Caudate Nuclei Degeneration in Multiple Sclerosis: A Multi-Modal Quantitative MRI Approach

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Introduction: The human caudate nuclei (CN) are important deep subcortical basal structures that are involved in fine motor and cognitive functions. The caudate nuclei volume (CNV) loss is considered to be a marker of gray matter atrophy in both natural aging and disease **[1].** The CNV has been reported to be smaller in multiple sclerosis (MS) patients compared to age-matched healthy controls **[2]**. The caudate atrophy has been associated with fatigue, cognitive and emotional dysfunction in MS **[3-5]**. The normalized CN hypointensity has been correlated with disability and hypothesized to be related to the accumulation of non-heme iron [**2**]. The caudate atrophy has also been correlated with global lesion load **[4,5]**. Diffusion tensor imaging (DTI) reports on the caudate in MS are scant; there is only one report on paradoxical increase in fractional anisotropy (FA) compared to controls **[6]**. We hypothesized that concomitant measurement of the intrinsic T_2 relaxation time and DTI-derived metrics along with CNV would provide important clues to understanding the pathogenesis of MS. In this report we used DTI at 3T combined with T_2 relaxation measurements along with caudate volumes on both age and gender-matched adult controls and relapsing-remitting (RRMS) patients to investigate the interplay between CNV, DTI metrics, T_2, age, disease duration (DD), and disability (EDSS) in order to explore the microstructural contributors that lead to the normal-appearing caudate "macrostructural" atrophy.

Methods: *Subjects*: We included a total of 34 **healthy adult controls** (13 men & 21 women; age = 37.7±11.2 years {mean ± SD}) and 32 age and gender - matched **RRMS patients** (8 men & 24 women; see **Table 1**). *Conventional and DT- MRI Acquisition*: All 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), FLAIR (TE/TI/TR=80/2500/80), dual inversion recovery sequence for suppressing CSF and WM ($TE/T_{I1}/T_{I2}$/TR= 32/325/3400/15,000 msec) **[7-8].** The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme **[1],** 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; FOV=24x24 cm^2. The number of b=0 images was 8; in addition each diffusion encoding was repeated twice and magnitude averaged **[1]**.

Data Processing: The entire normal-appearing caudate nuclei were delineated manually using the double IR (see **Fig. 1**) volumes after coregistration with the maps of computed T_2 and DTI-derived metrics (see **Fig. 1**; details are provided in **1]**. Correlations between CNV, age, EDSS, DD and DTI-derived metrics were computed using Spearman and Pearson coefficients. Group means, slopes and rates of change were compared using multivariate analysis.

Table 1 RRMS	Men	Women	M & W	M. vs. W (p)	Test
Number of Patients	8	24	32	0.005	Chi^2
Age (years) mean ± sd [Min-Max], Med	43.0±8.8 25.6-51.3 46.2	41.1±9.0 21.9-56.6 41.6	41.6±8.9 21.9-56.6 43.3	0.61	t-test
DD (years) mean ± sd [Min-Max],Med	7.7±9.0 0.2-22.3 2.5	9.4±9.1 0.1-30.3 8.8	9.0±9.0 0.1-35.3 5.3	0.65	t-test
EDSS (mean±sd) [Min-Max] Median	2.2 ±1.6 0.0-5.5 2.0	1.8±1.8 0-6.5 1.9	1.9±1.7 0.0-6.5 2.0	0.79	Mann-Whitney

Fig 1.

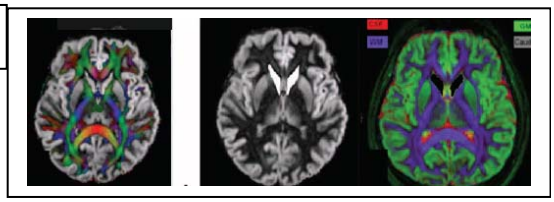
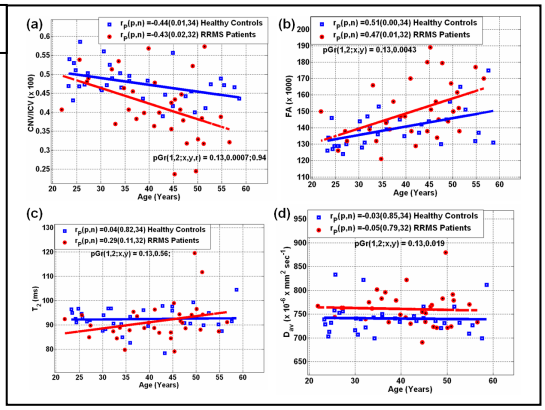


Fig 2.



Results: **Figure 2** shows the scatter plots of age vs. (a) CNV-to-ICV percentage (*CNVp*) **(b)** FA **(c)** T2 (ms), and **(d)** average diffusivity (D_{av}) for both the **healthy controls** and **RRMS** patients. Note the decrease in *CNVp* and increase in FA with age in both controls and MS. The T_2 did not show significant correlations with age, while FA, and D_{av} are significantly larger in RRMS compared to age-matched controls. In the RRMS group, there were moderate to strong correlations of entire caudate metrics and clinical scores: r(*CNVp*, DD) = -0.50 (p=0.004); r(*CNVp*, EDSS) = -0.27 (p=0.13); r(FA,DD) = 0.47 (p=0.007); r(FA,EDSS) = 0.26 (p=0.15); r(T_2,DD) = 0.42 (p=0.02) and r(T_2, EDSS) = 0.51 (p=0.003) (Data not shown). There were no significant correlations between the mean diffusivity, DD and EDSS (r<0.05; p>0.8).

Discussion: This is the first study using reasonably sized cohorts of age-matched adult controls and RRMS that reports simultaneous measurements of the caudate volume and its intrinsic MRI metrics (T_2, D_{av}, & *FA*). The decrease in CNV and its fraction relative to the intracranial volume is consistent with earlier reports on the naturally aging healthy controls that documented both cortical and subcortical gray matter loss [**1,9,10**]. The increase of caudate FA with age is consistent with previous reports on controls [see **1** for more details]. Our results show significantly smaller *CNVp* in RRMS compared to healthy controls and confirm a previous quantitative report **[2]**. The elevated FA in the entire caudate duplicates the observations in a previous DTI-ROI study which did not report elevated mean diffusivity in RRMS [**6**]. Our results (**Figure 2.c**) show that T_2 values are not age-dependent in both controls and RRMS. The T_2 mean values were not significantly different between controls and MS in the normally-appearing CN. The elevated FA values are not explained by reduced signal-to-noise ratio (SNR) with age. CSF contamination, although not likely due to careful delineation of CN, would have increase T_2, mean diffusivity and would have resulted in reduced FA. The increase in FA with age along with stable T_2 measurements rule out DTI-SNR estimation biases. The rather insignificant T_2 values between RRMS and controls do not support the "direct" iron accumulation hypothesis to explain caudate atrophy **[2]**. The interpretation of in vivo DTI and T_2 measurements in gray matter remain to be a challenging endeavor in MRI which continues to benefit from advances in comparative histopathological and animal studies **[11].** Our results on the elevated FA and mean diffusivity in the normal-appearing caudate may be attributed to dendrite transaction which would decrease volume and increase diffusion coherence as a result of reduced barriers to diffusion [**1, 6**, **12-14**]. Our preliminary results may provide useful quantitative radiological markers of the neuronal substrates of multiple sclerosis disease.

References

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