



## White matter alterations and their associations with motor function in young adults born preterm with very low birth weight



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### ABSTRACT

Very low birth weight (VLBW;  $\leq 1500$  g) individuals have an increased risk of white matter alterations and neurodevelopmental problems, including fine and gross motor problems. In this hospital-based follow-up study, the main aim was to examine white matter microstructure and its relationship to fine and gross motor function in 31 VLBW young adults without cerebral palsy compared with 31 term-born controls, at mean age  $22.6 \pm 0.7$  years. The participants were examined with tests of fine and gross motor function (Trail Making Test-5; TMT-5, Grooved Pegboard, Triangle from Movement Assessment Battery for Children-2; MABC-2 and High-level Mobility Assessment Tool: HiMAT) and diffusion tensor imaging (DTI). Probabilistic tractography of motor pathways of the corticospinal tract (CST) and corpus callosum (CC) was performed. Fractional anisotropy (FA) was calculated in non-crossing (capsula interna in CST, body of CC) and crossing (centrum semiovale) fibre regions along the tracts and examined for group differences. Associations between motor test scores and FA in the CST and CC were investigated with linear regression. Tract-based spatial statistics (TBSS) was used to examine group differences in DTI metrics in all major white matter tracts. The VLBW group had lower scores on all motor tests compared with controls, however, only statistically significant for TMT-5. Based on tractography, FA in the VLBW group was lower in non-crossing fibre regions and higher in crossing fibre regions of the CST compared with controls. Within the VLBW group, poorer fine motor function was associated with higher FA in crossing fibre regions of the CST, and poorer bimanual coordination was additionally associated with lower FA in crossing fibre regions of the CC. Poorer gross motor function was associated with lower FA in crossing fibre regions of the CST and CC. There were no associations between motor function and FA in non-crossing fibre regions of the CST and CC within the VLBW group. In the TBSS analysis, the VLBW group had lower FA and higher mean diffusivity compared with controls in all major white matter tracts. The findings in this study may indicate that the associations between motor function and FA are caused by other tracts crossing the CST and CC, and/or by alterations in the periventricular white matter in the centrum semiovale. Some of the associations were in the opposite direction than hypothesized, thus higher FA does not always indicate better function. Furthermore, widespread white matter alterations in VLBW individuals persist into young adulthood.

**Abbreviations:** AD, axial diffusivity; CC, corpus callosum; CST, corticospinal tract; DTI, diffusion tensor imaging; FA, fractional anisotropy; HiMAT, high-level mobility assessment tool; MABC-2, movement assessment battery for children-2; MD, mean diffusivity; MNI, Montreal neurological institute; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit; RD, radial diffusivity; ROI, region-of-interest; TBSS, tract-based spatial statistics; SES, socioeconomic status; TMT-5, Trail Making Test-5; VLBW, very low birth weight; VOI, volume-of-interest

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## 1. Introduction

Being born preterm with very low birth weight (VLBW:  $\leq 1500$  g) is associated with increased risk of disturbances in perinatal brain development (Volpe, 2009) and later neurodevelopmental problems (Aarnoudse-Moens et al., 2009; de Kieviet et al., 2009). Fine and gross motor problems are common and have been found to persist into young adulthood, also when excluding participants with cerebral palsy (Husby et al., 2013).

The preterm brain is particularly susceptible to diffuse white matter injury, related to a disrupted maturation of pre-oligodendrocytes into oligodendrocytes, important for axonal myelination (Volpe, 2009). Myelination deficits may affect structural and functional connectivity, leading to slower signalling in the brain. In normal brain development, diffusion tensor imaging (DTI) (Basser and Pierpaoli, 1996) shows that fractional anisotropy (FA) increases and mean diffusivity (MD) decreases as white matter pathways mature and myelinate, starting during gestation and continuing into adulthood (Cascio et al., 2007; Lebel et al., 2008). Preterm birth disrupts the normal maturation of white matter, and the preterm brain typically exhibits lower FA and higher MD compared with term-born controls at birth, adolescence and young adulthood (Li et al., 2014; Pandit et al., 2013). Several white matter tracts are affected, including motor pathways such as the corticospinal tract (CST) and the corpus callosum (CC) (Eikenes et al., 2011; Groeschel et al., 2014). Although most studies have reported lower FA in VLBW individuals compared with controls, segmented analyses of the CST have demonstrated that FA varies significantly along the tract. In crossing fibre regions, such as the corona radiata and centrum semiovale, FA has been shown to be higher in VLBW young adults than controls, while FA was lower in the VLBW group in non-crossing fibre regions, such as the capsula interna (Groeschel et al., 2014; Jurcoane et al., 2016). This indicates that crossing fibres affect FA differently in the two groups.

To find a structural explanation for the commonly seen fine and gross motor problems in VLBW individuals, some studies have searched for microstructural correlates to motor problems in the whole brain and in specific motor tracts. Better fine motor performance at two years has been found to correlate with higher FA in all major white matter tracts by TBSS in very preterm infants at term equivalent age (van Kooij et al., 2012). Another study did not find any correlation between motor function and FA at two years of age in very preterm children without major motor problems and focal lesions (Counsell et al., 2008). In older VLBW children and adolescents, reduced FA in several white matter tracts has been shown to be associated with motor problems (de Kieviet et al., 2014; Li et al., 2014; Skranes et al., 2007), while FA in the CST of VLBW adults was not associated with motor problems at eight years (Jurcoane et al., 2016). Hence, the few existing studies investigating structural white matter correlates to motor problems yield mixed findings, possibly due to variation in DTI analysis and motor assessments. Furthermore, there are no studies examining associations between fine and gross motor function and DTI metrics in segmented regions of motor tracts in preterm populations.

The aim of this study was to investigate associations between fine and gross motor function and FA in non-crossing and crossing fibre regions of the CST and CC with probabilistic tractography in VLBW young adults without cerebral palsy compared with a term-born control group. Moreover, we wanted to examine group differences in DTI metrics in the whole brain by tract-based spatial statistics (TBSS). We hypothesized that, within the VLBW group, poorer motor function would be associated with lower FA in motor pathways of the CST and CC, especially in non-crossing fibre regions. More specifically, we hypothesized that poorer basic fine motor function was associated with lower FA in the CST from the primary motor cortex and that poorer complex fine motor function was associated with lower FA in the CST from the primary and premotor cortices. Furthermore, we hypothesized that poorer bimanual coordination was associated with lower FA in the

CC connecting the primary motor and premotor cortices in addition to FA in the CST from the primary motor and premotor cortices. For gross motor function, we hypothesized that lower scores on automatic tasks were associated with lower FA in the CST from the primary motor cortex, and that lower scores on tasks involving planning were associated with lower FA in the CST from the premotor cortex. As for group differences in DTI metrics, we hypothesized that VLBW young adults had lower FA and higher MD in all major white matter tracts by TBSS compared with controls.

