Differing Contributions of Whole Brain Fractional Anisotropy, Axon Density and Axon Dispersion to Neurodevelopmental Outcomes of Children Born Very Preterm

Claire E Kelly[1], Deanne K Thompson[1,2], Jian Chen[1,3], Alexander Leemans[4], Christopher L Adamson[1], Terrie E Inder[5], Jeanie LY Cheong[1,6], Lex W Doyle[1,6], and Peter J Anderson[1,7]

[1]Murdoch Childrens Research Institute, Melbourne, VIC, Australia, [2]Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia, [3]Monash University, Melbourne, VIC, Australia, [4]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands, [5]Brigham and Women's Hospital, Boston, MA, United States, [6]Royal Women's Hospital, Melbourne, VIC, Australia, [7]University of Melbourne, Melbourne, VIC, Australia

TARGET AUDIENCE: Researchers involved in applications of magnetic resonance imaging (MRI) methods, pediatric researchers, clinicians.

PURPOSE: Children born very preterm (VPT; <32 weeks' gestation) are at high risk of neurodevelopmental delays in wide-ranging domains compared with their term-born (≥37 weeks' gestation) peers. These delays have been associated with altered brain white matter microstructural health and organization quantified using diffusion tensor imaging (DTI).[1] However, while DTI parameters such as the fractional anisotropy (FA) are highly sensitive to changes in tissue microstructure, they are inherently non-specific, being unable to distinguish between properties such as the density, myelination and spatial layout of axons.[2] Alternatively, Neurite Orientation Dispersion and Density Imaging (NODDI) disentangles two key factors contributing to FA- the axon density and axon orientation dispersion.[3] We have previously found that VPT 7-year-olds have lower FA and more dispersed axons in widespread white matter fiber tracts compared with term-born controls.[4] The current study aimed to determine whether whole brain FA, axon density and axon dispersion are associated with neurodevelopmental outcomes in VPT 7-year-olds. We hypothesized that lower FA in widespread tracts would be associated with poorer neurodevelopmental outcomes, which would be related to increases in axon dispersion and/or decreases in axon density.

METHODS: **Participants:** This study examined 145 VPT children, who were born <30 weeks' gestation and/or <1250 g birthweight and followed up at age 7 years. **Neurodevelopmental assessments:** Domains assessed included: IQ using the Wechsler Abbreviated Scale of Intelligence (WASI); motor skills using the Movement Assessment Battery for Children (MABC-2); academic skills (math computation and reading) using the Wide Range Achievement Test (WRAT4); behavioral and emotional problems using the Strengths and Difficulties Questionnaire (SDQ). **MRI:** All children underwent 3T multi-shell diffusion MRI with echo planar imaging sequences (Shell 1: TR 12000 ms, TE 96 ms, FOV 250 x 250 mm, matrix size 144 x 144, voxel size 1.7 mm^3, 25 non-collinear gradient directions, *b*-values from 50 to 1200 in 50 s/mm^2 increments, one $b= 0$ s/mm^2 volume; Shell 2: TR 7400 ms, TE 106 ms, FOV 240 x 240 mm, matrix size 104 x 104, voxel size 2.3 mm^3, 45 non-collinear gradient directions, $b= 3000$ s/mm^2, six $b= 0$ s/mm^2 volumes). **Image pre-processing:** All diffusion images were motion and eddy current distortion corrected using ExploreDTI version 4.8.2.[5] The DTI model was fitted to shell 1 using the weighted linear least squares algorithm. The NODDI model was fitted to both shells (which were registered and merged together, and normalized by their respective $b= 0$ s/mm^2 volumes to account for their different TEs) using the NODDI matlab toolbox version 0.9.[3] NODDI parameters generated included the orientation dispersion index (axon dispersion) and intra-cellular volume fraction (axon density). **Tract-Based Spatial Statistics (TBSS)**[6]: FA and NODDI images were analyzed using TBSS. All FA images were aligned to 1mm^3 MNI152 standard space using nonlinear registrations; the mean FA image was skeletonized and thresholded (FA>0.2); all aligned FA images were projected onto the mean FA skeleton; the nonlinear registrations were applied to the NODDI images, which were then projected onto the skeleton. **Statistical analysis**: Voxelwise statistical analyses of the projected data were performed using Randomise (a non-parametric permutation based tool).[7] Correlations between whole brain FA, axon density and axon dispersion in VPT 7-year-olds and neurodevelopmental outcomes were investigated separately for each outcome, identifying voxels that correlated at $p<0.05$, adjusted for the family-wise error rate (FWE) and age at MRI. Each statistical test was performed with Threshold-Free Cluster Enhancement (TFCE) and 5000 permutations. Results were localized to white matter tracts using the JHU White Matter Tractography atlas and JHU ICBM-DTI-81 white-matter labels atlas.

