Developmental characterization of sub-cortical white matter tracts

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Background: Neural communication is facilitated by white matter (WM) comprised of both short and long-range tracts[1]. Diffusion Tensor Imaging (DTI) has been used to describe the developmental, age-related changes in *long-range* WM tracts[2]. There remains a limited understanding of these changes in *short-range* WM tracts, or u-fibers. U-fibers are thought to underlie local neural processing and regional cortical network function[3]. Recent investigations have implicated microstructural abnormalities in u-fiber development in Autism spectrum disorder[4] and Schizophrenia[5]. The present study aims to describe typical u-fiber development in healthy children and adolescents using DTI. Establishing a developmental model of age-related change in u-fiber maturation will be of benefit to researchers interested in the connectivity of large-scale neural networks, as well as clinicians interested in the contributions of these networks to neuropsychiatric diseases.

Methods: Thirty-five typically developing children and adolescents were scanned at the Hospital for Sick Children in Toronto (SickKids), British Columbia Children's Hospital in Vancouver (BCCH) and the Alberta Children's Hospital in Calgary (ACH). Seventy-three DTI-MR scans were obtained, with the majority of subjects (86%) receiving two or more chronologically concurrent scans at least a year apart. MR images were acquired at SickKids (n=40) using a GE LX 1.5T MRI scanner with 8 channel head coil (GE Healthcare, Milwaukee, Wis.) and at the BCCH (n=19) and ACH (n=4) using a Siemens 1.5T MRI scanner with 12 channel head coil (Siemens Canada Ltd., Mississauga, On.). Imaging parameters were: 3D-T1 FSPGR gradient echo, inversion recovery prepared sequence (IR time=400 ms; TE/TR=4.2/10.056 ms; 116–124 contiguous axial slices; NEX=1; 256×192 matrix, interpolated to 256×256; FOV=24×24 cm; rbw=162.734 kHz; slice thickness=1.5 mm) and a diffusion-weighted sequence (single shot spin echo DTI sequence with EPI readout: 25–31 directions; b=1000 s/mm2; TE/TR=85.5/15000 ms; 45–50 contiguous axial slices; NEX=1; 128×128 matrix, interpolated to 256×256; FOV=24×24 cm; rbw=1953.12 kHz; slice thickness=3 mm). Probabilistic tractography was used to delineate u-fiber tracts within discrete lobar regions (fig 1). DTI indices were analyzed using growth curve modelling.

Results and Discussion: Growth curve analyses revealed significant age-related change in u-fibers of the frontal (FA: t= 3.172, p<0.01, RD: t= -3.624, p<0.01), parietal (FA: t= 3.252, p<0.01, RD: t= -2.52, p<0.05) and temporal lobes (FA: t= 2.14, p<0.05; RD: t= -3.121, p<0.05). U-fibers did not change significantly in the occipital lobes (FA: t= 1.66, p=0.102; RD: t= -0.874, p=0.421). Increases in FA and decreases in RD are consistent with previous developmental studies that highlight this pattern of white matter change as an index of increasing axonal coherence and improved myelin integrity with age[6]. Furthermore, the significant effects in the parietal and temporal lobes were primarily driven by changes in the left hemisphere (fig 2 & 3); [left parietal lobe (FA: p<0.001, RD: p<0.05), right parietal lobe (FA: p<0.05, RD: p<0.1); left temporal lobe (FA: p<0.01, RD: p<0.05), right temporal lobe (FA: p<0.1, RD: p<0.1)]. These changes are consistent with left hemisphere lateralization during development, and suggest the possible involvement of u-fibers in the development of left-lateralized functions.

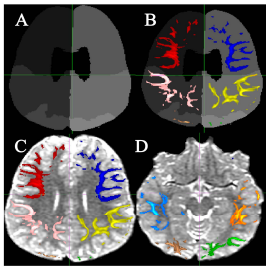

Fig. 1: **A-B**:Intra-lobar white matter reconstruction showing regional masks and white matter. **C-D**:U-fibres represented within individual lobes, frontal (red and blue), temporal (orange and light blue) and parietal areas (pink and yellow)

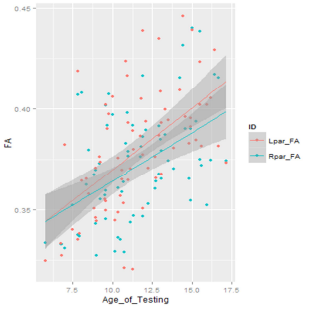

Fig. 2: Significant change in parietal u-fibers driven by changes in the left parietal lobe

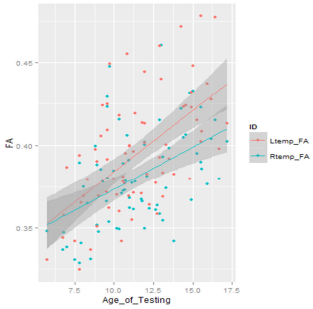

Fig. 3: Significant change in temporal u-fibers driven by changes in the left temporal lobe

Conclusions: To our knowledge, this study is one of the first to clearly elucidate the developmental trajectory of u-fibers in a cohort of normal-developing children and adolescents. Future work will examine the relationship between u-fibers and cognitive measures, as well as investigate the developmental trajectory of u-fibers in pediatric brain tumor populations.

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