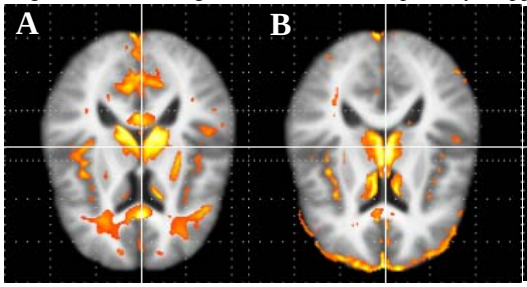

Fig 1. TBM results based on two sample t-test of (A) Log Jacobian Determinant and (B) *tanh(GA)* between normal group and EDSS=0 group.

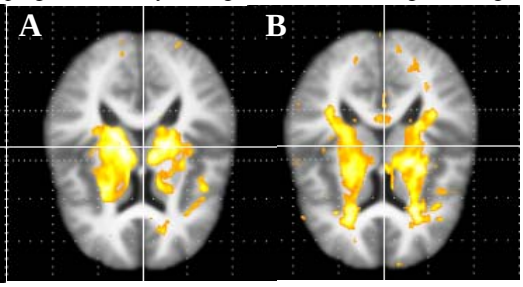

Fig 2. TBM results based on two sample t-test of (A) Log Jacobian Determinant and (B) *tanh(GA)* between MS subject groups A and B.

Results and Discussion:

Statistical analysis based on two sample t-test was performed using SPM2 http://www.fil.ion.ucl.ac.uk/spm/software/spm2/ to analyze atrophy and shape changes between normals and MS subjects. Figure 1A shows statistical significant atrophy in DGM structures of a group of MS subjects with EDSS 0 when compared with a group of 20 normal subjects. Significant shape changes in DGM structures were also observed (Fig. 1B). In order to assess the changes in DGM structures with disease progression, all MS subjects were classified into two groups: group A patients with EDSS ≤ 3.5 (75 subjects) and group B with EDSS ≥ 4.0 (13 subjects). DGM atrophy and shape changes between these two groups are shown in Figure 2. In the absence of clinical disability as assessed by EDSS, significant atrophy of thalamus and putamen was observed (Fig. 1A), whereas significant shape change was observed in thalamus, but not in putamen (Fig. 1B). As can be seen from Figure 1, the caudate nucleus shows significant shape change but not atrophy. Shape change in the frontal region of the cortex (Fig. 1B) could be attributed to the different methods used for extrameningeal tissue removal in OASIS and our database. With disease progression, thalamus and putamen continue to show significant atrophy (Fig. 2A), but only putamen was affected by significant shape change (Fig. 2B). Table 1 summarized the correlations between mean LJD (atrophy) and mean *tanh*(GA) for each DGM structures with EDSS for all MS subjects. Among all the DGM structures, atrophy of thalamus and the shape change in putamen were highly correlated with EDSS. The atrophy of hippocampus and amygdala were not correlated with EDSS, however the shape changes in these structures showed moderate correlation with EDSS.

Table 1. The correlation (r, p) between MLJD and mean *tanh(GA)* of deep gray matter (GM) structures with EDSS.

DGM Structures	MLJD with EDSS	Mean *tanh(GA)* with EDSS
Thalamus	-0.51, 3.85×10^{-7}	0.36, 4.87×10^{-4}
Caudate Nucleus	-0.43, 2.35×10^{-5}	0.40, 1.11×10^{-4}
Putamen	-0.36, 6.12×10^{-4}	0.46, 6.00×10^{-6}
Septal Nuclei	-0.39, 1.75×10^{-4}	0.38, 2.47×10^{-4}
Red Nucleus	-0.30, 4.55×10^{-3}	0.25, 1.48×10^{-2}
Hippocampus	---	0.26, 1.31×10^{-2}
Amygdala	---	0.32, 2.22×10^{-3}

Conclusions:

Tensor based morphometry (TBM) was applied to determine the atrophy and shape changes of deep gray matter (DGM) structures in 88 relapsing remitting multiple sclerosis (RRMS) patients. Significant correlations of atrophy and shape change with EDSS were observed for various DGM structures. These studies suggest the importance of both atrophy and shape changes of DGM in MS.

Acknowledgment: This work was supported by the NIH Grant EB002095.

References: [1] Marcus et al., J. of Cognitive Neuroscience 19: 1498-1507, 2007; [2] Tao et al., IEEE EMBS 3957-3960,2008; [3] Hua et al., NeuroImage 41: 19-34, 2008; [4] Lepore et al., IEEE Trans. Med. Imag. 27: 129-141, 2008.