Accelerated Corpus Callosum Development in Prematurity Predicts Improved Outcome

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Abstract: *Objectives:* To determine: (1) whether corpus callosum (CC) size and microstructure at 7 years of age or their change from infancy to 7 years differed between very preterm (VP) and full-term (FT) children; (2) perinatal predictors of CC size and microstructure at 7 years; and (3) associations between CC measures at 7 years or trajectories from infancy to 7 years and neurodevelopmental outcomes. *Experimental design:* One hundred and thirty-six VP (gestational age [GA] <30 weeks and/or birth weight <1,250 g) and 33 FT children had usable magnetic resonance images at 7 years of age, and of these, 76 VP and 16 FT infants had usable data at term equivalent age. The CC was traced and divided into six sub-regions. Fractional anisotropy, mean, axial, radial diffusivity and volume were measured from tractography. Perinatal data were collected, and neurodevelopmental tests administered at 7 years' corrected age. *Principal observations:* VP children had smaller posterior CC regions, higher diffusivity and lower fractional anisotropy compared with FT 7-year-olds. Reduction in diffusivity over

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time occurred faster in VP than FT children ($P \leq 0.002$). Perinatal brain abnormality and earlier GA were associated with CC abnormalities. Microstructural abnormalities at 7 years or slower development of the CC were associated with motor dysfunction, poorer mathematics and visual perception. *Conclusions:* This study is the first to demonstrate an accelerated trajectory of CC white matter diffusion following VP birth, associated with improved neurodevelopmental functioning. Findings suggest there is a window of opportunity for neurorestorative intervention to improve outcomes. *Hum Brain Mapp* 36:3733–3748, 2015. © 2015 Wiley Periodicals, Inc.

Key words: preterm; MRI; diffusion-weighted imaging; white matter; neurodevelopment

INTRODUCTION

The corpus callosum (CC) is the largest white matter (WM) tract in the brain and is important for inter-hemispheric communication, having an important role in processing sensory, motor and higher order information. The basic structural development of the CC is completed by 18–20 weeks' gestational age (GA) [Maligner and Zakut, 1993], but its size more than triples during post-natal development; with the most dramatic growth in the first 2 years and continuing into adolescence [Giedd et al., 1999; Keshavan et al., 2002]. In general, the CC grows from anterior to posterior [Ren et al., 2006], but myelinates posteriorly to anteriorly [Bloom and Hynd, 2005; van der Knaap and Valk, 1995].

Given the sequence of CC development, it is not surprising that very preterm (VP) infants CC development is compromised by term-equivalent age compared with full-term (FT) infants and in a region-specific manner [Thompson et al., 2011]. However, until now, no study has longitudinally followed up a group of VP infants into childhood to test whether early abnormalities to the CC persist or even worsen.

A VP infant's brain (born <32weeks' GA) may be exposed to multiple insults, leading to increased rates of WM abnormality [Volpe, 2009]. Other risk factors for altered neurodevelopment in VP infants are earlier GA at

birth, bronchopulmonary dysplasia and being small for GA. Some of these risk factors are associated with CC alterations in VP infants at term equivalent age [Thompson et al., 2012], however, it remains to be seen whether early adverse exposures continue to negatively impact CC structure later in childhood.

Preterm children have a wide range of neurodevelopmental deficits including lower intelligence [Kerr-Wilson et al., 2012], poorer academic skills [Anderson and Doyle, 2008], attention [Murray et al., 2014], working memory [Omizzolo et al., 2014], language [Reidy et al., 2013], visual perception [Molloy et al., 2013] and motor functioning [Williams et al., 2010] than their FT peers, which likely stem from brain injury or abnormal brain development [Mathur et al., 2010; Volpe, 2009]. It has been put forward that neurodevelopmental impairment following preterm birth represents a disease of connectivity [Lubsen et al., 2011], thus callosal connections may play a role. The CC connects homologous as well as nonhomologous regions inter-hemispherically, and in general, the genu connects pre-frontal areas and is assumed to be involved in planning and cognition. The rostral body connects the hemispheres of the pre-motor and sensorimotor cortices and is thought to be involved in motor planning and coordination. The anterior mid-body connects motor regions between hemispheres, with involvement in motor functioning. The posterior mid-body connects the somatosensory and posterior parietal cortices and is likely to be involved in sensory processing, while the isthmus includes inter-hemispheric superior temporal and posterior parietal fibres associated with hearing, language and sensory processing. Finally, the splenium includes mainly fibres connecting inter-hemispheric occipital and inferior temporal regions, and is reportedly involved in vision [Funnell et al., 2000; Witelson, 1985]. Therefore, altered growth and microstructural development of the CC, particularly functionally specific callosal sub-regions [Funnell et al., 2000; Hofer and Frahm, 2006; Witelson, 1985], may partially explain some of these difficulties VP children face.

Previously, we have characterised the CC in VP and FT infants at term equivalent age [Thompson et al., 2011], and found that VP infant CC measures, mainly higher mean diffusivity (MD) and radial diffusivity (RD) within the splenium of preterm infants, were associated with poorer

Abbreviations

AD	axial diffusivity
AMB	anterior mid-body
CC	corpus callosum
FA	fractional anisotropy
FT	full-term
GA	gestational age
MD	mean diffusivity
PMB	posterior mid-body
RB	rostral body
RD	radial diffusivity
SD	standard deviation
VIBeS	Victorian Infant Brain Studies
VP	very preterm
WM	white matter

motor development at 2 years of age [Thompson et al., 2012]. However, little is known about the development of the CC after term-equivalent age in preterm populations. Therefore, the objective of this study was to study CC development in early childhood in VP children.