RESULTS: **IQ:** Increasing FA within most of the brain's major fiber tracts (including the cerebellar peduncle, cerebral peduncle, corticospinal tract, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, anterior thalamic radiation, external and internal capsules, corpus callosum, forceps major and minor, cingulum, fornix, optic radiation, superior longitudinal fasciculus and corona radiata) correlated with higher full-scale IQ scores in VPT children (encompassing a total of 58176 voxels, Fig. 1A). However, axon density and dispersion did not correlate with full-scale IQ. **Motor skills:** Again, increasing FA within most major tracts correlated with higher (better) MABC-2 total standardized scores (78857 voxels, Fig. 1B). Additionally, decreasing axon dispersion within many of the same tracts correlated with better MABC-2 total standardized scores (23433 voxels, Fig. 1C). **Academic skills:** Increasing FA within widespread tracts correlated with higher (better) math computation scores (52384 voxels, Fig. 1D) and reading scores (22711 voxels, Fig. 1E). Axon density and dispersion did not correlate with math computation or reading scores. **Behavioral/emotional problems:** Increasing FA in most major tracts correlated with lower (better) SDQ total scores (65423 voxels, Fig. 1F). Additionally, increasing axon density within most of the same tracts correlated with better SDQ total scores (38108 voxels, Fig. 1G). Decreasing axon dispersion also correlated with better SDQ total scores, but these correlations were mainly limited to the corpus callosum genu and forceps minor (data not shown).

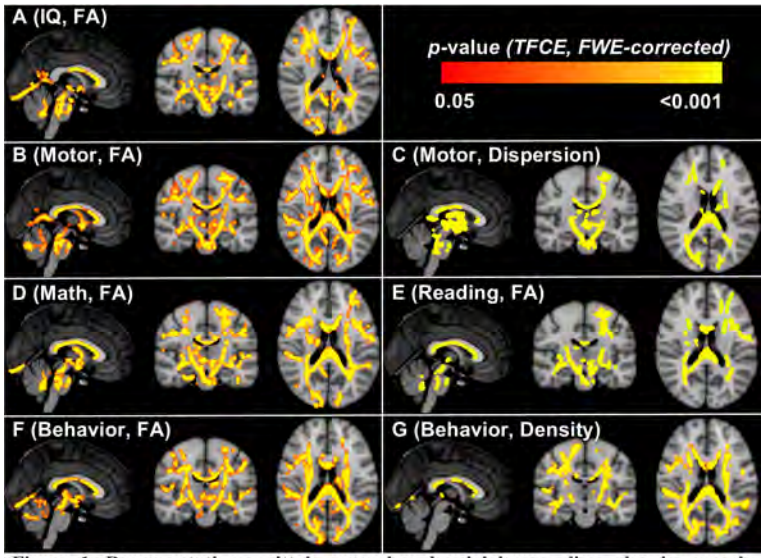

Figure 1. Representative sagittal, coronal and axial image slices showing voxels where FA, axon density or axon dispersion correlated with neurodevelopmental outcomes in VPT children. The *p*-value images (displayed in red-yellow) have been thickened for visualization and overlaid on the MNI T1 image. Only $p<0.05$ are shown. All correlations have been adjusted for the family-wise error rate (FWE) and age at scan.

DISCUSSION AND CONCLUSION: The results using DTI demonstrate that FA in a distributed network of white matter fiber tracts is associated with IQ, motor, academic and behavioural/emotional outcomes in VPT 7-year-olds. Furthermore, NODDI revealed that associations between low FA and motor delay are related to increases in the dispersion of axons, while associations between low FA and behavioural and emotional problems are related to decreases in axon density. This study therefore establishes that NODDI generates important additional parameters that provide increased biological specificity compared with DTI, enabling identification of the particular white matter microstructural changes contributing to neurodevelopmental delays in VPT children.

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