Atlas-based Quantification of Brain Normal-Appearing White and Gray Matter Volume, Relaxation Time and Diffusion Tensor Metrics in Multiple Sclerosis

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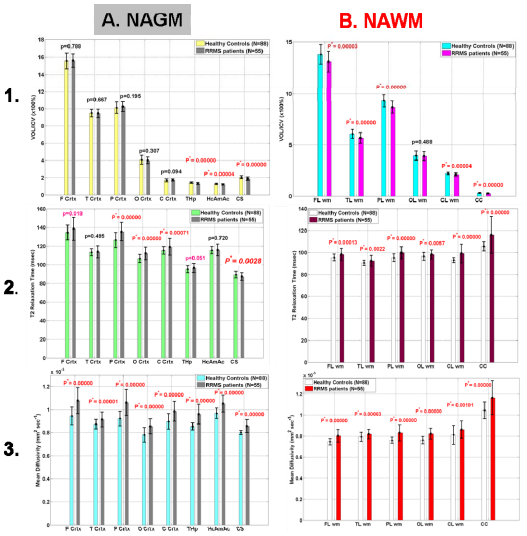
Introduction: Magnetic resonance imaging (MRI) methods offer a host of noninvasive biomarkers to assess neurodegeneration in multiple sclerosis (MS). These include tissue macrostructure or volume and corresponding microstructural attributes such as relaxation, mean diffusivity and anisotropy **[1,2].** Due to the presence of lesions, multimodal MRI volume data are usually coaligned and used to segment normal-appearing white matter (NAWM) and normal-appearing gray matter (NAGM) **[3].** There have been a plethora of reports using whole brain or regional metrics combined with voxel-based and fiber tracking approaches **[1].** To date there has been no comprehensive report of the application of brain atlas quantitative methods on both regional NAWM and NAGM in the MS brain relative to healthy controls. We used lesion spatial mapping **[4-6]** and **FreeSurfer** volumetry **[7]** in combination with relaxation and diffusion tensor imaging methods **[2, 5]** to obtain regional attributes of both NAWM and NAGM in a cohort of relapsing and remitting (RRMS) patients and healthy adult controls. We demonstrate the utility of this approach by showing strong correlations of regional metrics with the expanded disability status score (EDSS).

Methods: *Subjects*: We included a total of 88 healthy adult controls (41 men and 47 age-matched women; age = 37.9±10.1; range = 22.7-61.8 years) and 55 RRMS patients (15 men and 40 women; age = 41.1±10.7; range = 22.9-60.8 yrs), disease duration = 10.7±9.1 (range = 0.1-31.4 years), EDSS=1.7±1.5 (range=0-6.5) and total lesion load 0.8-44.3 mL. *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 T1-weighted 3D-SPGR with isotropic voxel size = 0.9375 mm for tissue volumetry, dual fast spin echo (DSE;TE_1/TE_2/TR= 11/90/6800), and fluid-attenuated inversion recovery (FLAIR; TE/TI/TR=80/2500/80) sequences. The DTI data was acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme [2], 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 and a square field-of-view=240 mm. *Data Processing*: All MRI data sets were masked to remove non-brain tissues and the intracranial volume (ICV) was computed to reduce the effects of gender and brain size in volume comparisons **[2].** Lesions were segmented using the DSE and FLAIR data as described elsewhere **[3].** Lesions were spatially normalized to a standard brain atlas as described elsewhere **[4, 5]**. The T2 transverse relaxation time (T2) and proton density (PD) maps were obtained from the dual echo sequence **[2].** Tissue volumes were obtained by the application of FreeSurfer on the T1-weighted volume **[6,7].** The DTI analysis pipeline provided fractional anisotropy (FA), axial, radial and mean diffusivity maps, respectively (D_{av}, LT, LA). All volumes (Lesion, T2, PD, FA, D_{av}, LT, LA) were registered with T1-wighted data where regions are labeled using the FreeSurfer atlas [**6, 7**]. The **FreeSurfer** brain volumes *demodulated by the lesion masks* were used to obtain the regional average values for all atlas labels. The brain atlas covered the frontal, temporal, parietal, occipital and cingulate cortices and corresponding white matter. In addition, FreeSurfer provided deep subcortical structures such as thalamus proper (THp), corpus striatum (CS = caudate, putamen, globus pallidus), and the hippocampus, amygdale and accumbens (HC/Am/Ac). The NAWM of the corpus callosum (CC) was also included. The cerebellum, brain stem and insula were excluded. Correlations between age, EDSS, DD and regional metrics (ICV-normalized volumetry, T2, FA, D_{av}) were computed using the Pearson correlation or Spearman coefficients. Here we only report group comparisons between all healthy controls and RRMS patients in addition to correlations of the RRMS data with EDSS (significant $p < 0.05$).

Results: The absolute **NAGM** and **NAWM** volumes and age curves were compared between **RRMS** and controls. As expected, regional volumes were larger in men than women ($p<0.001$) and all volumetry results were normalized by ICV. The effects of group were much larger than those due to side and gender; hence all bilateral microstructural metrics were volume-averaged. **Figure 1** compares ICV-normalized volumetry and corresponding T2 and D_{av} between the two groups. Note that D_{av} is significantly larger in all **NAWM** and **NAGM** in **RRMS** compared to controls. The T2 relaxation is larger in all **NAWM** *regions and most* ***NAGM*** regions *except the corpus striatum* where *T2 is reduced* in RRMS. Group analysis of LT and LA diffusivities (*data not shown*) indicated that these metrics are also elevated in RRMS. The correlation of EDSS with all regional brain metrics are summarized in the **Table**.