## 2. Materials and methods

### 2.1. Study design

The present study is part of a prospective hospital-based study of a preterm born VLBW group (birth weight  $\leq 1500$  g) and a term-born control group (gestational age  $\geq 37$  weeks). Clinical tests and cerebral magnetic resonance imaging (MRI) have been carried out at 1, 5, 14 and 20 years of age (Eikenes et al., 2011; Skranes et al., 2007; Skranes et al., 1997; Skranes et al., 1993). The VLBW children were born in 1986–1988 and admitted to the Neonatal Intensive Care Unit (NICU) at St. Olavs Hospital, Trondheim University Hospital, Norway. The control children were included at birth in the same period. They were born to a 10% random sample of women living in the Trondheim region, originally selected for follow-up during pregnancy in a multicentre study (Bakketeig et al., 1993). At 23 years, we aimed to include the VLBW and control participants from the 14-year follow-up in order to compare motor function longitudinally (Husby et al., 2013).

### 2.2. Participants

#### 2.2.1. VLBW group

At age 23, we contacted 54 VLBW young adults, whereof 18 (33%) did not consent, leaving 36 (67%) VLBW young adults for motor and MRI examinations. Four (11%) of these had cerebral palsy and were therefore excluded from the study. Additionally, one VLBW participant was excluded due to image artefacts, leaving data from 31 VLBW participants suitable for analyses.

#### 2.2.2. Control group

At age 23, we contacted 48 controls matched to the VLBW participants by age and sex. Two of the contacted controls were not testable due to pregnancy, five had moved too far away and four did not consent. Thus, 37 (77%) controls underwent motor and MRI examinations, whereof six were excluded due to image artefacts, leaving data from 31 control participants suitable for analyses.

#### 2.2.3. Non-participants

There were no significant differences between those who participated and those who did not consent to or were not contacted for participation at age 23 in either group with regard to perinatal data, parental socioeconomic status (SES) or motor skills at 14 years (data not shown).

### 2.3. Clinical characteristics

Perinatal data included birth weight, gestational age, birth head circumference, Apgar scores, days in NICU, days on mechanical ventilator, proportion of infants with intraventricular haemorrhage and maternal age. At 14 years, parental SES was calculated according to Hollingshead's Two factor index of social position (Hollingshead, 1957), rated from 1 (lowest) to 5 (highest) based on a combination of parents' education and occupation.

## 2.4. Motor assessments

The motor assessments were carried out by experienced examiners, blinded to neonatal history, clinical characteristics and results from previous follow-up. The dominant hand was defined as the writing hand and the dominant foot was self-reported or defined as the preferred foot for one leg stand.

### 2.4.1. Trail Making Test-5 (TMT-5)

TMT-5 is part of the standardized Delis-Kaplan Executive Function System and measures motor speed (Delis et al., 2001). The task is to draw a line as fast as possible (time in seconds) between 32 circles in the order directed by a dotted line. The test is performed with the dominant hand only and we considered it as a test of basic fine motor function.

### 2.4.2. Grooved Pegboard

Grooved Pegboard requires complex visual-motor coordination and measures how quickly (time in seconds) the participants can insert pegs into 25 keyhole-shaped holes with various orientations in a  $5 \times 5$  matrix with each hand separately (Grooved Pegboard Test. User instructions, 2002). We considered this test as a test of complex fine motor function.

### 2.4.3. Triangle from Movement Assessment Battery for Children-2 (MABC-2)

MABC-2 is a comprehensive motor test battery that identifies and evaluates children's motor development (Henderson et al., 2007). We used the item Triangle as a test for bimanual coordination. The task is to form a triangle out of three strips, nuts and bolts with both hands as fast as possible. Raw scores (time in seconds) were used in this study.

### 2.4.4. High-level Mobility Assessment Tool (HiMAT)

HiMAT examines gross motor function (Williams et al., 2005a; Williams et al., 2005b) and raw scores of the seven timed items (in seconds) were used in this study. We grouped these items in two categories based on the involvement of automatic or planned movements; HiMAT automatic (Walk, Walk on toes, Run) and HiMAT planned (Walk backwards, Walk over obstacle, Skip, Hop forward).

## 2.5. Image acquisition

At 23 years, DTI was acquired on a 3 T Siemens Trio with Quantum gradients (30 mT/m) and a 12-channel head matrix coil (Siemens AG, Erlangen, Germany) at St. Olavs Hospital, Trondheim University Hospital, Norway. To reduce movement, foam pads were placed around the participants' heads. DTI was acquired with a single-shot balanced-echo EPI sequence with  $b = 1000 \text{ s/mm}^2$  in 30 non-collinear directions using the following parameters: TR = 6800 ms, TE = 84 ms, FOV =  $240 \times 240 \text{ mm}$ , slice thickness 2.5 mm, acquisition matrix  $96 \times 96$ , giving isotropic voxels of 2.5 mm. Full brain coverage was obtained with 55 transversal slices with no gap. For each slice, six images without diffusion weighting ( $b = 0$ ) were acquired. The DTI sequence was repeated two times for increased signal-to-noise ratio. To correct for image distortion caused by magnetic susceptibility artefacts (Holland et al., 2010), two additional  $b_0$  images were acquired with opposite phase-encode polarity.

## 2.6. Image analyses

The DTI analyses were performed with the tools of the FMRIB Software Library (FSL; Oxford Centre for Functional MRI of the Brain, UK; [www.fmrib.ox.ac.uk/fsl](http://www.fmrib.ox.ac.uk/fsl)). Image artefacts due to motion and eddy current distortions were minimized by registration of all DTI acquisitions to the mean  $b = 0$  image using affine registration. Image distortion caused by magnetic susceptibility artefacts was minimized with a

nonlinear B0-unwarping method using paired images with opposite phase-encode polarities (Holland et al., 2010). The brain was extracted using Brain Extraction Tool (BET, part of FSL). FMRIB's Diffusion Toolbox (FDT) was used to fit a diffusion tensor model to the raw diffusion data in each voxel. Voxel-wise maps of FA, MD, axial (AD;  $\lambda_1$ ) and radial diffusivity (RD;  $(\lambda_2 + \lambda_3) / 2$ ) were calculated for the VLBW and control group.

### 2.6.1. Probabilistic tractography

Fibre tractography of the CST and CC was performed using BedpostX, a probabilistic tractography routine implemented in FSL based on a multifibre model (Behrens et al., 2007). The following parameters were used: 5000 streamline samples, 0.5 mm step lengths, curvature thresholds = 0.2.

**2.6.1.1. Corticospinal tract (CST).** A region-of-interest (ROI) approach was used to track the CST fibres connecting from a seed ROI in the cerebral peduncles to three different target ROIs in the primary motor and premotor cortices. The seed ROI was placed manually in three contiguous slices in the cerebral peduncle on each participant's colour-coded FA map in individual space based on anatomical landmarks in the FA map (Fig. 1).