This study aimed to examine the CC at 7 years of age and: (1a) determine whether there are differences in the whole and regional CC area, volume and diffusion tensor imaging measures of VP versus FT children; (1b) investigate perinatal predictors of CC measures in the whole CC of VP children; (1c) investigate associations between CC measures and neurodevelopmental functioning in VP children. As a second objective we explore the *change in CC measures from term to 7 years* and: (2a) compare growth and microstructural development in VP and FT children; and (2b) investigate associations between CC growth and development measures and neurodevelopmental functioning at 7 years in VP children. We hypothesised that the CC would be less developed in VP 7-year-olds, and that perinatal brain abnormality would be associated with this delay. We expected that VP children would demonstrate a slower trajectory of CC development than FT children, which would be associated with poorer neurodevelopmental outcomes. In particular, we expected genu maturation to be associated with intelligence, academic skills, working memory and attention; rostral body and anterior mid-body growth with motor outcomes; posterior mid-body with visual perception; isthmus with language and visual perception and the splenium with visual perception and motor outcomes.

METHODS

Participants and Scanning

Two hundred and twenty-four surviving VP infants without congenital abnormalities (GA < 30 weeks' and/or BW < 1,250 g) were recruited from the Royal Women's Hospital in Melbourne, Australia between July 2001 and December 2003, as part of the Victorian Infant Brain Studies (ViBeS) cohort. A group of 46 FT infants (37–42 weeks' GA and $\geq 2,500$ g) were also recruited from the Royal Women's Hospital. Infants had brain MRI at the Royal Children's Hospital, Melbourne in a 1.5 T General Electric scanner at term equivalent age (38–42 weeks' GA). T_1 -weighted images (0.8–1.6-mm coronal slices; flip angle 45°; repetition time 35 ms; echo time 9 ms; field of view 21×15 cm²; matrix 256×192) and linescan diffusion-weighted images (4–6 mm axial slices; two baselines, $b = 5$; six non-collinear gradient directions, $b = 700$ s/mm²) were acquired. Of those recruited, 106 VP and 22 FT infants had both structural and diffusion images of sufficient quality for CC analysis (47%). The remainder either were not scanned with the diffusion-weighted imaging sequence, which was only installed half way through the study

($n = 92$, 34%), or were unable to be analysed due to imaging artefact, primarily motion ($n = 51$, 19%).

A total of 198 VP and 43 FT children were followed up at approximately 7 years of age. Of those who were followed up, 160 VP and 36 FT children underwent MRI, but 27 of these either did not have full diffusion datasets acquired or scans were unusable due to movement artefact. Thus, 70% ($n = 169$: 136 VP, 33 FT) of the original cohort of children had scans of sufficient quality for analysis at 7 years. Of these, 92 (76 VP, 16 FT) children had usable MRI data at both time-points (infancy and 7 years). Children had brain MRI at the 7-year time-point on a 3 T Siemens MRI scanner at the Royal Children's Hospital, Melbourne. T_1 -weighted (0.85 mm sagittal slices, flip angle = 9°, repetition time = 1,900 ms, echo time = 2.27 ms, field of view = 210×210 mm, matrix = 256×256), and two sets of echo-planar diffusion-weighted images were acquired; one with 25 non-collinear gradient directions and b -values ranging up to 1,200 s/mm² (repetition time = 12,000 ms; echo time = 96 ms; matrix = 144×144 ; field of view = 250×250 mm; isotropic voxel size = 1.7 mm³), and another with 45 gradient directions and a b -value of 3,000 s/mm² (repetition time = 7,400 ms; echo time = 106 ms; matrix = 104×104 ; field of view = 240×240 mm; isotropic voxel size = 2.3 mm³).

All subjects were recruited, scanned and assessed in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki), with parental consent and approval from the Royal Children's Hospital Human Research Ethics Committee. Perinatal data were collected from chart review at the time of discharge on GA at birth, sex, birth weight standard deviation (SD) score computed relative to the British Growth Reference data [Cole et al., 1998], bronchopulmonary dysplasia (oxygen dependency at 36 weeks' corrected age), infection (defined as one or more episodes of necrotising enterocolitis or sepsis) and total brain abnormality score, which was graded qualitatively, as previously described and validated [Kido-koro et al., 2013].

Magnetic Resonance Image Analysis

The linescan diffusion images at term-equivalent age were processed using FSL software (www.fmrib.ox.ac.uk/fsl), where eddy current and motion correction was performed [Jenkinson and Smith, 2001], and the diffusion tensor model was linearly fitted [Behrens et al., 2003]. The $b = 1,200$ s/mm² data at 7 years were processed using 'ExploreDTI' software [Leemans et al., 2009]. Data were corrected for motion and eddy current induced distortions, incorporating re-orientation of the b -matrix [Leemans and Jones, 2009]. The diffusion tensor model was fitted using a robust tensor estimation approach [Veraart et al., 2013]. Axial diffusivity (AD), RD, MD and FA maps were generated for both the infant and 7-year data. Constrained spherical deconvolution was applied to the $b = 3,000$ s/mm²

Figure 1.