55 RRMS	VOLp		T2		FA		D_{av}		LT		LA	
Corr. With EDSS	r	p	r	p	r	p	r	p	r	p	r	p
THp	-0.238	0.083	**0.295**	**0.03**	-0.048	0.73	0.151	0.276	0.12	0.388	0.114	0.411
HcAmAc	-0.061	0.661	**0.4**	**0.003**	**-0.35**	**0.01**	0.229	0.096	0.253	0.065	0.107	0.441
CS	-0.228	0.097	0.123	0.377	-0.045	0.747	0.174	0.209	0.203	0.141	0.112	0.422
Frontal Lobe gm	0.211	0.125	**0.286**	**0.036**	-0.21	0.127	**0.38**	**0.005**	**0.401**	**0.003**	**0.367**	**0.006**
TL gm	-0.025	0.859	**0.344**	**0.011**	-0.136	0.325	**0.425**	**0.001**	**0.411**	**0.002**	**0.416**	**0.002**
PL gm	0.111	0.425	**0.317**	**0.02**	-0.238	0.084	**0.416**	**0.002**	**0.433**	**0.001**	**0.384**	**0.004**
OL gm	0.058	0.677	**0.342**	**0.011**	**-0.313**	**0.021**	0.106	0.447	0.152	0.271	0.028	0.839
Cing gm	0.057	0.684	**0.453**	**0.001**	-0.141	0.308	**0.481**	**0.0001**	**0.468**	**0.0001**	**0.477**	**0.0001**
Frontal Lobe wm	**-0.314**	**0.021**	**0.379**	**0.005**	-0.069	0.618	0.171	0.215	0.14	0.314	0.23	0.094
TL wm	**-0.363**	**0.007**	**0.338**	**0.012**	-0.216	0.117	**0.277**	**0.043**	0.264	0.054	0.231	0.093
PL wm	**-0.335**	**0.013**	**0.27**	**0.048**	-0.156	0.26	0.137	0.323	0.141	0.309	0.121	0.382
OL wm	-0.184	0.182	**0.301**	**0.027**	**-0.369**	**0.006**	0.197	0.154	0.257	0.061	0.071	0.612
Cing wm	**-0.413**	**0.002**	**0.434**	**0.001**	-0.236	0.086	**0.438**	**0.001**	**0.404**	**0.002**	**0.396**	**0.003**
CC	**-0.505**	**0.0001**	**0.433**	**0.001**	-0.199	0.148	**0.446**	**0.001**	**0.382**	**0.004**	**0.492**	**0.0001**

CC= Corpus Callosum; **Cing** = Cingulate; **CS**= Corpus Striatum (Putamen, Caudate and Globus Pallidus); **HcAmAc**=Hippocampus, Amygdala and Accumbens; THp=Thalamus Proper. D_{av} = Mean Diffusivity; LT= Radial Diffusivity. LA= Axial Diffusivity



Discussion: To the best of our knowledge**,** this is the first qMRI report of atlas-based regional tissue volumetry and corresponding microstructural attributes such as T2 relaxometry, diffusivity and anisotropy in a large cohort of RRMS patients and controls. The analysis pipeline adopted in this work **[2,5,6]** used validated methods such as **FreeSurfer** volumetry in combination with lesion mapping methods after careful fusion with FLAIR, dual echo and DTI maps to localize lesions and quantify T2 relaxation and diffusion metrics **[6].** Our volumetry results on the atrophic RRMS brain consolidate published literature to-date **[1]** that showed patterns of regional tissue loss or thinning in both cortical **[8],** subcortical gray **[2,9]** and white matter **[8,9]** using different qMRI methods (e.g. voxel based, whole brain, and tractography) **[1,12,13].** Our results on elevated T2 in NAWM are consistent with a recent work **[13].** Our results of reduced T2 in the corpus striatum are consistent with several reports **[2].** The reduction in T2 relaxation in the corpus striatum and not any other gray matter may be attributed to iron accumulation or impaired mechanisms to intake iron into the tissue. Our data show that the cingulate cortex and corresponding white matter correlated strongly with the EDSS (see **Table**). The elevated D_{av} in all **NAWM** and **NAGM** regions indicate the utility and sensitivity of this simple metric to detect tissue disorganization as a result of demyelination and axonal loss. Our data indicate that MS pathology may be propagated through systemic means *in addition* to lesion load, activity and proximity to normal tissue.

References: **[1]** Filippi M, Agosta F. JMRI 2010;31:770-88 **[2]** Hasan KM et al. JMRI. 2009;29:70-7 **[3]** Sajja BR et al. Ann Biomed Eng 2006;34:142–51 **[4]** Zijdenbos AP et al. IEEE TMI. 2002;21:1280-91 **[5]** Hasan KM et al. MRM 2010;64:1382-89**. [6]** Walimu IS et al. Comp Biol. Med 2011 (*in press*) **[7]** Fischl B et al. Neuron. 2002;33:341-55**. [8]** Sailer M et al. Brain 2003;126:1734–44 **[9]** Tao G et al. J. N Sci. 2009;282:39-46. **[10]** Benedict RH et al. JNNP. 2009;80:201-6. **[11]** Roosendaal SD et al. Neuroimage 2009;44:1397-403 **[12]** Ceccarelli A et al. J Neurol. 2007;254:513-8. **[13]** Neema M et al. Neuroimage. 2009;46:633-41.