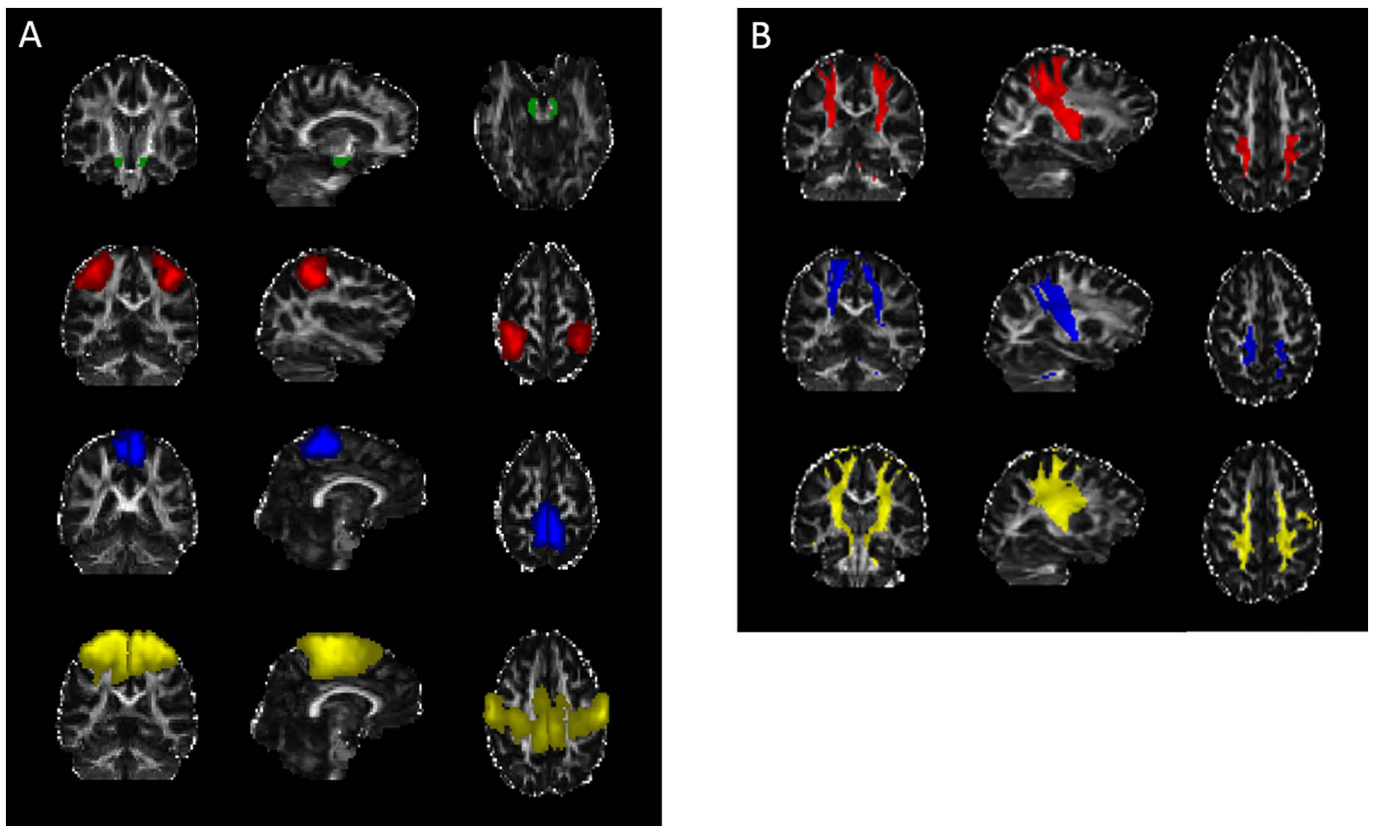
For the primary motor cortex, we wanted to select the hand and foot areas specifically as target ROIs for tracking of  $\text{CST}_{\text{hand}}$  and  $\text{CST}_{\text{foot}}$ . Due to the difficulty of depicting the foot area of the primary motor cortex based on anatomy or template based atlases, both foot and hand ROIs were based on functional ROIs obtained in a group of young healthy adults in MNI space (Berntsen et al., 2008).

For the  $\text{CST}_{\text{premotor}}$  tracking, the target ROI was placed in the premotor cortex as defined by the Juelich Histological atlas in FSL (Eickhoff et al., 2005) in MNI space. The target ROIs in the primary motor and premotor cortices were transformed from MNI space to each participant's individual FA space using linear and non-linear registration (FLIRT and FNIRT, FMRIB's Linear and Non-Linear Image Registration Tool) between each participant's FA map and the MNI FA-template (FMRIB58\_FA\_1mm).

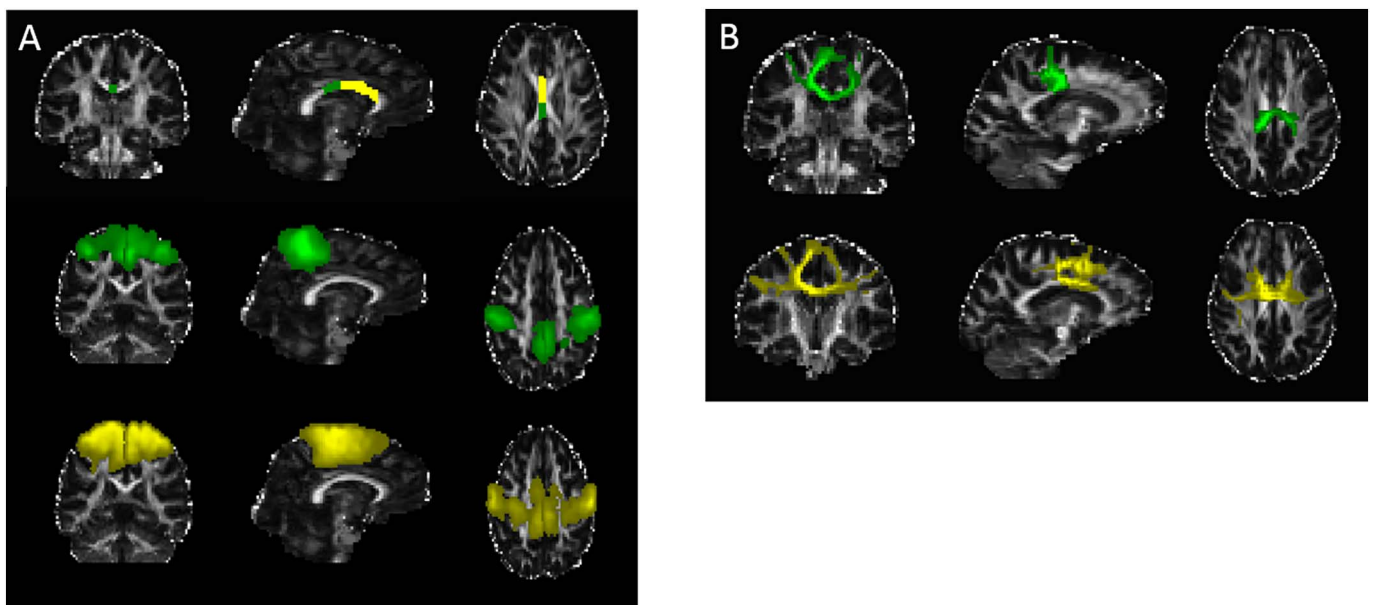
Only streamlines passing through the seed ROI and the target ROI were included in the analyses. The CST tracking was performed separately for the left and right hemispheres. An exclusion mask (not shown) was included in the midline of the brain dividing the two hemispheres, and streamlines were discarded if they entered the exclusion mask.