(a) Preterm infant CC traced on mid-sagittal slice of the T_1 image. (b) The same subject's CC at 7 years of age, traced on the mid-sagittal slice of the T_1 image. (c) Representation of the sub-divisions of the CC obtained at term and 7 years. (d) Tractography of the CC at 7 years of age.

diffusion-weighted data at 7 years using 'MRtrix' software [Tournier et al., 2012], creating a map of fibre orientation distributions in each voxel. A maximum harmonic order of six was used. Intracranial volumes were obtained at term-equivalent age using a semi-automatic method based on the T_1 -weighted image [Kikinis et al., 1992], and then manually corrected, and at 7 years of age from the T_1 -weighted image using 'Freesurfer' software [Fischl, 2012].

CC Measures

In infancy, the CC was traced on the mid-sagittal slice of the structural T_1 scan that had been manually aligned along the anterior-posterior commissure line, using 3D slicer software (www.slicer.org; Fig. 1a). The intraclass correlation coefficient on 12 subjects randomly chosen for reliability analysis was 0.84 ($P=0.003$). The CC was also traced on the mid-sagittal slice of the structural T_1 scan in alignment with the anterior-posterior commissures at 7 years of age, using ITK-SNAP software (www.itkmap.org; Fig. 1b). Reliability of the 7-year CC was undertaken on 20 randomly chosen subjects, giving an intraclass correlation

coefficient of 0.94 ($P<0.001$). CC tracing was performed conservatively to avoid partial volume effects.

Matlab software (www.mathworks.com/products/matlab) was used to divide the CC of the infants and 7-year-olds into six sub-regions (genu, rostral body, anterior mid-body, posterior mid-body, isthmus and splenium) based on both Witelson's scheme [Witelson, 1989] and Hofer and Frahm's [2006] sub-divisions, as previously described [Thompson et al., 2011]. Cross-sectional CC areas were obtained (Fig. 1c).

The diffusion and T_1 images were co-registered in order to overlay the CC and sub-regions on the diffusion image in native space using FSL's linear registration tool [Jenkinson and Smith, 2001]. For the infants, probabilistic diffusion tensor tractography was initiated from CC regions using the FSL diffusion toolbox [Behrens et al., 2003], as previously described [Thompson et al., 2011]. Tract volume was normalised for the number of voxels in the seed region of interest, and thresholded to eliminate tracts with a low probability of lying within the CC. For the 7-year-olds, probabilistic tractography was initiated from CC regions using 'MRtrix' software [Tournier et al., 2012; Fig. 1d]. A maximum fibre orientation distribution amplitude of 0.3 was used, initial tracking was specified to occur in the left-right direction, and thresholding removed potentially

spurious tract voxels containing less than 3/100 streamlines. The $b = 1,200 \text{ s/mm}^2$ and $b = 3,000 \text{ s/mm}^2$ data were co-registered and diffusion tensor parameters were obtained from the tracts by multiplying the $b = 1,200 \text{ s/mm}^2$ diffusion maps by the binary tract volumes.

Seven-Year Neurodevelopmental Assessments

At 7 years' corrected age, participants were invited to undertake an extensive battery of neurodevelopmental tests. The following assessments were relevant to this study, for which standardised scores were used. The Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999] was used to estimate general intelligence with a mean (M) of 100 and SD of 15. Basic academic skills (reading and mathematics, $M = 100$, $SD = 15$) were assessed using the Wide Range Achievement Test 4 [Wilkinson and Robertson, 2005]. Attention was assessed using the Score sub-test ($M = 10$, $SD = 3$) of the Test of Everyday Attention for Children [Manly et al., 1999]. General language ability was measured using the Core Language scale ($M = 100$, $SD = 15$) from the Clinical Evaluation of Language Fundamentals—4th Edition Australian [Semel et al., 2006]. Working memory was assessed using the Backward Digit Recall sub-test ($M = 10$, $SD = 3$) from the Working Memory Test Battery for Children [Pickering and Gathercole, 2001]. Visual perceptual skills were estimated using the Visual Closure sub-test ($M = 10$, $SD = 3$) of the Test of Visual Perceptual Skills—3rd Edition [Martin, 2006]. Overall motor functioning was assessed using the standard score ($M = 10$, $SD = 3$) from the Movement Assessment Battery for Children—version 2 [Henderson et al., 2007].

Statistical Analyses

All statistical analyses were performed using Stata 13.1. Sample characteristics were compared between children who did and did not have useable MRI data on the CC at the 7-year follow up from the original cohort using t -tests, chi-squared tests or Mann–Whitney U tests, as appropriate, and are summarised for those with follow-up data separately in the VP and FT groups.

Mean differences between VP and FT 7-year-old children in whole and regional CC measures (area, tract volume, FA, MD, AD and RD) were assessed using linear regression models. Results are presented as a percentage of the average size of the region in the FT group along with its 95% confidence interval. Associations between perinatal variables (GA at birth, gender, birthweight SD score, bronchopulmonary dysplasia, infection and infant brain abnormality) and whole CC measures at age 7 in the VP group were determined using linear regression, as were associations between whole and regional CC measures and neurodevelopmental outcomes at 7 years of age again restricted to the VP group. All estimates were

adjusted for age at MRI. Additionally, the results for area and volume were adjusted for intracranial volume.

