Microstructural development of the corpus callosum ‘catches up’ between term and 7 years in children born <30 weeks’ gestation or <1250 g

Deanne K Thompson[1,2], Loeka Van Bijnen[1], Katherine J Lee[1,3], Alexander Leemans[4], Leona Pascoe[1], Shannon E Scratch[1], Christopher Adamson[1], Gary F Egan[5,6], Lex W Doyle[7], Terrie E Inder[8], and Peter J Anderson[1,3]

[1]*Murdoch Childrens Research Institute, Melbourne, Victoria, Australia,* [2]*Florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia,* [3]*Paediatrics, University of Melbourne, Melbourne, Victoria, Australia,* [4]*Imaging Science Institute, Utrecht, Netherlands,* [5]*Biomedical Imaging, Monash University, Melbourne, Victoria, Australia,* [6]*florey Institute of Neuroscience and Mental Health, Melbourne, Victoria, Australia,* [7]*Royal Women's Hospital, Melbourne, Victoria, Australia,* [8]*Brigham and Women's Hospital, Boston, Massachusettes, United States*

Target audience: Basic research scientists, Neuroscientists, Clinicians (pediatricians, neonatologists), Allied health professionals, Psychologists

Purpose

The corpus callosum (CC) is the largest white matter tract, important for interhemispheric communication of sensory, motor and higher-order information. The CC develops dramatically in the first two years of life, continuing throughout childhood and adolescence[1]. Prematurity provides a model for understanding the development of the human CC. Very preterm (VP) infants are born during a very sensitive time of brain development and therefore suffer increased rates of white matter abnormality and subsequent impairment to cognitive and motor skills compared with term-born children. The VP CC is known to be compromised in infancy[2], but it is unknown whether these differences persist or resolve over time, and whether associations between longitudinal CC development and neuropsychological development exist. Thus, the aims of this study were to determine whether growth and microstructural development from term to 7 years occurs faster or slower in VP children compared with full-term (FT) controls; and to determine associations between the rate of growth and microstructural development from term to 7 years and neurodevelopmental functioning in VP 7 year olds.

Methods

Participants and scanning: VP [gestational age (GA) <30 wks’ and/or birth weight < 1250 g] and FT (37 to 42 weeks’ GA and ≥ 2500 g) infants underwent brain MRI in a 1.5 T GE scanner at term equivalent age (38 to 42 weeks’ GA). T_1 weighted images (0.8-1.6 mm coronal slices; flip angle 45°; repetition time 35ms; echo time 9ms; field of view 21 x 15cm^2; matrix 256 x 192) and linescan diffusion weighted images (4-6 mm axial slices; 2 baselines, b = 5; six non-collinear gradient directions, b = 700 s/mm^2) were acquired. Children were followed-up at age 7 years’ corrected age with T_1 weighted (0.85mm sagittal slices, flip angle = 9°, repetition time = 1900ms, echo time = 2.27ms, field of view = 210 x 210mm, matrix= 256 x 256), and two sets of echo-planar diffusion-weighted images; one with 25 non-collinear gradient directions and *b*-values ranging up to 1200 s/mm^2 (TR= 12000 ms; TE= 96 ms; matrix= 144 x 144; FOV= 250 x 250 mm; isotropic voxel size= 1.7 mm^3), and another with 45 gradient directions and a *b*-value of 3000 s/mm^2 (TR= 7400 ms; TE= 106 ms; matrix= 104 x 104; FOV= 240 x 240 mm; isotropic voxel size= 2.3 mm^3). 92 (76 VP, 16 FT) children had usable MRI data at both time-points (infancy and 7 years).

CC analysis: The CC was traced on the mid-sagittal slice of the structural T_1 scan at term-equivalent (Figure 1a) and 7 years (Figure 1b) and divided into 6 sub-regions (Figure 1c). Diffusion data were corrected for motion and eddy current induced distortions. The diffusion tensor model was fitted (*b*=1200 data for 7 year scans). Axial (AD), radial (RD), and mean diffusivity (MD), and fractional anisotropy (FA) maps were generated for both the infant and 7 year data. The T_1 and diffusion images were aligned to overlay the CC and sub-regions on the diffusion image. At term, probabilistic diffusion tensor tractography was initiated from CC regions using the FSL diffusion toolbox. For the 7 year olds, probabilistic constrained spherical deconvolution tractography was initiated from CC regions using MRTrix software (Figure 1d), and diffusion values were obtained from within the tracts.

Neurodevelopmental assessments: At 7 years corrected age, general intelligence was measured using the Wechsler Abbreviated Scale of Intelligence (WASI). Motor functioning was assessed using the Movement Assessment Battery for Children – version 2 (MABC2).

