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Characterization of the corpus callosum in very preterm and full-term infants utilizing MRI

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ABSTRACT

The corpus callosum is the largest white matter tract, important for interhemispheric communication. The aim of this study was to investigate and compare corpus callosum size, shape and diffusion characteristics in 106 very preterm infants and 22 full-term infants. Structural and diffusion magnetic resonance images were obtained at term equivalent. The corpus callosum was segmented, cross-sectional areas were calculated, and shape was analyzed. Fractional anisotropy, mean, axial and radial diffusivity measures were obtained from within the corpus callosum, with additional probabilistic tractography analysis. Very preterm infants had significantly reduced callosal cross-sectional area compared with term infants ($p=0.004$), particularly for the mid-body and posterior sub-regions. Very preterm callosi were more circular ($p=0.01$). Fractional anisotropy was lower ($p=0.007$) and mean ($p=0.006$) and radial ($p=0.001$) diffusivity values were higher in very preterm infants' callosi, particularly at the anterior and posterior ends. The volume of tracts originating from the corpus callosum was reduced in very preterm infants ($p=0.001$), particularly for anterior mid-body ($p=0.01$) and isthmus tracts ($p=0.04$). This study characterizes callosal size, shape and diffusion in typically developing infants at term equivalent age, and reports macrostructural and microstructural abnormalities as a result of prematurity.

Introduction

The corpus callosum (CC) is the largest white matter (WM) fibre bundle in the human brain. It is the major interhemispheric commissure that connects the majority of the neocortical areas (Schmahmann and Pandya, 2006), important for interhemispheric communication of sensory, motor and higher-order information. The basic structure of the CC is completed by 18–20 weeks' gestation, but continues to increase in size over the third trimester (Malinger and Zakut, 1993), and grows dramatically over the first 2 postnatal years (Keshavan et al., 2002). The CC grows from anterior to posterior (Richards et al., 2004). However, myelination of the CC progresses from posterior to anterior (van der Knaap and Valk, 1995), while pre-oligodendrocytes are thought to appear first in the 'ends' of the CC: the genu and splenium (Huppi et al., 1998). Thus, very preterm (VPT) birth at <30 weeks' gestational age (GA) occurs during a sensitive period of CC development.

Structural MRI can be used to determine size and shape of the CC, while diffusion tensor imaging (DTI) provides insight into the microstructure and connectivity of the CC. The mean diffusivity (MD) is a measure of overall diffusion; a larger MD is associated with reduced integrity of the WM. The movement of water in a preferred direction can be measured by fractional anisotropy (FA). Lower FA is associated with loss or disorganization of axons or myelin. The principal direction of diffusion, assumed to be oriented parallel to the

Abbreviations: AC-PC, anterior commissure to posterior commissure line; AMB, anterior mid-body; BPD, bronchopulmonary dysplasia; CC, corpus callosum; DWI, diffusion weighted image; DTI, diffusion tensor imaging; FA, fractional anisotropy; FOV, field of view; FSL, Oxford centre for functional magnetic resonance imaging of the brain software library; FT, full-term; GA, gestational age; IUGR, intrauterine growth restriction; IVH, intraventricular hemorrhage; MD, mean diffusivity; MDI, mental developmental index; PCS, postnatal corticosteroids; PDI, psychomotor developmental index; PMB, posterior mid-body; VPT, very preterm; PVL, periventricular hemorrhage; RB, rostral body; ROI, region of interest; TE, echo time; TR, repetition time; WM, white matter; $\lambda_{\parallel}$, axial diffusivity; $\lambda_{\perp}$, radial diffusivity.

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fibre direction, is known as axial diffusivity ($\lambda_{\parallel}$), and can be used to estimate WM tracts by tractography (Melhem et al., 2002). Larger $\lambda_{\parallel}$ in the context of infants corresponds to immaturity (Partridge et al., 2004). The average of the medium and minor diffusion directions, known as radial diffusivity ($\lambda_{\perp}$), is assumed to be oriented perpendicular to the fibre direction. Larger $\lambda_{\perp}$ values are thought to correspond to reduced myelin integrity (Beaulieu, 2002). Higher WM anisotropy and lower overall diffusion are associated with increasing age and maturation (Huppi et al., 1998; Schneider et al., 2004) as water content decreases and myelination increases (Partridge et al., 2004).

There is little published on the characterization of the CC around the time of birth, either for healthy full-term (FT) or VPT infants using MRI. MRI at term equivalent age has been previously used to show that premature birth disrupts brain structure (Inder et al., 2005; Peterson et al., 2000) and microstructural characteristics (Counsell et al., 2006; Huppi et al., 1998). However the effect of prematurity on the infant corpus callosum has not been extensively described. In contrast, the effects of prematurity on CC size (Caldu et al., 2006; Lawrence et al., 2010; Narberhaus et al., 2007; Nosarti et al., 2004; Peterson et al., 2000), and diffusion (Andrews et al., 2010; Constable et al., 2008; Kontis et al., 2009; Nagy et al., 2009, 2003) have been previously examined in children, adolescents and adults. While a few studies have reported altered CC diffusion in VPT infants (Anjari et al., 2007; Rose et al., 2008; Skiold et al., 2010), no studies have examined the size and shape of the CC in VPT infants using MRI, or characterized the microstructural integrity and connectivity of the neonatal VPT CC using tractography. Thus, the overall aims of this study were to investigate and compare CC development in FT and VPT infants at term with cross-sectional area, global and local shape analyses on MRI, as well as diffusion measures and tractography within the CC and its sub-regions using DTI.