Differences in growth or microstructural development of the CC from term to 7 years were compared between VP and FT children using random effects models including a fixed effect of age and group and an interaction between age and group allowing the relationship between age and the CC measurement to vary by group, with a random effect to allow for the repeated observations within an individual. Associations between the rate of change in whole and regional CC measures from infancy to 7 years and neurodevelopmental outcomes in VP children were evaluated using separate linear regression models for each predictor–outcome combination. The predictor was rate of change in CC measure per year. All estimates were adjusted for the measure at baseline (infancy) as well as age at 7-year assessment. Analyses involving CC area and volume measures were additionally adjusted for intracranial volume at baseline (infancy) and intracranial volume as a time dependent covariate.

All linear regression models were fitted using generalised estimating equations and robust standard errors to allow for the clustering of multiple births. Given the multiple comparisons, results were interpreted as overall patterns and magnitudes of differences, rather than focusing on individual P values.

RESULTS

Sample Characteristics

Characteristics were generally similar between those who had usable MRI data at 7 years and those originally recruited but not included, except that participants had less postnatal corticosteroid exposure ($P = 0.002$) and lower brain abnormality scores than non-participants ($P = 0.001$). At 7 years of age, the proportion of males, small for GA and GA at scan were similar between the VP and FT groups, but as expected, there were differences in all other perinatal variables (Table I). At 7 years of age, the VP sample had smaller intracranial volumes and worse functioning on virtually all neurodevelopmental measures compared with the FT group (Table I). The 76 VP and 16 control children in the longitudinal cohort differed on the same variables as those with 7-year data overall (data not shown).

Seven Years of Age: VP Versus FT

Means and SDs for regional CC measures for the VP and FT groups are presented in Supporting Information Table I.

The posterior half of the mid-sagittal area of the CC was reduced in VP children compared with FT children, with strong evidence of a difference between the groups, especially for the splenium (Fig. 2a). The tract volume was also

reduced in VP children for the posterior half of the CC compared with FT children, particularly for the isthmus (Fig. 2b). Lower FA values were found in the whole CC tracts, with most evidence for lower FA within the splenium of VP children compared with FT children (Fig. 2c). There was some evidence for higher MD in the VP compared with the FT children across all of the regions (Fig. 2d). There was also evidence for higher AD in VP compared with FT children, mainly for the body and isthmus (Fig. 2e). There was some evidence for higher RD in VP compared with FT children, particularly for the splenium (Fig. 2f).

Seven Years of Age: Perinatal Predictors of CC Measures in VP Children

Within the VP group, the brain abnormality score in infancy was associated with lower CC area, volume and FA and increased MD, AD and RD at 7 years of age. There was also some evidence for associations between older GA at birth and a larger CC area and volume at age 7 years, and a lower CC FA in VP females. There was little evidence that infection, bronchopulmonary dysplasia or birth-weight SD score were associated with CC measures.

Seven Years of Age: Associations Between CC Measures and Neurodevelopmental Functioning in VP Children

Within the VP group, there was evidence for an association between a smaller CC area, including rostral body and anterior mid-body, at 7 years of age and higher intelligence and reading skills. Additionally, a smaller rostral body area was associated with better working memory performance (Fig. 4a), while a smaller rostral body volume was weakly associated with higher attention scores (Fig. 4b). FA in most regions of the CC, but particularly in the whole CC and splenium, was positively associated with mathematics skills. Furthermore, there was evidence for associations between higher FA, particularly in the whole CC and anterior mid-body (Fig. 4c), and lower MD, AD and RD in the CC, more so for the anterior mid-body, the genu and splenium (Fig. 4d, e, f) and better motor ability. There was little evidence for associations between CC measures and language and visual perception in VP children at 7 years of age (Fig. 4).

Infancy to 7 Years: VP Versus FT

CC growth between infancy and 7 years (over and above that of the whole brain) was similar in the VP and FT groups, as measured on the mid-sagittal slice and from CC tract volume. There was also little evidence of differences between VP and FT children in the development of FA over time. There was a much greater reduction in MD, AD

and RD over time for the VP children compared with FT children (Table II).

Infancy to 7 Years: Associations Between CC Measures and Neurodevelopmental Functioning in VP Children

Within the VP group, smaller gains in rostral body area over time were associated with higher performance on measures of intelligence and attention, with some evidence for smaller gains in anterior mid-body area over time and better attention (Fig. 5a). Furthermore, smaller gains in rostral body tract volume over time in VP children were associated with higher intelligence, better reading and possibly better mathematics ability (Fig. 5b). There was some evidence that a greater increase in splenium volume over time was associated with higher visual perception scores (Fig. 5b). Greater reductions in MD, RD and AD over time, particularly within the anterior mid-body, also associated with better visual perception (Fig. 5d–f). There was evidence that larger gains in FA, particularly within the anterior mid-body over time in VP children, were associated with better motor ability (Fig. 5c). There was also evidence for an association between greater reductions in MD and RD in the anterior mid-body and splenium over time, as well as greater reductions in AD within the anterior mid-body and better motor ability (Fig. 5d–f).

DISCUSSION

This study is the first to investigate longitudinal development of the CC from infancy to childhood in VP children compared with term controls. Longitudinal analyses revealed an intriguing novel finding contrary to our hypothesis, whereby the rate of CC microstructural development in VP children reflects a steeper trajectory than that of FT children. While these findings suggest the VP group may exhibit developmental catch-up in early childhood, posterior regions of the CC in this group were still adversely affected at 7 years of age. Further, our analyses provide new insights into the vulnerabilities of CC development in VP children, such as earlier birth and perinatal brain abnormality. Finally, this study revealed interesting structure–function relationships specific to callosal sub-regions, including motor, visual and academic functions.