**2.6.1.2. Corpus callosum (CC).** For tracking of the CC, a three ROI approach was used to select the CC fibres connecting the primary motor ( $\text{CC}_{\text{motor}}$ ) and the premotor ( $\text{CC}_{\text{premotor}}$ ) cortices (Fig. 2). The seed ROIs were placed manually on each participant's colour-coded FA map in individual space in three contiguous sagittal slices of CC region number II and III according to Hofer and Frahm (2006), comprising premotor and motor fibres, respectively (Hofer and Frahm, 2006). The target ROIs were placed in the primary motor and the premotor cortices in the left and right cerebral hemispheres, as defined by the Juelich Histological atlas in FSL (Eickhoff et al., 2005). The target ROIs were given in MNI space, and were transformed from MNI to each participant's individual FA space using FLIRT and FNIRT. Only streamlines passing through the seed ROI and the target ROIs were included in the analyses. An exclusion mask (not shown) was included in the axial slice inferior to the sagittal seed ROIs, and streamlines were discarded if entering the exclusion mask. We chose to use the whole primary motor cortex instead of the hand and foot areas in the CC tracking, because pilot testing showed that few streamlines passed through the CC to the hand area lateral in the primary motor cortices. The difficulty of resolving lateral projections of the CC has been described earlier (Hofer and Frahm, 2006).

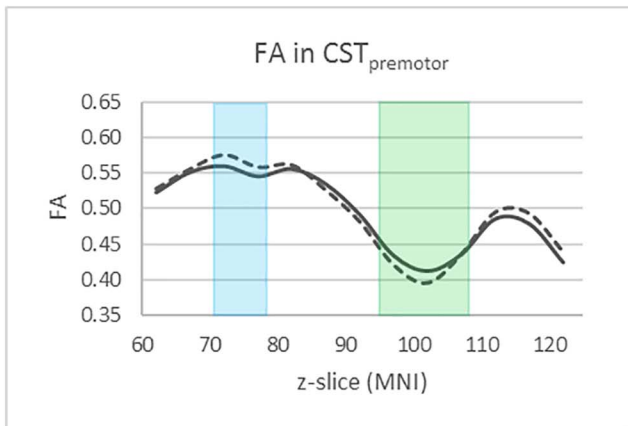
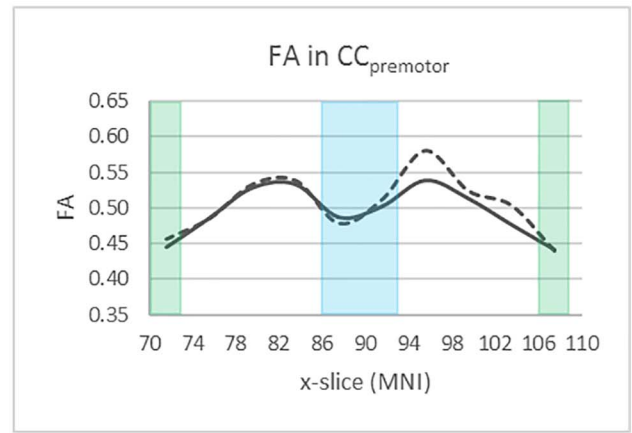
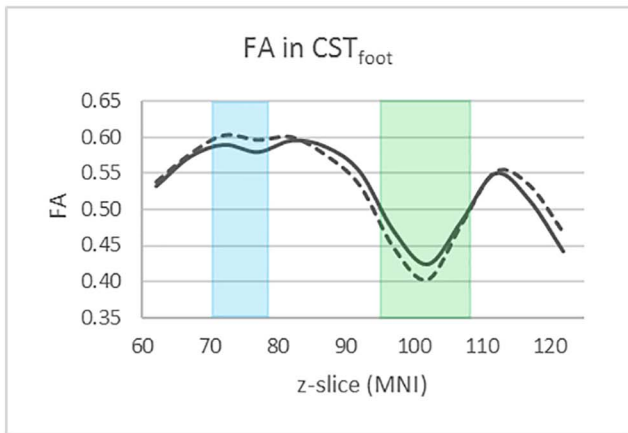
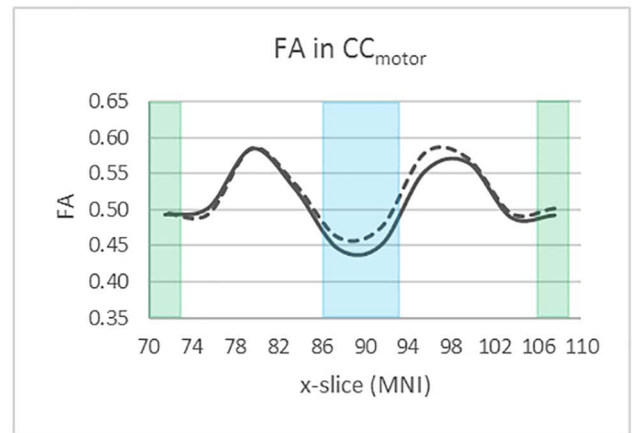
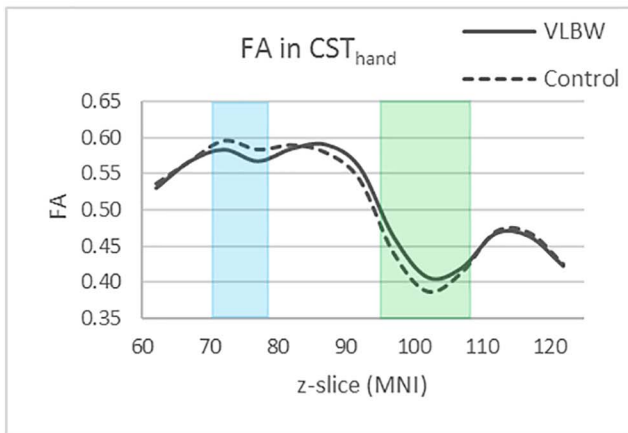
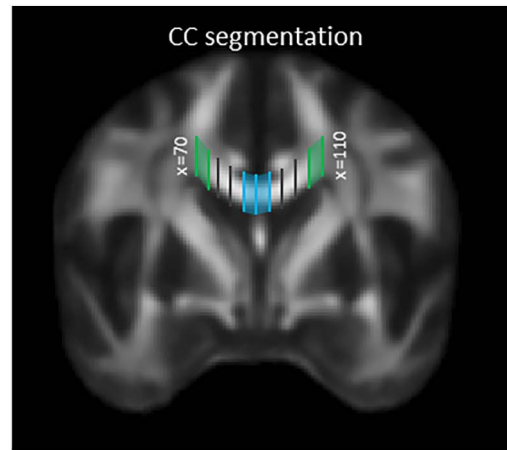
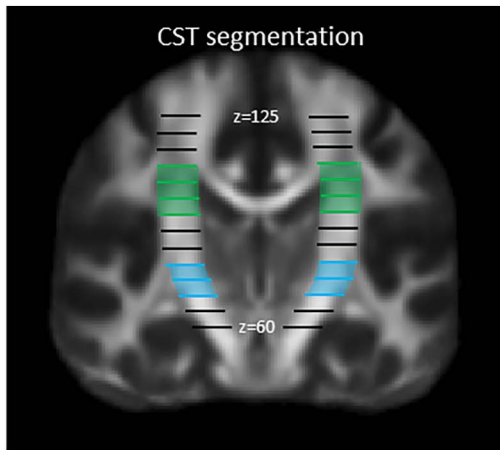
**2.6.1.3. Quality control.** The registration of the ROIs from MNI to individual space and resulting fibre tracts were visually inspected for



