A Diffusion Tensor Imaging Surrogate Marker of Brain Atrophy in Multiple Sclerosis

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Introduction: Magnetic resonance imaging methods offer a host of noninvasive biomarkers to assess neurodegeneration in multiple sclerosis. Brain parenchymal fraction (BPF) is a commonly used index to quantify disease progression and efficacy of therapeutic intervention [**1-8**]. The brain parenchyma is also known to decrease with natural aging **[9-10],** and hence use of such measures may be confounded with age-related trends. Generally BPF is determined based on tissue segmentation using high resolution anatomical MRI or multi-modal MRI. An alternative of determining the BPF is to exploit the inherently high contrast between gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) in diffusion tensor imaging (DTI). In this report we used a validated DTI-based method [**11-14**] to determine BPF on a cohort of relapsing-remitting (RRMS) patients and healthy adult controls. We demonstrate the utility of this approach in providing correlation with the expanded disability status score (EDSS) and disease duration (DD).

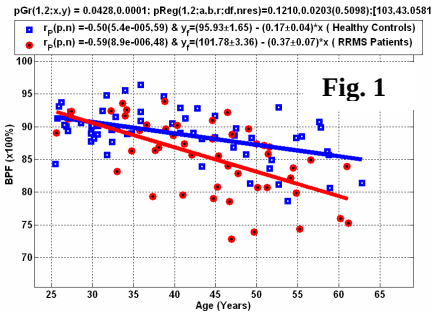
Methods: *Subjects*: We included a total of 59 healthy adult controls (24 men/35 women) and 48 RRMS patients (***Table 1*** **&** Table 2). All subjects provided informed consent *Conventional and DT-MRI Acquisition*: MRI studies were performed on a 3T Philips Intera scanner with a dual quasar gradient system and an eight channel SENSE-compatible head coil. The MRI protocol included dual-echo FSE (TE_1/TE_2/TR= 11/90/6800), fluid-attenuated inversion recovery (FLAIR; TE/TI/TR=80/2500/80). The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme **[7],** b=1000 sec mm^{-2}, T_R/T_E = 6100/84 msec. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; square field-of-view = 240x240 mm^2. The number of b~0 magnitude image averages was 8; in addition each diffusion encoding was repeated twice and magnitude averaged to enhance the signal-to-noise ratio. The total DTI acquisition time was approximately 7 minutes [**13-14**].

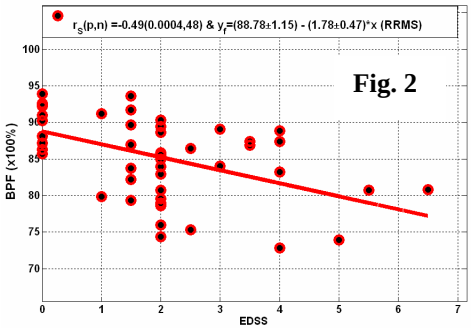
Data Processing: Diffusion-weighted data were distortion corrected using the mutual information maximization approach. All data sets were masked to remove non-brain tissues and the intracranial volume (**ICV** = ***WM+GM+Lesion Volume***+*CSF*=***BPV***+*CSF*) was computed. The DTI-based segmentation approach starts with a training region-of-interest set obtained from all tissue types in controls and MS patients to identify the DTI-thresholds for the segmentation. The thresholds are further optimized by using the distribution of all voxels corresponding to the identified compartments (normally appearing white and gray matter, CSF, lesion type and flow) **[11,13].** BPF was computed using the DTI-estimated CSF volume as ***BPF = 1-CSFV/ICV***. Correlations between age, BPF, EDSS, DD and DTI-derived metrics were computed using the Pearson correlation or Spearman coefficients. Slopes and rates of change were compared using multivariate analysis.

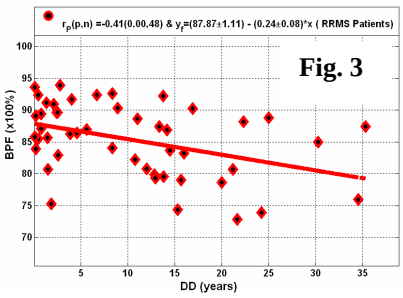
Table1 Healthy Controls	**Men**	**Women**	**All**	**M. vs. W (p)**	**Test**
N	24	35	59	0.0002	Chi^2
Age (years) mean ± sd [Min-Max]Med	40.0±10.8 25.9-58.9 35.4	40.2±11.0 25.5-62.8 39.7	40.1±10.8 25.5-62.8 38.7	0.96	t-test

Table 2 RRMS	**Men**	**Women**	**All**	**M vs. W (p)**	**Test**
N	11	37	48	0.0002	Chi^2
Age (years) mean ± sd [Min-Max], Med	45.1±9.1 25.6-61.2 46.5	43.8±9.0 27.1-61.0 44.6	42.7±9.9 21.9-61.2 45.0	0.67	t-test
DD (years) mean ± sd [Min-Max],Med	7.9±8.2 0.2-22.3 2.6	11.1±9.9 0.1-35.3 11.0	10.4±9.6 0.1-35.3 8.6	0.34	t-test
EDSS (m ± s) [Min-Max] Median	2.3 ±1.3 0.0-5.5 2.0	1.8±1.6 0-6.5 1.9	2.0±1.6 0.0-6.5 2.0	0.60	Mann-Whitney

Results: **Fig. 1** plots BPF as function of age for the RRMS and health control groups. Note the steady decrease in BPF with age in both controls and RRMS. BPF in the RRMS group is significantly smaller than that of controls (p=0.0001). Although the slope of decrease of the BPF in RRMS with age is steeper than that in the controls they were not significantly different (p=0.5) (possibly a reflection of the relatively small sample sizes). **Fig. 2** shows a strong and significant correlation between BPF and EDSS (r=-0.49; p=0.004). **Fig. 3** demonstrates a strong correlation of BPF with disease duration in the RRMS group (r=-0.41; p<0.001).







Discussion: This is the first report on the use of DTI-based quantitative contrast methods to estimate and relate the whole brain parenchymal fraction in both controls and multiple sclerosis patients (**Fig. 1**). Our results on the reduction of BPF with age in both controls **[4-10**] and RRMS **[1-8]** are consistent with documented trends [**1-10, 14**]. DTI exam can be accomplished under 7 minutes and provides both microstructural scalar and vectorial metrics to assess the tissue microstructural integrity. In this work we have extended the utility of quantitative DTI methods to provide macrostructural (volumetry) in addition to morphological information (tissue coherence, anisotropy and connectivity). The approach adopted here utilizes the intrinsic contrast of CSF **[11-13]** using diffusion-based quantitative methods as described recently **[13]** and applied in a lifespan study on normative brain tissue development and aging **[14]**. Since all DTI-derived metrics are coaligned, no additional registration or inhomogeniety correction steps are needed **[11-14]**. The volume loss in normal aging has been attributed to neuronal and white matter degeneration [**9-10**]. In the RRMS population additional neurodegenerative mechanisms such as neuronal loss in gray matter, white matter demyelination and Wallerian degeneration due to axonal damage would accelerate the natural loss of tissue. Future studies may combine regional metrics of DTI connectivity to model the contributors to tissue degeneration. Our studies also highlight the importance of having a normative aging baseline for the interpretation of the patterns detected in RRMS.

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