At 7 years of age, the size of the posterior half of the CC was smaller in VP compared with FT children, similar to our findings at term-equivalent age [Thompson et al., 2011]. The current study also showed that between infancy and 7 years of age, VP and FT children's corpora callosa increase in size at a similar rate when taking into consideration changes in whole brain growth. Thus, VP infants have a smaller posterior CC that persists into childhood. Considering the CC grows from anterior to posterior [Ren et al., 2006], one may expect posterior regions to be most

TABLE I. Perinatal characteristics and 7-year outcomes of the very preterm (VP) and full-term (FT) cohorts

Perinatal characteristics	VP, <i>n</i> = 136	FT, <i>n</i> = 33	Mean difference (95% CI)	<i>P</i>
GA at birth (weeks), mean (SD)	27.6 (1.8)	38.9 (1.3)	−11.3 (−12.0, −10.6)	<0.001
Birth weight (g), mean (SD)	978 (225)	3,244 (501)	−2,265 (−2,380, −2,151)	<0.001
Birth weight SD score, ^a mean (SD)	−0.52 (0.93)	0.01 (0.92)	−0.53 (−0.88, −0.18)	0.0036
GA at scan (weeks), mean (SD)	40.5 (2.2)	40.8 (1.5)	−0.23 (−1.04, 0.58)	0.57
Intracranial volume (cc), mean (SD)	400 (63.6) ^b	424 (45.9) ^c	−23.8 (−50.3, −2.82)	0.079
			Proportion difference (95% CI)	<i>P</i>
Male, <i>n</i> (%)	65 (47.8)	16 (48.5)	−0.007 (−0.20, 0.18)	0.94
Singleton, <i>n</i> (%)	69 (50.7)	31 (93.9)	−0.43 (−0.55, −0.32)	<0.001
Small for GA, <i>n</i> (%)	12 (8.8)	1 (3.0)	0.06 (−0.02, 0.13)	0.26
Antenatal corticosteroids, <i>n</i> (%)	119 (87.5) ^d	0 (0)	0.88 (0.83, 0.94)	<0.001
Postnatal corticosteroids, ^e <i>n</i> (%)	7 (5.1)	0 (0)	0.05 (0.01, 0.09)	0.18
Sepsis, <i>n</i> (%)	40 (29.4)	1 (3.0)	0.26 (0.17, 0.36)	0.002
Necrotizing enterocolitis, <i>n</i> (%)	6 (4.4)	0 (0)	0.04 (0.01, 0.08)	0.22
Infection, <i>n</i> (%)	43 (31.6)	1 (3.0)	0.29 (0.19, 0.38)	<0.001
Bronchopulmonary dysplasia, <i>n</i> (%)	39 (28.7)	0 (0)	0.29 (0.21, 0.36)	<0.001
Intraventricular haemorrhage grade III/IV, <i>n</i> (%)	1 (0.7)	0 (0)	0.007 (−0.007, 0.02)	0.62
Cystic periventricular leukomalacia, <i>n</i> (%)	4 (2.9)	0 (0)	0.03 (0.001, 0.06)	0.32
			<i>Z</i> value	<i>P</i>
Brain abnormality score, median (25th–75th percentile)	4 (3–7) ^d	1 (1–2)	6.38	<0.001
7-year characteristics			Mean difference (95% CI)	<i>P</i>
Age at scan (years), mean (SD)	7.54 (0.24)	7.60 (0.21)	−0.06 (−0.15, 0.03)	0.20
Total intracranial volume (cm ³), mean (SD)	1,330 (121)	1,421 (103)	−90.5 (−136, −45.3)	<0.001
Intelligence, mean (SD)	99.5 (13.1)	109.5 (11.4)	−9.96 (−14.8, −5.06)	<0.001
Reading, mean (SD)	101 (18.1) ^d	109 (17.8)	−8.01 (−14.9, −1.09)	0.024
Mathematics, mean (SD)	91.9 (17.2) ^d	98.7 (14.5)	−6.88 (−13.3, −0.47)	0.036
Attention, mean (SD)	7.92 (3.54) ^f	8.67 (3.09)	−0.75 (−2.08, 0.58)	0.27
Working memory, mean (SD)	88.3 (15.0) ^f	98.8 (15.9) ^g	−10.50 (−16.4, −4.58)	<0.001
Language, mean (SD)	94.3 (15.9) ^h	108 (11.1) ^g	−13.3 (−19.2, −7.47)	<0.001
Visual perception, mean (SD)	8.91 (3.50) ⁱ	10.59 (3.45) ^g	−1.68 (−3.05, −0.32)	0.016
Motor ability, mean (SD)	9.15 (3.16) ^j	11.16 (2.71) ^g	−2.01 (−3.21, −0.81)	0.001

CI, confidence interval; GA, gestational age; SD, standard deviation.

