DTI, T2 relaxation and Volumetry of the Human Brain Corpus Striatum across the Lifespan

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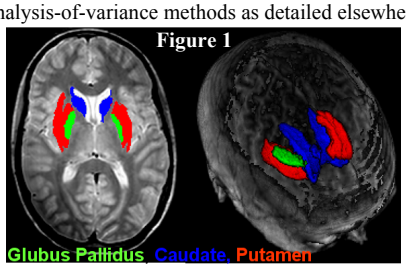
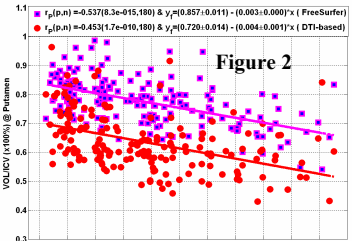
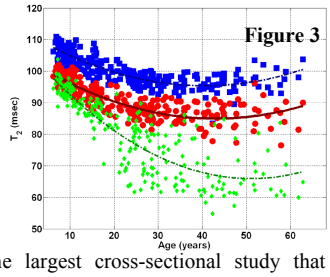
Introduction: The human brain corpus striatum (CS) is composed of the caudate nucleus (CN), putamen (PUT) and globus pallidus (GP) which are three interconnected structures of the basal ganglia. These three structures are involved in several aspects of human cognition and behavior (**1**). The degeneration CS has been associated with natural aging (**2**), and several pathologies. In addition, the abnormal morphometry of these structures has been used as a marker of several acquired, psychiatric, therapy, and neurodevelopmental conditions. The neuronal mass, dendritic architecture and connectivity of these structures have also been shown to decrease using histological assessment due to natural aging (**3**). Since these structures are also known to contain different iron levels (**4**), they have been used in MRI literature as benchmarks to model the interplay between MRI intrinsic parameters such as T2 relaxation and diffusion tensor metrics (**5, 6**). In this work, we report for the first time using brain atlas-based volumetric methods a comprehensive account of the macro and microstructure of CS on a large healthy cohort across the lifespan.

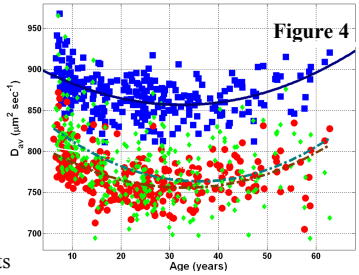
Methods: The participants included 281 healthy children, adolescents, young and older adults aged 6-63 years. The cohort consisted of 147 males (age mean ± S.D = 31.2 ± 11.5 years), and 134 females (age mean ± S.D = 34.8 ± 11.7 years). All volunteers were identified as neurologically normal by review of medical history and were medically stable at the time of the assessments. Written informed consent was obtained from the adults, guardians and adolescents and assent from the children participating in these studies. *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 fast dual-echo ($TE_1/TE_2/TR$= 9/90/6800) for transverse or T2 relaxation mapping and a high resolution (voxel size 0.9375 mm) 3D axially acquired T1-weighted spoiled gradient sequence. The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence, b=1000 sec mm^{-2}, T_R/T_E = 6100/84 msec **(5)**. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; FOV=240x240 mm^2 and matching the dual echo sequence. The number of b=0 images was 8; in addition each diffusion encoding was repeated twice and magnitude averaged to enhance signal-to-noise ratio. Tissue Volume was estimated (**Fig. 1**) using a novel brain atlas and DTI-based tissue segmentation approach (**7**). The DTI-based method for volume estimation was also compared with FreeSurfer applied on the 3D T1-weighted volumes (**8**). *Data Processing and Statistical Analyses*: The intracranial-volume (ICV) normalized volumes, and corresponding T2 relaxation and DTI metrics (e.g., fractional anisotropy = FA; radial diffusivity = $\lambda_\perp$; axial diffusivity = $\lambda_\parallel$) were computed **(5)** and modeled for both males and females as $y_f=\beta_0+\beta_1*age+\beta_2*age^2$, then the general least-squares were used to compute the coefficients, standard errors and their significance using analysis-of-variance methods as detailed elsewhere **(9)**.



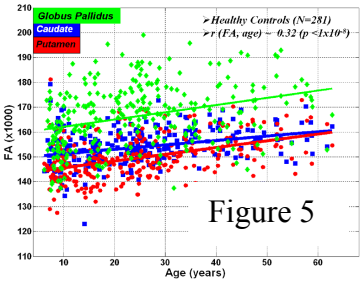


Results: To demonstrate the validity of the segmentation approach used in this work to obtain estimates of volume, T2 and DTI metrics, we plotted the normalized volume age trajectories obtained using both the DTI method and FreeSurfer on a subset of 180 controls. Both DTI and **FreeSurfer** predicted a side and gender-independent loss of caudate, putamen and globus pallidus volume (see **Fig 2** for the **putamen**). The lifespan mean T2, Mean diffusivity and FA trajectories for the **CN**, **PUT** and **GP** are shown in Figure 3, 4 and 5, respectively. Note the linear age-dependence and the statistically significant ($p<0.001$) anisotropy spatial heterogeneity trend FA(GP) > FA(CN) > FA(PUT). Note also that T2 (CN) > T2(PUT) > T2 (GP) at all ages. The mean diffusivity and T2 relaxation follow quadratic curves across the lifespan. The peak at minimum mean diffusivity is attained ~ 33 years, whereas the T2 relaxation minimum is attained at ~ 43 years reflecting that diffusion and relaxation mechanisms may have unique neuronal mechanisms **(10)**.





Discussion: To the best of our knowledge, this is the largest cross-sectional study that reports simultaneous measurements of volume, and corresponding T2 relaxation and DTI metrics to elucidate the interplay between MRI macro and microstructural attributes of deep basal tissue. We used validated atlas-based T1w, DTI, and T2w methods for tissue segmentation. The steady decrease in CN, PUT and GP volume with age is consistent with histological (**3**). Our results on the volume loss are also consistent with MRI-volumetry studies that reported subcortical and frontostriatal connectivity loss (**2**, **11**, **12**), but some inconsistencies need to be noted in published literatures (**13**).



The loss in **CN**, **PUT** and **GP** volume may relate to the degradation in cognitive and motor skills in healthy aging (**5, 11**). The decrease in T2 with age has been attributed to iron accumulation (**4, 5, 14**). The rise in T2 in the mid forties seems to reduce the sensitivity and specificity of this metric to iron as a result of increased extracellular water **(10)**. This hypothesis is substantiated by the observed commensurate increase in mean diffusivity (**10**) which seems to be earlier and more sensitive predictor tissue integrity than T2. Our observation of steady increase in caudate and putamen FA across the lifespan is consistent with previous reports (**6, 15, 16, 17**). The increase in FA may not be explained by partial volume averaging as an increase in mean diffusivity due to CSF (e.g. ventricular enlargement) would have decreased FA. Note that iron accumulation may not be the main contributor to the increase in FA as putaminal iron concentration is expected to be larger than that in CN (**4**). The increase in anisotropy may be a result of the loss of dendrites and connections between these structures, frontal lobe, thalamus and deeper structures such as the substantia nigra (**6**). Our work shows that these deep gray matter and iron rich structures may be used as benchmarks or surrogate neuroimaging markers to test and model the neuronal contributors to tissue volume loss in both health and disease.

References

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