Statistical analyses: Change over time was measured as ‘7 year CC measure – infant CC measure’. Generalized Estimating Equations (STATA 13) fitted with an exchangeable correlations structure and robust standard errors to allow for correlations between twins/triplets in the study were used to compare change over time in CC measures (tract volume, tract FA, MD, AD, and RD) from term to 7 years between VP and FT, as well as associations between change over time and 7 year outcomes in the VP group. Group-wise differences were adjusted for change in intracranial volume (ICV) from term to 7 years as well as age at MRI (infancy) and time difference between infant and 7 year scan, while associations with outcomes were adjusted for age at assessment and change in ICV from term to 7 years.

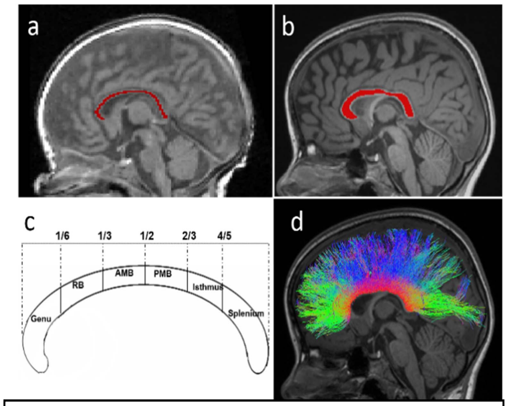

Figure 1. (a) VP infant CC. (b) The same subject’s CC at 7 years. (c) Subdivisions of the CC obtained at term and 7 years. (d) Tractography of the CC at 7 years of age.

Results

CC tract volume: VP children’s whole CC volume increased more than FT children between infancy and 7 years, particularly for the rostral body (RB) (p=0.001) and anterior mid-body (AMB) (p=0.006) regions. *CC tract diffusion measures:* There was similar FA development in VP and FT children over time. There was a much greater reduction in diffusivity measures over time for the VP children compared with FT children in all sub-regions of the CC [Whole CC: MD (p<0.001), AD (p<0.001) and RD (p<0.001)]. *Neurodevelopmental associations:* In the VP children, greater reductions over time in MD (p=0.03), AD (p=0.03) and RD (p=0.04) of the RB were associated with higher IQ scores at age 7 years. Greater reductions in MD (p=0.03) and AD (p=0.03) over time in the RB, were also associated with better motor scores at 7 years. There was little association between changes in CC tract volume or tract FA over time and either the IQ or motor scores.

Discussion

VP CC tracts increased in volume during childhood more than FT CC tracts, particularly for the RB and AMB. The basic structure of the CC is completed by about 18-20 weeks’ GA, and grows from front to back[3]. The apparent ‘catch up’ of VP CC tract volume to that of FT peers may be because growth of the CC is least hindered in anterior sub-regions of VP children. Anterior sub-regions develop earlier than posterior sub-regions, and therefore may not be as vulnerable to the insults associated with VP birth. Diffusivity decreased over time in VP children more than FT children. Lower diffusivity generally reflects changes in white matter fiber diameter or density, myelination or membrane permeability. Diffusivity measures decrease with age and maturation[4], and therefore the normal reduction in MD, AD and RD in white matter during development occurred at a higher rate in the VP CC. These findings suggest that CC white matter tracts appear to undergo compensatory ‘catch-up’ after insults associated with VP birth. Improvements in microstructural development in the RB over time were correlated with better intellectual motor functioning in VP children. The RB connects premotor and sensorimotor hemispheres and is generally thought to be involved in planning and coordination of movement[5].

Conclusion

Over time, the VP CC tracts appear to mature quicker than FT tracts, reflecting ‘catch-up’ via compensatory mechanisms. This suggests that known group differences in infancy may reflect *delay* in the VP CC rather than permanent disruption. Improvements in microstructural development over time were weakly correlated with higher intelligence and better motor functioning in VP children. Future follow-up will reveal whether CC microstructural development continues to catch up in adolescence. This study is the first to report developmental neuroplasticity of the white matter following VP birth, and hence suggests exciting potential for early clinical interventions to improve outcomes following early brain insults.

References.

1.Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, et al. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog Neuropsychopharmacol Biol Psychiatry*. 1999;23(4):571-588. **2**. Thompson DK, Inder TE, Faggian N, Johnston L, Warfield SK, Anderson PJ, et al. Characterization of the corpus callosum in very preterm and full-term infants utilizing MRI. *Neuroimage*. 2011;55(2):479-490. **3**. Ren T, Anderson A, Shen WB, Huang H, Plachez C, Zhang J, et al. Imaging, anatomical, and molecular analysis of callosal formation in the developing human fetal brain. *Anat Rec A Discov Mol Cell Evol Biol*. 2006;288(2):191-204. **4**. Huppi PS, Maier SE, Peled S, Zientara GP, Barnes PD, Jolesz FA, et al. Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatr Res*. 1998;44(4):584-590. **5**. Funnell MG, Corballis PM, Gazzaniga MS. Insights into the functional specificity of the human corpus callosum. *Brain*. 2000;123 (Pt 5):920-926.