^aComputed relative to the British Growth Reference data [Cole et al. 1998].^b*n* = 115.^c*n* = 25.^d*n* = 135.^ePostnatal dexamethasone, usual dose 0.15 mg/kg per day for 3 days, reducing over 10 days: total dose 0.89 mg/kg.^f*n* = 130.^g*n* = 32.^h*n* = 134.ⁱ*n* = 125.^j*n* = 129.

vulnerable to early developmental disturbances. Our results are in agreement with previous studies that have shown CC size is reduced in preterm populations, particularly posterior regions [Lawrence et al., 2010; Nosarti et al., 2004; Stewart et al., 1999]. The only other group to examine CC growth longitudinally in a preterm population (between 15 and 19 years of age) was Allin et al. [2007], who reported a greater rate of increase in CC size in VP adolescents compared with FT peers. Together our findings suggest a different developmental trajectory for the CC in VP survivors.

In terms of callosal microstructure, lower FA and higher diffusivity were found for the CC in VP compared with FT children at 7 years of age, which appeared to be driven

mainly by the splenium sub-region. During normal development, FA increases and diffusivity decreases over time [Mukherjee and McKinstry, 2006]. Therefore, our findings represent abnormal microstructural development, such as reduced myelination, fewer or less densely packed fibres, larger axon diameter or higher tissue water content in the CC [Jones et al., 2013]. The splenium appeared particularly vulnerable, indicating that WM organisation of these slower conducting, small diameter axons [Aboitiz et al., 1992] may be particularly compromised in VP children. Furthermore, the splenium is one of the first sub-regions of the CC to myelinate [Bloom and Hynd, 2005; van der Knaap and Valk, 1995], which may explain its

Figure 2.

Comparison of overall and regional CC (a) area (mm²), (b) volume (cm³), (c) fractional anisotropy, (d) mean, (e) axial and (f) radial diffusivity ($\times 10^{-3}$ mm²/s), in very preterm and full-term children at 7 years of age. Results are presented as the mean difference between the groups as a percentage of the average

size of the region in the control group. All estimates are adjusted for age at 7 year MRI. The results for area and volume are also adjusted for intra-cranial volume. CI = confidence interval, RB = rostral body, AMB = anterior mid-body, PMB = posterior mid-body.

vulnerability. Consistent with our findings, the splenium is commonly reported to be microstructurally disorganised due to prematurity [Constable et al., 2008; Counsell et al., 2006; Mullen et al., 2011; Nagy et al., 2003]. Other studies have reported general reductions in FA in the CC of preterm infants [Anjari et al., 2007; Rose et al., 2009; Skiold et al., 2010], adolescents [Vangberg et al., 2006] and adults [Allin et al., 2011; Eikenes et al., 2011] as well as increased MD in the CC of preterm infants [Skiold et al., 2010] and young adults [Eikenes et al., 2011] compared with FT controls, but very few studies have investigated AD and RD in the CC of preterm populations.

We have shown that reductions in MD, AD and RD over time, which occur during normal WM development [Mukherjee and McKinstry, 2006], occurred at a higher rate in the VP CC compared with FT children. These novel

findings were contrary to our expectations and suggest that CC WM tracts may undergo some developmental 'catch-up'. However, it is uncertain whether these findings reflect accelerated typical development or an atypical developmental trajectory.

The main perinatal predictor of CC abnormalities at 7 years was brain abnormality, which mirrors our findings at term-equivalent age [Thompson et al., 2012]. These findings suggest that the ill effects of brain abnormality in the perinatal period persist into childhood. The mechanism by which CC development is altered is likely to be via hypoxia-ischemia [Back et al., 2001], but infection and inflammation may also lead to possible necrosis, apoptosis, astrogliosis, microgliosis or reduction in pre-myelinating oligodendrocytes [Volpe, 2009]. In agreement with our study, other studies have reported smaller CC volume,

TABLE II. Rate of change in CC per year (with 95% confidence interval) in very preterm and FT children from term-equivalent to 7 years of age

