Corpus callosum alterations in preterm infants at term predict motor outcomes at 5 years

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Introduction: The brains of very preterm infants (VPT, <30 weeks' gestational age, or <1250 g at birth) are vulnerable to damage, often leading to impaired motor development[1]. Injury to the white matter is the most common cause of brain alterations in prematurity[2]. The largest white matter tract is the corpus callosum (CC), which has an important role in inter-hemispheric communication of sensory, motor and higher-order information. Poor motor performance in VPT children has been associated with a smaller CC[3]. However, to date altered callosal size, connectivity and diffusion characteristics in VPT infants have not been related to later motor outcomes.

Aim: To investigate the association between impaired motor functioning in VPT infants at 5 years of age and CC size, microstructural integrity and inter-hemispheric connectivity as determined by structural and diffusion MRI at term equivalent.

Methods: MRI scans were obtained from a 1.5 T General Electric MRI scanner at term equivalent (38 - 42 weeks) without sedation. Whole brain structural 3-D T1 spoiled gradient recalled images were acquired (1.2mm coronal; flip angle 45°;TR 35ms; TE 9ms; FOV 21 x 15cm^2; matrix 256 x 192). Diffusion images were acquired utilizing the line scan protocol (2 baselines, b=5, b=700s/mm^2; 6 gradient directions, in-plane resolution 0.86mm, axial slices 4-6mm). 106 VPT infants had both T1 and diffusion scans that were of sufficient quality to be analyzed. The CC was traced on the mid-sagittal slice of the T1 (Fig 1a). The CC was divided into 6 sub-regions [genu, rostral body (RB), anterior mid-body (AMB), posterior mid-body (PMB), isthmus, and splenium] based on Witelson's parcellation scheme[4] (Fig 1b), and cross-sectional area of the CC and sub-regions was obtained (corrected for mid-sagittal area of the brain). The T1 images (and consequently the CC and sub-regions) were registered to the diffusion image (Fig 1c). Probabilistic tractography was initiated from the CC region of interest (ROI) using the FSL diffusion toolbox. The fractional anisotropy (FA), mean diffusivity (MD), axial ($\lambda_\parallel$), and radial ($\lambda_\perp$) diffusivity measures were obtained within the CC white matter fibre tracts. Inter-hemispheric connectivity (volume of the normalized and thresholded fibre tracts) was also calculated. The Movement Assessment Battery for Children (MABC) was administered at 5 years corrected age in 89 of the 106 VPT infants, and VPT infants were divided into either impaired motor functioning ($\leq$ 5th centile, n=20) or normal motor functioning (> 5th centile, n=69). Statistical analyses were performed using linear regression analyses within PASW statistics Release 18.0.0.

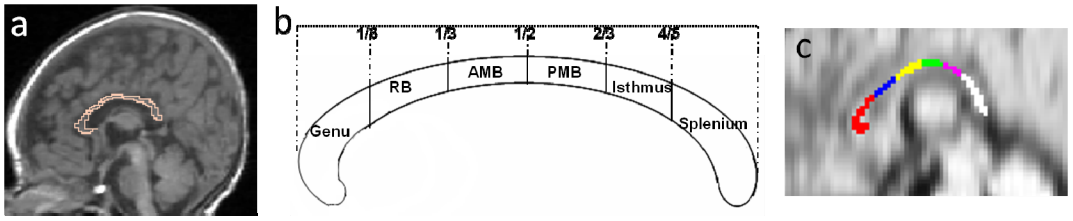

Figure 1: (a) CC traced on mid-sagittal slice of T1. (b) Sub-regional parcellation scheme for the CC. (c) CC sub-regions overlaid on the diffusion image.