**Fig. 1.** A) ROIs used for the probabilistic tractography of the left and right corticospinal tract (CST): Seed ROI in the cerebral peduncles (green) and target ROIs in the hand area in the primary motor cortex (red), foot area in the primary motor cortex (blue) and premotor cortex (yellow). B) Probabilistic tractography results of the  $CST_{hand}$  (red),  $CST_{foot}$  (blue) and  $CST_{premotor}$  (yellow). Underlying coronal, sagittal and axial gray scaled image is the FA map for one of the participants in the study in individual space. Abbreviations: ROI, region-of-interest; CST, corticospinal tract; FA, fractional anisotropy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 2.** A) ROIs used for probabilistic tractography of the corpus callosum (CC): Seed ROIs in the CC corresponding to areas connecting the primary motor (green) and premotor cortices (yellow), target ROIs in the primary motor cortex (green) and premotor cortex (yellow). B) Probabilistic tractography results of the  $CC_{motor}$  (green) and  $CC_{premotor}$  (yellow). Underlying coronal, sagittal and axial gray scaled image is the FA map for one of the participants in the study in individual space. Abbreviations: ROI, region-of-interest; CC, corpus callosum; FA, fractional anisotropy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



(caption on next page)

**Fig. 3.** Segmentation of the corticospinal tract (CST) and the corpus callosum (CC) are shown in MNI template space in the first row. The graphs show fractional anisotropy (FA) (y-axis) in the contralateral CST to the dominant hand and CC slice-wise along the tracts (x-axis) in MNI template space for the VLBW group (solid lines) and the control group (dashed lines). Blue and green areas are volumes of interest indicating regions of the tracts with predominantly non-crossing and crossing fibres, respectively.

each participant, and the tractography results were thresholded (50 for the CST and 300 for the CC) in order to include only anatomical plausible pathways. All manually placed ROIs were drawn by the same researcher, blinded to neonatal history, clinical characteristics and results from previous follow-up.

**2.6.1.4. Segmentation of the CST and CC.** Segmentation of the tracts was performed by generating slice-wise tract profiles along the z-axis (inferior-superior) for the CST<sub>hand</sub>, CST<sub>foot</sub> and CST<sub>premotor</sub> and along the x-axis (left-right) for the CC<sub>motor</sub> and CC<sub>premotor</sub> in order to calculate FA at equivalent levels across individuals. These tract profiles are shown in Fig. 3. The slices were defined in MNI space and warped into each participant's individual space using the corresponding warp field computed in the TBSS procedure with FLIRT/FNIRT.

For the CST tracts, the slice-wise measurements were acquired for five contiguous slices from the cerebral peduncles ( $z = 60$ ) to above the lateral ventricles ( $z = 124$ ), thus generating 13 volumes-of-interest (VOIs). For the CC tracts, the slice-wise measurements were acquired for four contiguous slices between the lateral parts of the CC from left to right ( $x = 70$ – $109$ ), thus generating 10 VOIs. Furthermore, the slice-wise measurements were divided into regions of predominantly non-crossing and crossing fibres. For the CST, non-crossing regions were defined as an area with few large crossing fibres, corresponding to the capsula interna ( $z = 70$ – $79$ ), and crossing fibre regions were defined as the area where the superior longitudinal fascicle crosses the CST, corresponding to the centrum semiovale and corona radiata ( $z = 95$ – $109$ ) (Fig. 3). For the CC, the non-crossing region was defined as the medial part, corresponding to the body of the CC where there are less crossing fibres ( $x = 86$ – $93$ ) (Groeschel et al., 2014), while the crossing fibre regions were defined as the lateral parts of the CC, corresponding to the centrum semiovale ( $x = 70$ – $73$  and  $x = 106$ – $109$ ) (Fig. 3). FA was measured at the intersection of the VOIs and the streamlines. Mean FA was calculated for non-crossing and crossing fibre regions for the CST<sub>hand</sub>, CST<sub>foot</sub>, CST<sub>premotor</sub>, CC<sub>motor</sub> and CC<sub>premotor</sub> tractography results in all VLBW and control individuals.

### 2.6.2. Tract-based spatial statistics (TBSS)

Voxel-wise statistical analysis was performed using TBSS (part of FSL) (Smith et al., 2006). A detailed description is given elsewhere (Eikenes et al., 2011). Voxel-wise statistics of the skeletonized FA, MD, AD and RD were carried out on the white matter skeleton using Randomise (part of FSL) to test for group differences between the VLBW and control group. Randomise performs non-parametric permutation-based testing and inference using Threshold-Free Cluster Enhancement (Nichols and Holmes, 2002) with a correction for multiple comparisons ( $p < 0.05$ , corrected for sex and age at MRI).

### 2.7. Statistical analyses

Student's *t*-test was used for approximately normally distributed data; else the Mann–Whitney *U* test was applied. Normality was assessed by visual inspection of Q-Q plots of the residuals. Linear regression was applied to explore associations between motor test scores and FA in non-crossing and crossing fibre regions of the CST and CC. Motor test scores were entered separately as dependent variables, whereas FA, group, sex, age and the interaction FA  $\times$  group were entered as independent variables. The interaction term was added to test if the effect of FA was different in VLBW and control participants. We re-categorized the left and right CST into contralateral CST to the dominant and non-dominant hand. For motor tests performed with one hand (TMT-5 and Grooved Pegboard), only the contralateral CST in the

brain was included in the association analyses to reduce the number of analyses. For motor tests performed with two hands (MABC-2 Triangle) or the whole body (HiMAT), the right and left CST were averaged in the association analyses as this gave similar results as separate analyses of each side. Two-sided *p*-values  $< 0.05$  were considered statistically significant. Given the relatively small sample size, no correction for multiple comparisons was applied for linear regression. SPSS 22.0 was used for statistical analyses.