Methods

Subjects and scanning

Between the period of July 2001 and December 2003, a prospective observational cohort study was conducted at the Royal Women's Hospital in Melbourne, Australia. Three-hundred and forty-eight eligible VPT infants (<30 weeks' GA and/or <1250 g at birth) were admitted into the neonatal nursery over the study period. Two hundred and twenty-seven VPT infants (65% of those eligible) were recruited as described previously (Thompson et al., 2007). Infants with congenital anomalies were excluded (3%). Inability to obtain parental consent was the most common reason for failure to recruit (22%). There were no significant differences between participating and non-participating infants for gender, GA at birth, bronchopulmonary dysplasia (BPD: oxygen requirement at 36 weeks' corrected GA), grade 3 or 4 intraventricular hemorrhage (IVH), or cystic periventricular leukomalacia (PVL). Forty-seven clinically healthy FT infants (≥37 weeks' GA) whose parents agreed to participate in the study were also recruited from the Royal Women's Hospital postnatal wards or via response to advertising in recruiting hospitals. All FT infants had an unremarkable antenatal course and labor, and were free of neonatal complications, and congenital or chromosomal abnormalities. Informed parental consent was obtained for all subjects and the study was approved by the Research and Ethics Committees at the Royal Women's Hospital. A total of 106 stable VPT infants and 22 healthy FT infants were able to be analyzed for the current study (47% of those recruited). The major reasons that infants recruited were not included in this study were that DTI was not attempted (34%), or DTI was unsuccessful or of insufficient quality for further analysis (17%), largely due to movement or imaging artifact. The reason for excluding the remaining infants who were recruited was that structural MRI was unsuccessful or of insufficient quality to analyze (2%).

MRI acquisition

All infants were scanned at term equivalent (median 40, range 38–42 weeks' GA) in a 1.5T General Electric MRI scanner. Infants were fed and tightly swaddled, immobilized in a vacuum fixation bean-bag and scanned while sleeping, without sedation. Each infant underwent whole brain structural 3D T1 spoiled gradient recalled imaging with 0.8–1.6 mm coronal slices; flip angle 45°; repetition time (TR) 35 ms; echo time (TE) 9 ms; field of view (FOV) 21×15 cm^2; matrix 256×192, as well as T2 dual echo fast spin echo sequences with interleaved acquisition (1.7–3 mm coronal slices; TR 4000 ms; TE 60/160 ms; FOV 22×16 cm^2; matrix 256×192, interpolated 512×512). Linescan diffusion imaging sequences (4–6 mm axial slices; 2 baselines, $b=5$; six non-collinear gradient directions, $b=700$ s/mm^2) were acquired within the same session. Post-acquisition MRI analyses were undertaken on sun Microsystems workstations (Palo Alto, CA).

MR image preprocessing

T1-weighted images were individually aligned along the anterior commissure to posterior commissure line (AC-PC) by manual rotation and translation (Talairach and Tournoux, 1988) and were brain extracted by applying an intracranial cavity map file. The intracranial cavity (brain versus non-brain) mask was semi-automatically created based on the T1-weighted image, and then manually corrected (Kikinis et al., 1992).

Diffusion weighted images (DWI) were preprocessed using the Oxford centre for functional magnetic resonance imaging of the brain software library (FSL). Eddy current distortions and simple head motion were corrected (Jenkinson and Smith, 2001). A binary brain mask was created on the baseline image (Smith, 2002). Local fitting of the diffusion tensor model at each voxel of the diffusion image was achieved (Behrens et al., 2003), and probabilistic diffusion orientation and local diffusion parameters were characterized and estimated at each voxel with Markov Chain Monte Carlo sampling (Behrens et al., 2003). The averaged diffusion maps, obtained by averaging together the six diffusion gradient direction images, were co-registered with the AC-PC aligned T1 structural images. All registrations were performed using FSL's linear registration tool (Jenkinson and Smith, 2001) using optimized parameters including mutual information, 12 degrees of freedom, and sinc interpolation.

Corpus callosum segmentation

Corpus callosi were manually delineated on the mid-sagittal slice of the AC-PC aligned T1-weighted image using 3D slicer software (www.slicer.org). The operator (D.K.T.) was blind to group (FT or VPT). Reference was made to anatomical atlases (Bayer and Altman, 2004; Mai et al., 1997). Tracing was performed conservatively, and to further avoid partial volume effects each CC was delineated twice, and the overlap of the two delineations was obtained and used as the final mask.

Reliability analyses were performed using 12 randomly chosen subjects, including 2 FT and 10 VPT infants. The CC was re-traced twice, at least 3 months after the initial CC mask was generated, and the overlap was obtained. The Dice overlap score (Pfefferbaum et al., 2006) was 0.89 (range 0.82–0.96, SD 0.04). The intraclass correlation coefficient using a two-way mixed effects model with absolute agreement on average measures was 0.84 (95% CI 0.45, 0.95; $p=0.003$).

The CC mask was divided into six regions based on a hybrid scheme, which generally incorporated the divisions proposed by Witelson's post-mortem morphological analysis of the CC (Witelson,