	Very preterm	Full-term	Interaction <i>P</i>
Area (mm²)			
Whole CC	8.991 (1.451, 16.531)	11.277 (2.584, 19.970)	0.27
Genu	3.157 (0.870, 5.443)	3.256 (0.629, 5.882)	0.87
RB	0.715 (−0.699, 2.129)	1.195 (−0.441, 2.831)	0.23
AMB	0.833 (−0.228, 1.894)	0.797 (−0.431, 2.024)	0.90
PMB	0.577 (−0.314, 1.467)	0.973 (−0.062, 2.009)	0.13
Isthmus	0.389 (−0.655, 1.432)	0.631 (−0.574, 1.836)	0.41
Splenium	3.368 (0.717, 6.018)	4.391 (1.355, 7.427)	0.14
Tract volume (cm³)			
Whole CC	1.738 (1.001, 2.476)	1.379 (0.536, 2.222)	0.06
Genu	−0.593 (−1.197, 0.012)	−0.610 (−1.307, 0.087)	0.92
RB	0.182 (−0.310, 0.673)	0.181 (−0.388, 0.750)	0.99
AMB	0.299 (−0.118, 0.716)	0.106 (−0.375, 0.587)	0.09
PMB	0.691 (0.268, 1.114)	0.852 (0.356, 1.348)	0.22
Isthmus	0.310 (−0.050, 0.671)	0.424 (0.009, 0.840)	0.27
Splenium	0.364 (−0.298, 1.025)	0.190 (−0.571, 0.951)	0.34
Fractional anisotropy			
Whole CC	0.040 (0.040, 0.041)	0.040 (0.038, 0.041)	0.96
Genu	0.033 (0.033, 0.034)	0.033 (0.032, 0.035)	0.64
RB	0.028 (0.027, 0.029)	0.028 (0.026, 0.030)	0.89
AMB	0.028 (0.027, 0.029)	0.027 (0.025, 0.029)	0.37
PMB	0.027 (0.026, 0.028)	0.025 (0.024, 0.027)	0.17
Isthmus	0.027 (0.026, 0.028)	0.025 (0.023, 0.027)	0.11
Splenium	0.037 (0.036, 0.038)	0.037 (0.036, 0.039)	0.43
Mean diffusivity (×10^{−3} mm²/s)			
Whole CC	−0.088 (−0.090, −0.086)	−0.073 (−0.077, −0.068)	<0.001
Genu	−0.094 (−0.096, −0.091)	−0.080 (−0.085, −0.075)	<0.001
RB	−0.099 (−0.102, −0.096)	−0.085 (−0.091, −0.078)	<0.001
AMB	−0.091 (−0.094, −0.088)	−0.076 (−0.082, −0.070)	<0.001
PMB	−0.091 (−0.093, −0.088)	−0.073 (−0.079, −0.067)	<0.001
Isthmus	−0.094 (−0.097, −0.091)	−0.074 (−0.080, −0.068)	<0.001
Splenium	−0.086 (−0.089, −0.084)	−0.069 (−0.073, −0.064)	<0.001
Axial diffusivity (×10^{−3} mm²/s)			
Whole CC	−0.058 (−0.061, −0.055)	−0.041 (−0.046, −0.035)	<0.001
Genu	−0.075 (−0.077, −0.072)	−0.059 (−0.065, −0.053)	<0.001
RB	−0.087 (−0.091, −0.083)	−0.070 (−0.079, −0.062)	0.002
AMB	−0.077 (−0.081, −0.073)	−0.061 (−0.069, −0.052)	<0.001
PMB	−0.079 (−0.082, −0.076)	−0.060 (−0.067, −0.052)	<0.001
Isthmus	−0.083 (−0.087, −0.080)	−0.062 (−0.070, −0.054)	<0.001
Splenium	−0.061 (−0.064, −0.058)	−0.039 (−0.046, −0.032)	<0.001
Radial diffusivity (×10^{−3} mm²/s)			
Whole CC	−0.104 (−0.106, −0.102)	−0.089 (−0.093, −0.085)	<0.001
Genu	−0.103 (−0.105, −0.101)	−0.091 (−0.095, −0.086)	<0.001
RB	−0.106 (−0.108, −0.103)	−0.092 (−0.098, −0.086)	<0.001
AMB	−0.098 (−0.101, −0.096)	−0.084 (−0.090, −0.079)	<0.001
PMB	−0.097 (−0.099, −0.094)	−0.079 (−0.085, −0.074)	<0.001
Isthmus	−0.100 (−0.102, −0.097)	−0.080 (−0.086, −0.075)	<0.001
Splenium	−0.099 (−0.101, −0.097)	−0.083 (−0.088, −0.079)	<0.001

Results for CC area and volume are adjusted for intracranial volume at baseline (infancy) and change in intracranial volume.
 RB, rostral body; AMB, anterior mid-body; PMB, posterior mid-body.

reduced FA and increased diffusivity in the CC with increasing WM injury in preterm infants [van Pul et al., 2012], and reduced FA in the CC associated with WM injury in preterm adolescents [Feldman et al., 2012].

There was also evidence that increasing GA was associated with a larger CC for VP 7-year-olds. Our group [Thompson et al., 2012] and others have reported similar findings in preterm infants [Hasegawa et al., 2011; van Pul

Figure 3.

Perinatal predictors of overall CC (a) area (mm²), (b) volume (cm³), (c) fractional anisotropy, (d) mean, (e) axial and (f) radial diffusivity ($\times 10^{-1}$ mm²/s), in very preterm children at 7 years of age. Results are presented as mean difference with 95% confidence interval (CI) adjusted for age at 7 year MRI. BPD = bronchopulmonary dysplasia, BW = birthweight, SD = standard deviation.

et al., 2012]. Furthermore, Narberhaus et al. [2007] found that adolescents born earliest had the smallest corpora callosa [Narberhaus et al., 2007]. Thus, the impact of being born earlier on the size of the CC continues to exert its effect at 7 years, and also into adolescence.

There was some evidence for a lower FA in the CC of VP females compared with males. This may not necessarily indicate an abnormality, as healthy females reportedly have lower callosal FA than males [Shin et al., 2005]. While one study has reported that females born preterm have a more vulnerable CC than males [Kontis et al., 2009], another study revealed the opposite [Rose et al., 2009].

We report associations between adverse functioning and altered callosal microstructure, which could relate to reduced efficiency of inter-hemispheric information transfer [Westerhausen et al., 2006]. A functional correlate for

CC abnormality both over time and at 7 years of age was motor dysfunction. It is not surprising that better microstructural organization of anterior mid-body tracts, which connect left and right motor cortices, was related to better motor functioning. The same can be said of splenium tracts that are involved mainly in visual functioning, but upon which motor functioning is critically dependent. Consistent with these findings, others have reported associations between motor dysfunction and reduced FA in the CC [van Kooij et al., 2012], and lower anterior mid-body FA measures in preterm infants [Mathew et al., 2013]. Although the genu is not traditionally linked with motor functioning, this finding may be a reflection of the association we found between diffusion measures in the CC as a whole and motor functioning in VP 7-year-olds. Similarly, a study by Rademaker et al. [2004] found associations between mid-sagittal area of all regions of the CC,

Figure 4.