### 2.8. Ethics

The project complies with the principles of the Declaration of Helsinki and the study protocol was approved by the Regional Committee for Medical and Health Research Ethics in Central Norway (REK number 4.2005.2605). Written informed consent was obtained from the participants.

## 3. Results

### 3.1. Clinical characteristics

Table 1 shows the clinical characteristics of the VLBW and the control group. Birth weight and gestational age differed by definition between the groups and, as expected, head circumference at birth and Apgar scores were lower in the VLBW group. There were no statistically significant group differences in maternal age, parental SES, age at follow-up or sex distribution.

### 3.2. Motor function

Table 2 shows fine and gross motor test scores in the VLBW and the control group. The VLBW group used longer time than controls on all fine

**Table 1**  
Clinical characteristics of the VLBW group compared with the control group at 23 years of age.

	VLBW (n = 31)		Control (n = 31)		p-value
	Mean	(SD)	Mean	(SD)	
Birth weight (g)	1238	(219)	3603	(364)	< 0.001
Gestational age (weeks)	29.4	(2.7)	39.5	(1.1)	< 0.001
Birth head circumference (cm) <sup>a</sup>	27.4	(2.3)	35.3	(1.2)	< 0.001
Apgar score after 1 min <sup>b</sup>	6.7	(1.9)	8.9	(0.4)	< 0.001
Apgar score after 5 min <sup>c</sup>	8.4	(1.7)	9.7	(1.7)	0.005
Maternal age	28.8	(5.2)	30.2	(4.2)	0.262
Parental SES at 14 years <sup>c</sup>	3.4	(1.2)	3.7	(1.0)	0.462
Age at follow-up	22.5	(0.7)	22.7	(0.7)	0.253
	n	(%)	n	(%)	
Boys	11	(35.5)	14	(42.2)	0.437
Intraventricular haemorrhage <sup>d</sup>	2	(6.7)	NA	NA	
	Median	(Range)	Median	(Range)	
Stay in NICU (days) <sup>e</sup>	60	(25–386)	NA	NA	
Mechanical ventilation (days) <sup>e</sup>	1	(0–44)	NA	NA	

Analyses performed with Student's *t*-test and Mann-Whitney *U* test.

Abbreviations: VLBW, very low birth weight; SES, socioeconomic status; NICU, neonatal intensive care unit; NA, not applicable.

<sup>a</sup> Data missing for seven VLBW and two control participants.

<sup>b</sup> Data missing for three control participants.

<sup>c</sup> Data missing for two control participants.

<sup>d</sup> Grade I and II.

<sup>e</sup> Data missing for two VLBW participants.

**Table 2**  
Motor test scores in the VLBW group compared with the control group at 23 years of age.

	VLBW (n = 31)		Control (n = 31)		p-value
	Mean	(SD)	Mean	(SD)	
<b>Fine motor tests (sec)</b>					
Trail Making Test-5	28.5	(11.1)	19.7	(5.7)	< 0.001
Grooved Pegboard dom. hand	68.6	(17.2)	63.5	(9.9)	0.161
Grooved Pegboard non-dom. hand	73.6	(13.5)	68.1	(11.0)	0.080
MABC-2 triangle	36.5	(12.0)	32.8	(7.4)	0.152
<b>Gross motor tests (sec)</b>					
HiMAT automatic	10.6	(1.8)	10.1	(1.6)	0.247
Walk	3.9	(0.7)	3.9	(0.6)	0.614
Walk on toes	4.8	(1.0)	4.5	(1.0)	0.234
Run	1.9	(0.3)	1.7	(0.2)	0.045
HiMAT planned	16.6	(3.5)	15.3	(2.4)	0.088
Walk backwards	5.4	(1.8)	4.8	(0.8)	0.071
Walk obstacle	4.1	(0.7)	4.0	(0.7)	0.377
Skip	3.0	(0.6)	2.9	(0.6)	0.227
Hop forward	4.7	(2.7)	3.6	(0.8)	0.039

Analyses performed with Student's t-test.

Abbreviations: VLBW, very low birth weight; dom, dominant; MABC-2, Movement Assessment Battery for Children-2; HiMAT, High-level Mobility Assessment Tool.

motor tests, however only significant for TMT-5 (Table 2). On gross motor tests, there were no significant group differences for HiMAT automatic and HiMAT planned. However, VLBW young adults were significantly slower than controls on the items Run and Hop forward (Table 2).

### 3.3. Probabilistic tractography

Table 3 shows that FA was lower in non-crossing fibre regions and higher in crossing fibre regions of the CST in the VLBW group compared with the control group. There were no group differences in FA of the CC (Table 3). Fig. 3 shows graphs of FA in the segmented parts of the CST and CC.

**Table 3**

Mean fractional anisotropy in predominantly crossing and non-crossing fibre regions of the corticospinal tract (CST)<sup>a</sup> and the corpus callosum (CC)<sup>b</sup> in the VLBW group and the control group.

Motor tract	Tract region	VLBW (n = 31)		Control (n = 31)		p-value
		Mean	(SD)	Mean	(SD)	
CST <sub>hand</sub> dom	Non-crossing	0.575	(0.038)	0.589	(0.030)	0.100
	Crossing	0.430	(0.040)	0.413	(0.030)	0.063
CST <sub>hand</sub> non-dom	Non-crossing	0.572	(0.037)	0.596	(0.037)	0.012
	Crossing	0.440	(0.039)	0.423	(0.025)	0.046
CST <sub>foot</sub> dom	Non-crossing	0.584	(0.039)	0.600	(0.033)	0.097
	Crossing	0.459	(0.045)	0.443	(0.030)	0.108
CST <sub>foot</sub> non-dom	Non-crossing	0.587	(0.040)	0.609	(0.031)	0.017
	Crossing	0.468	(0.043)	0.442	(0.026)	0.006
CST <sub>premotor</sub> dom	Non-crossing	0.552	(0.040)	0.568	(0.031)	0.090
	Crossing	0.428	(0.027)	0.418	(0.024)	0.127
CST <sub>premotor</sub> non-dom	Non-crossing	0.544	(0.033)	0.544	(0.042)	0.995
	Crossing	0.434	(0.025)	0.424	(0.019)	0.086
CC <sub>motor</sub>	Non-crossing	0.448	(0.049)	0.469	(0.039)	0.066
	Crossing	0.492	(0.042)	0.499	(0.284)	0.456
CC <sub>premotor</sub>	Non-crossing	0.495	(0.030)	0.495	(0.037)	0.949
	Crossing	0.444	(0.034)	0.448	(0.032)	0.671

Analyses performed with Student's t-test. Dom and non-dom indicate the contralateral CST to the dominant and non-dominant hand, respectively.