Results (Table 1): There were no significant associations between CC mid-sagittal areas and motor outcomes as determined by the MABC at 5 years. In contrast, impaired motor functioning was related to smaller tract volume within the splenium of the CC, but no other callosal sub-regions. Within the callosal tracts, lower FA values were related to motor impairment in the whole CC, PMB, isthmus and splenium. Motor impairment was also associated with higher MD values within the whole CC, genu, PMB, isthmus and splenium. Higher $\lambda_\parallel$ was related to motor impairment in the isthmus and splenium, while higher $\lambda_\perp$ significantly correlated with impaired motor functioning in the whole CC, genu, PMB, isthmus and splenium. The only associations that remained after correcting for the effect of social risk and white matter injury were FA within the isthmus tracts, MD within the PMB, isthmus and splenium, $\lambda_\parallel$ within the splenium, and $\lambda_\perp$ within the PMB, isthmus and splenium.

	Whole CC		genu		RB		AMB		PMB		isthmus		splenium	
CC measure	B(95% CI)	p	B(95% CI)	p	B(95% CI)	p	B(95% CI)	p	B(95% CI)	p	B(95% CI)	p	B(95% CI)	p
Area (mm^2)	-0.004 (-0.01, 0.002)	0.2	-0.01 (-0.03, 0.006)	0.2	-0.03 (-0.09, 0.03)	0.3	-0.02 (-0.07, 0.02)	0.4	0.009 (-0.04, 0.06)	0.7	0.04 (-0.02, 0.09)	0.2	0.009 (-0.01, 0.03)	0.4
Tract volume (mm^3)	-0.02 (-0.04, 0.001)	0.06	-0.03 (-0.06, 0.01)	0.2	-0.03 (-0.08, 0.02)	0.2	-0.04 (-0.11, 0.02)	0.2	0.000 (-0.05, 0.05)	1.0	0.02 (-0.02, 0.07)	0.3	**-0.02 (-0.04, -0.004)**	**0.02**
Tract FA	**-3.8 (-7.1, -0.5)**	**0.03**	-1.1 (-4.4, 2.2)	0.5	-0.2 (-3.2, 2.7)	0.9	-3.4 (-6.8, 0.1)	0.06	**-4.1 (-7.3, -0.9)**	**0.01**	**-4.7 (-8.3, -1.0)**	**0.01***	**-3.5 (-6.6, -0.3)**	**0.03**
Tract MD (x10^{-3}mm^2/s)	**1.4 (0.5, 2.4)**	**0.003**	**0.8 (0.06, 1.6)**	**0.04**	0.5 (-0.05, 1.1)	0.07	0.6 (-0.2, 1.5)	0.1	**1.0 (0.3, 1.7)**	**0.007***	**1.2 (0.5, 2.0)**	**0.001***	**1.4 (0.8, 2.1)**	**<0.0005***
Tract $\lambda_\parallel$ (x10^{-3}mm^2/s)	0.8 (0.004, 1.6)	0.05	0.5 (-0.07, 1.2)	0.08	0.4 (-0.08, 0.8)	0.1	0.3 (-0.3, 0.9)	0.4	0.5 (-0.04, 1.1)	0.07	**0.8 (0.2, 1.4)**	**0.01**	**1.1 (0.5, 1.7)**	**0.001***
Tract $\lambda_\perp$ (x10^{-3}mm^2/s)	**1.6 (0.7, 2.5)**	**0.001**	**0.9 (0.1, 1.8)**	**0.03**	0.6 (-0.04, 1.3)	0.07	0.9 (0.003, 1.9)	0.05	**1.3 (0.5, 2.0)**	**0.002***	**1.5 (0.7, 2.2)**	**<0.0005***	**1.5 (0.8, 2.2)**	**<0.0005***

*Table 1. Associations between motor impairment on the MABC ($\leq$ 5th centile) and CC area, connectivity, and tract diffusion measures (FA, MD, $\lambda_\parallel$, and $\lambda_\perp$) for VPT infants at term equivalent. *Remained significant after correcting for white matter injury and social risk*

Conclusions: Altered callosal microstructure at term equivalent, mainly within the posterior regions, is associated with impaired motor development in 5 year old VPT children. Results indicate that reduced microstructural integrity and delayed or disrupted myelination of callosal tracts are important contributors to impaired motor outcomes related to prematurity. These results extend previous studies that showed that smaller posterior CC size is associated with worse motor performance, both as a result of prematurity[3], and neonatal encephalopathy[5]. This study provides important insights into the etiology of motor dysfunction common to VPT children.

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