Quantification of the Healthy Human Uncinate Fasciculus across the Lifespan using Diffusion Tensor Tractography

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Introduction: The human uncinate fasciculus (UF) is the largest cortico-cortical white matter pathway that connects *directly* the frontal and temporal lobes (**1, 2, 3**). The UF has been used in noninvasive magnetic resonance imaging (MRI) studies as a marker of tissue integrity in health (**4, 5**) and disease (**6-10**). There is no MRI literature on the normative UF volume and corresponding diffusion tensor imaging (DTI) metrics and their interplay with covariates such as age, gender and lateralization *across the human lifespan*. In this work, we examined using DT fiber tractography the UF volume and normalized volume with respect to each subject's intracranial volume (ICV) and the corresponding DTI metrics bilaterally on a cohort of *108 right-handed children and adults aged 7-68 years*. Our results provide the normative age, gender and laterality baseline to help in the interpretation of data from patients. Our DTI results on the development and aging of the UF consolidate previous normative studies that reported linear age trends on children and adults.

Methods: *Subjects***:** We included a total of 39 healthy right-handed children (21 boys, 21 girls, age range = 7-19 years) and 69 adults (26 men, 43 women, age range 20-68)**.** There were no group mean age differences between boys/girls (p=0.40), men/women (p=0.96) and males/females (p=0.24) in the entire population**.**

*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 ($TE_1/TE_2/TR$= 11/90/6800). The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme **(4, 11),** 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=240x240 mm^2. 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. *Data Processing and Statistical Analyses***:** The uncinate fasciculus was tracked in DTIstudio (**12**) as detailed elsewhere (**4, 8, 12, 13**; see **Fig. 1**). The DTI metrics (e.g., fractional anisotropy = FA; radial diffusivity = $\lambda_\perp$= LT; axial diffusivity = $\lambda_\parallel$ = L1) were 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 (**11, 14**). Interactions of sex with age (both terms) were examined, and trimmed where non-significant. If the quadratic age term was not significant, age and sex interactions were examined without this term, and trimmed if non-significant. All statistical analyses were conducted using SAS 9.1 and MATLAB R12.1 Statistical Toolbox v 3.0

Results: The intracranial volume and right UF volume (UFV) were larger in males compared to females (p<0.005). The UF volume-to-ICV percentage (UFV/ICVx100%) was not significantly different between males and females (p>0.14). There were no significant differences in DTI group mean values of the UF between males and females bilaterally. Therefore, results below reflect the group of *pooled males and females*. The scatter data, linear and quadratic least-squares fits of the normalized UF volume (**Fig 1A,B**), corresponding FA (**Fig 1C,D**), radial (**Fig 2.A,B**) and axial diffusivity (**Fig 2C,D**) are plotted for both right and left UF on children and adults and the entire population. Note the lack of dependence on age in the normalized UFV between children (p>0.2) and adults (p>0.13). The DTI metrics of the UF show that children have significant linear trends compared to adults which justified the adoption of non-linear quadratic least-squares modeling of the age effects. The age by sex interaction was non-significant. Comparison of linear and quadratic coefficients for both males and females indicated no significant differences between males and females (p>0.3). A significant age by hemisphere interaction was obtained; the absolute and ICV-normalized UF volumes were larger on the right side compared with the left side only in children (p=0.02). Laterality effects were not obtained for adults (p>0.56). The FA of the UF was significantly larger on the left side in children (p=0.05), adults (p=0.0012) and the entire sample (p=0.0002). This strong leftward asymmetry (Left > Right) in the diffusion anisotropy is explained by a leftward asymmetry in the axial diffusivity (p<0.0001), while the radial diffusivity showed no asymmetry (p>0.23).

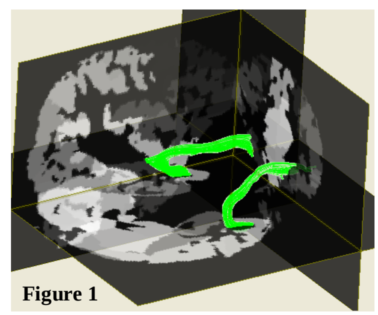

Figure 1

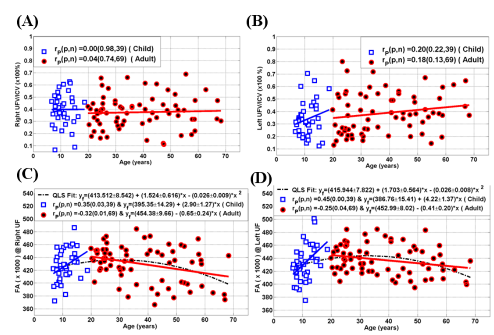

Figure 2

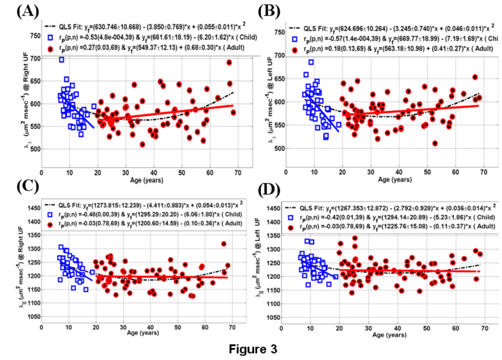

Figure 3

Discussion: The UF has been used as a marker of development, natural aging and disconnection of the temporal and frontal lobes that result from congenital, traumatic, surgical, and degenerative disorders (**1-10**). Quantitative MRI literature on the normative UF is generally scant. This is the first cross-sectional lifespan study on the development and aging of the UF in both hemispheres using DTI fiber tracking methods. We have presented and compared both absolute UF volumes and ICV-normalized values to reduce effects related to human brain size variability **(11).** The fiber-tracked UF volume and its ICV-normalized values exhibited larger scatter compared with the corresponding DTI metrics (Right UF: **Fig 2A** vs. Fig **2C & Left: Fig 2**B vs. Fig **2D**). It is noteworthy that only one **(9)** DTI fiber tracking publications on the UF reported its absolute volume or other specific measurements of the UF tract. Consistent with recent DTI reports on the healthy UF we report no sex differences on the normalized UF volume and corresponding DTI metrics (**5**). Our DTI results reproduce an inconsistently reported UF leftward asymmetry of the diffusion tensor anisotropy in healthy children **(4)** and adults **(5).** This trend has not been reported in other studies **(9)** or was even reversed **(8).** The UF DTI age trajectories resemble those published on whole brain white matter **(11),** regional white matter such as corpus callosum **(14)**, subcortical gray matter **(14)** and lobar volumes (**15**). In our study, the UF diffusion tensor anisotropy leftward asymmetry is more specifically related to a statistically significant leftward asymmetry in the axial diffusivity which could result from a more coherent or less tortuous alignment of fibers **(17, 18)**. Our study shows dissociation between volume-based (macrostructural) asymmetry with DTI-based asymmetry (microstructural).

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