Abbreviations: CST, corticospinal tract; CC, corpus callosum; VLBW, very low birth weight; dom, dominant.

<sup>a</sup> CST<sub>hand</sub>, CST from hand area in primary motor cortex; CST<sub>foot</sub>, CST from foot area in primary motor cortex; CST<sub>premotor</sub>, CST from premotor cortex.

<sup>b</sup> CC<sub>motor</sub>, CC connecting the primary motor cortices; CC<sub>premotor</sub>, CC connecting the premotor cortices.

### 3.4. Associations between motor function and fractional anisotropy of CST and CC by probabilistic tractography

There were significant between-group differences for some of the associations between fine motor test scores and FA in non-crossing and crossing fibre regions of the CST and CC (Table 4). Within the VLBW group, there were no significant associations between motor tests and FA in non-crossing fibre regions. However, there were several significant associations in crossing fibre regions of the CST and CC within the VLBW group, both positive and negative. For fine motor function, poorer performance on TMT-5 was associated with higher FA in crossing fibre regions of CST<sub>hand</sub> and poorer performances on Grooved Pegboard dominant hand and MABC-2 Triangle were associated with higher FA in crossing fibre regions of CST<sub>hand</sub> and CST<sub>premotor</sub>. In contrast, poorer performance on MABC-2 Triangle was associated with lower FA in crossing fibre regions of CC<sub>motor</sub>. For gross motor function, poorer performance on HiMAT planned was associated with lower FA in crossing fibre regions of CST<sub>foot</sub> and CC<sub>premotor</sub>. Within the control group, poorer performance on Grooved Pegboard non-dominant hand was associated with lower FA in non-crossing fibre regions of CST<sub>hand</sub> and CST<sub>premotor</sub>, and poorer performance on MABC-2 Triangle was associated with higher FA in crossing fibre regions of CC<sub>motor</sub>.

### 3.5. Tract-based spatial statistics (TBSS)

TBSS analysis demonstrated lower FA and higher MD in the VLBW group compared with controls in all major white matter tracts (Fig. 4). FA was lower in 34% and MD higher in 45% of the total voxels on the white matter skeleton at the group level. Lower FA was mainly caused by higher RD (83% of the voxels with lower FA) (data not shown). There were no voxels with higher FA and/or lower MD in the VLBW group compared with the control group.

## 4. Discussion

In this study, fine and gross motor function were associated with FA only in crossing fibre regions of the CST and CC in VLBW young adults without cerebral palsy. The associations between fine motor function and FA in the CST were in the opposite direction than expected, with poorer motor function being associated with higher FA. Moreover, the VLBW group had lower FA and higher MD in all major white matter tracts compared with controls at 23 years of age.

As hypothesized, the basic fine motor test (TMT-5) was associated with FA in the CST from the primary hand motor cortex, and the complex fine motor test (Grooved Pegboard) was additionally associated with FA in the CST from the premotor cortex. The test for bimanual coordination (MABC-2 Triangle) was as hypothesized associated with FA in the CST from the primary hand and premotor cortices, and with FA in the CC connecting the primary motor cortices. We expected this test to also be associated with FA in the CC connecting the premotor cortices, as the supplementary motor cortex is important for bimanual coordination (Johansen-Berg et al., 2007). For gross motor function, only HiMAT planned was significantly associated with FA in the CST and CC within the VLBW group, possibly indicating that the items of HiMAT automatic were too easy to detect differences between the groups. The finding of timed motor performances being associated with FA may support our former speculations that reduced motor speed is one of the key issues in preterm populations and is related to white matter microstructure in the preterm brain (Husby et al., 2013).

As we found an association between motor function and FA only in crossing fibre regions (centrum semiovale) of the CST, this may indicate that crossing tracts are causing the association and/or that the periventricular white matter is an especially vulnerable region in VLBW individuals (Volpe, 2003), affecting motor function. Furthermore, the direction of the associations was both positive and negative, which is

**Table 4**

Associations between motor test scores and mean FA in non-crossing and crossing fibre regions of the corticospinal tract (CST)<sup>a</sup> and corpus callosum (CC)<sup>b</sup> in the VLBW group and the control group at 23 years of age.