CC (a) area (mm²), (b) volume (cm³), (c) fractional anisotropy, (d) mean, (e) axial and (f) radial diffusivity ($\times 10^{-1}$ mm²/s), as predictors of concurrent neurodevelopmental outcomes in very preterm children at age 7 years. Results are presented as regression coefficients with 95% confidence interval (CI). All estimates are adjusted for age at the time of the assessment. Results for area and volume are also adjusted for intracranial volume.

Figure 5.

Association between the rate of change in CC (a) area (mm^2), (b) volume (cm^3), (c) fractional anisotropy, (d) mean, (e) axial and (f) radial diffusivity ($\times 10^{-1} \text{ mm}^2/\text{s}$) per year from term-equivalent age to 7 years and functional outcomes at 7 years of age in very preterm children. Results are presented as regres-

sion coefficients with 95% confidence interval (CI). All estimates are adjusted for the measure at baseline and age at assessment. Results for area and volume are also adjusted for intracranial volume at baseline (infancy) and change in intracranial volume over time.

including the frontal region and motor ability in VP children [Rademaker et al., 2004].

At 7 years of age, poorer mathematics performance was associated with lower FA (particularly in the splenium). Although not a diffusion study, Ng et al. [2005] found that the size and shape of the CC was related to mathematics proficiency in healthy Chinese children. In our study, lower reading, intelligence, attention and working memory scores were weakly associated with a larger CC area, particularly for the rostral body, but also the anterior mid-body. These findings are counter-intuitive, as others have reported dissimilar results, where *better* intelligence [Caldu et al., 2006; Peterson et al., 2000] and reading [Chiarello et al., 2012; Fine et al., 2007] are associated with larger CC. A possible explanation for our findings are that axon bundles of the CC are more tightly packed together making the mid-sagittal cross-sectional area appear smaller. Alternatively, a smaller CC may reflect a more refined pruning process during development [LaMantia and Rakic, 1990]. However, this may be a spurious finding, considering the magnitude of the effect is small, and there is large variability in our results across the diffusion measures and outcomes. Microstructural measures obtained by diffusion imaging may be more meaningful than measures of size in explaining neurodevelopmental outcomes related to the CC [Doron and Gazzaniga, 2008].

Contrary to our hypotheses, we were unable to detect associations between genu measures and cognitive functions such as intelligence, working memory or attention or isthmus measures and visual perception and language skills in VP children.

Many studies now directly use tractography to parcellate the CC connections between different cortical regions to obtain a more anatomically driven sub-division of the CC. However, we chose to use a well-established method based on functional sub-divisions of the CC [Hofer and Frahm, 2006; Witelson, 1989] for our 7-year-old children, which we had previously applied to this cohort in infancy. This was required considering the longitudinal nature of this study. Furthermore, future studies may benefit from more sensitive and specific measures of the WM microstructure than tensor-derived diffusion parameters, such as those obtained from composite hindered and restricted model of diffusion, or diffusion kurtosis imaging [Jones et al., 2013]. These techniques were not possible for the current longitudinal cohort considering the limitations of the diffusion data obtained at the infant time-point more than 10 years ago. There are further inherent limitations with longitudinal studies. We chose to use the most sophisticated scanning acquisitions available to us at each time-point and the most accurate analysis techniques for the data. Due to inevitable technological advancements over the course of this longitudinal study, different field strength, diffusion sequences, analysis techniques and software were used at the infant and 7-year time-points. In particular, it is known that differences in field strength, gradient strength, gradient directions and sampling

schemes all affect diffusion tensor measures [Jones, 2004; Jones et al., 2013; Melhem et al., 2000]. However, this is a systematic difference across all subjects, and is therefore, unlikely to confound our results. Furthermore, despite the use of different software at the two time-points, the diffusion tensor was fitted in the same way at both time-points, and would, therefore, give identical measures regardless of the software used. Due to limitations of the differing techniques as well as the large number of comparisons undertaken in this study, we consider our results to be exploratory. Our findings should be interpreted with caution and will require replication by other studies.

In conclusion, this study shows that the widespread microstructural differences in the CC present in infancy in VP compared with FT subjects had resolved to some degree by 7 years of age, however, the most posterior regions continue to be compromised. Over time, the VP CC tracts matured quicker than FT tracts, in terms of a greater reduction in diffusivity measures, which may suggest a different developmental trajectory for the CC after early insults associated with preterm birth. This study is the first to report that VP infants' CC development catches up at a higher rate to their FT peers throughout childhood, and has important implications, suggesting there is a window of opportunity for neuro-restorative intervention to improve WM microstructure and associated outcomes. This study found correlations between CC microstructural organization and neurodevelopmental functioning in VP children, suggesting that the alterations in VP compared with FT corpora callosa have functional consequences, and that there is regional specificity of the CC for different functions. It also suggests that some of the functional deficits VP children face, especially motor dysfunction, but also visual and academic dysfunction, may be partly explained by an abnormal or slower trajectory of CC microstructural development. This study suggests that the CC is a critical brain structure which may underpin many of the deficits commonly seen in VP children. However, to fully understand the CC development in VP survivors further analysis of this cohort is needed, as adolescence is likely to be another important developmental time-point.

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