	Mean FA of motor tracts	VLBW (n = 31)			Control (n = 31)			FA × group	
		B	(95% CI)	p-value	B	(95% CI)	p-value	p-value	
Fine motor tests (sec)	Motor tract	Tract region							
Trail Making Test-5 dominant hand	CST <sub>hand</sub>	Non-crossing	− 11.7	(− 96.6 to 73.2)	0.783	24.5	(− 82.2 to 125.2)	0.679	0.623
		Crossing	100.8	(24.0 to 177.6)	0.011	45.4	(− 50.4 to 141.2)	0.346	0.370
	CST <sub>premotor</sub>	Non-crossing	− 22.1	(− 101.0 to 56.8)	0.577	31.2	(− 68.8 to 131.2)	0.535	0.407
		Crossing	100.1	(− 16.7 to 217.0)	0.092	17.6	(− 108.4 to 143.7)	0.780	0.336
Grooved Pegboard dominant hand	CST <sub>hand</sub>	Non-crossing	− 75.3	(− 220.0 to 69.4)	0.302	− 7.7	(− 184.4 to 169.0)	0.931	0.558
		Crossing	177.7	(45.5 to 310.0)	0.009	− 42.1	(− 206.9 to 122.7)	0.611	0.042
	CST <sub>premotor</sub>	Non-crossing	− 71.5	(− 206.4 to 63.4)	0.293	− 7.3	(− 178.3 to 163.8)	0.933	0.558
		Crossing	207.8	(10.1 to 405.4)	0.040	− 61.6	(− 274.7 to 151.5)	0.565	0.066
Grooved Pegboard non-dominant hand	CST <sub>hand</sub>	Non-crossing	− 70.1	(− 193.2 to 53.1)	0.259	− 125.1	(− 248.1 to − 2.1)	0.046	0.526
		Crossing	88.2	(− 27.1 to 203.5)	0.131	− 180.5	(− 363.5 to 2.5)	0.053	0.015
	CST <sub>premotor</sub>	Non-crossing	2.9	(− 137.2 to 143.1)	0.967	− 121.5	(− 233.1 to − 9.8)	0.034	0.173
		Crossing	122.9	(− 62.3 to 308.1)	0.189	− 225.3	(− 466.7 to 16.0)	0.067	0.024
MABC-2 Triangle	CST <sub>hand</sub>	Non-crossing	8.2	(− 116.7 to 133.1)	0.895	29.9	(− 96.5 to 156.4)	0.637	0.807
		Crossing	139.8	(46.5 to 233.1)	0.004	62.7	(− 66.9 to 192.3)	0.337	0.336
	CST <sub>premotor</sub>	Non-crossing	45.5	(− 81.8 to 172.8)	0.477	− 1.7	(− 122.5 to 119.1)	0.978	0.594
		Crossing	174.9	(23.9 to 326.0)	0.024	97.5	(− 74.2 to 269.3)	0.260	0.494
	CC <sub>motor</sub>	Non-crossing	− 42.3	(− 121.8 to 37.1)	0.290	11.5	(− 82.7 to 105.7)	0.807	0.371
		Crossing	− 102.0	(− 179.6 to − 24.4)	0.011	155.6	(40.6 to 270.7)	0.009	0.000
	CC <sub>premotor</sub>	Non-crossing	46.3	(− 76.2 to 168.8)	0.452	51.8	(− 46.2 to 149.8)	0.294	0.944
		Crossing	8.9	(− 97.4 to 115.2)	0.868	57.6	(− 55.8 to 171.1)	0.313	0.533
Gross motor tests (sec)									
HiMAT automatic	CST <sub>foot</sub>	Non-crossing	− 12.6	(− 31.1 to 5.9)	0.178	6.4	(− 15.6 to 28.4)	0.561	0.189
		Crossing	− 2.8	(− 19.3 to 13.7)	0.737	− 16.7	(− 41.0 to 7.5)	0.173	0.335
	CST <sub>premotor</sub>	Non-crossing	− 7.8	(− 29.7 to 14.1)	0.477	6.0	(− 14.8 to 26.8)	0.565	0.365
		Crossing	− 2.3	(− 29.2 to 24.5)	0.862	− 24.9	(− 55.5 to 5.6)	0.108	0.264
	CC <sub>motor</sub>	Non-crossing	6.8	(− 6.8 to 20.5)	0.320	− 6.6	(− 22.8 to 9.6)	0.417	0.196
		Crossing	− 4.2	(− 18.9 to 10.6)	0.576	12.3	(− 9.6 to 34.2)	0.266	0.220
	CC <sub>premotor</sub>	Non-crossing	7.4	(− 13.9 to 28.6)	0.491	− 5.3	(− 22.3 to 11.7)	0.538	0.355
		Crossing	− 8.9	(− 27.1 to 9.3)	0.332	− 9.3	(− 28.7 to 10.1)	0.342	0.976
HiMAT planned <sup>c</sup>	CST <sub>foot</sub>	Non-crossing	− 13.3	(− 44.9 to 18.3)	0.404	4.6	(− 32.9 to 42.2)	0.805	0.465
		Crossing	− 36.0	(− 65.5 to − 6.6)	0.017	− 30.0	(− 70.2 to 10.2)	0.140	0.805
	CST <sub>premotor</sub>	Non-crossing	− 0.6	(− 37.5 to 36.4)	0.975	5.6	(− 29.5 to 40.7)	0.751	0.810
		Crossing	− 40.3	(− 86.1 to 5.4)	0.083	− 40.1	(− 91.0 to 10.8)	0.120	0.994
	CC <sub>motor</sub>	Non-crossing	17.1	(− 5.2 to 39.4)	0.131	− 19.2	(− 45.9 to 7.4)	0.154	0.036
		Crossing	− 8.7	(− 33.5 to 16.1)	0.485	18.0	(− 19.2 to 55.2)	0.337	0.239
	CC <sub>premotor</sub>	Non-crossing	2.8	(− 33.1 to 38.7)	0.876	− 14.4	(− 43.3 to 14.5)	0.321	0.455
		Crossing	− 35.6	(− 65.3 to − 5.9)	0.020	− 22.2	(− 53.2 to 8.8)	0.157	0.534

Regression coefficient B for FA in a linear regression with motor tests as dependent variables and FA, group and FA × group (indicating between-group differences) as independent variables. Adjusted for sex and age. For motor tests performed with one hand, FA in the contralateral CST was used in the analyses. For Triangle and HiMAT, mean FA in CST right and left was used in the analyses.

Abbreviations: FA, fractional anisotropy; CST, corticospinal tract; CC, corpus callosum; VLBW, very low birth weight; MABC-2, Movement Assessment Battery for Children-2; HiMAT, High-level Mobility Assessment Tool.

<sup>a</sup> CST<sub>hand</sub>, CST from hand area in primary motor cortex; CST<sub>foot</sub>, CST from foot area in primary motor cortex; CST<sub>premotor</sub>, CST from premotor cortex.

<sup>b</sup> CC<sub>motor</sub>, CC connecting the primary motor cortices; CC<sub>premotor</sub>, CC connecting the premotor cortices.

<sup>c</sup> Data missing for one participant in each group.

difficult to explain. We speculate that the association between poorer motor function and higher FA may be related to the effect of crossing fibres. The superior longitudinal fasciculus is the largest tract crossing the CST in centrum semiovale, and was found to have lower FA in VLBW young adults than controls in the present study as well as other studies (Allin et al., 2011; Eikenes et al., 2011). These crossing fibres with lower FA will to a lesser extent than in controls reduce the apparent AD and thereby reduce the FA value in the voxels of this crossing fibre region. These voxels are therefore likely to show higher FA in VLBW individuals compared with controls, which was found in our study and has also been shown in other studies (Groeschel et al., 2014; Jurcoane et al., 2016). In crossing fibre regions, higher FA in VLBW individuals compared with controls is therefore less likely to be a sign of improved white matter integrity, but rather a general sign of axon loss, poorer branching and dysmyelination, which may lead to poorer motor function. Thus, higher FA does not always indicate better function, as also shown in other studies (Hoefl et al., 2007; Steele et al., 2012). However, we also found associations between poorer motor function and lower FA in crossing fibre regions of CST<sub>foot</sub> and CC. These fibres

are located closer to the lateral ventricles than the CST<sub>hand</sub>, and may therefore be more affected by periventricular white matter damage. However, we do not know if and how this may affect the direction of the associations. Interesting future work could be to address these crossing fibre regions more closely by either performing tractography of selected crossing fibres in the areas of CST and CC where we found correlations between motor function and FA, performing other whole-brain tractography analysis methods, or by employing more advanced diffusion acquisitions and analysis which may give the opportunity to study multiple fibre orientations in each voxel.

Other studies have found an association between better motor function and higher FA in VLBW populations at different ages (de Kieviet et al., 2014; Skranes et al., 2007; Sripada et al., 2015; van Kooij et al., 2012), while some studies have not found any association between motor function and FA (Counsell et al., 2008; Jurcoane et al., 2016). However, it is difficult to compare the results from the various studies due to large differences in methodologies and age at examination. The relationship between motor function and FA might change during the course of development, and two of the studies did not assess



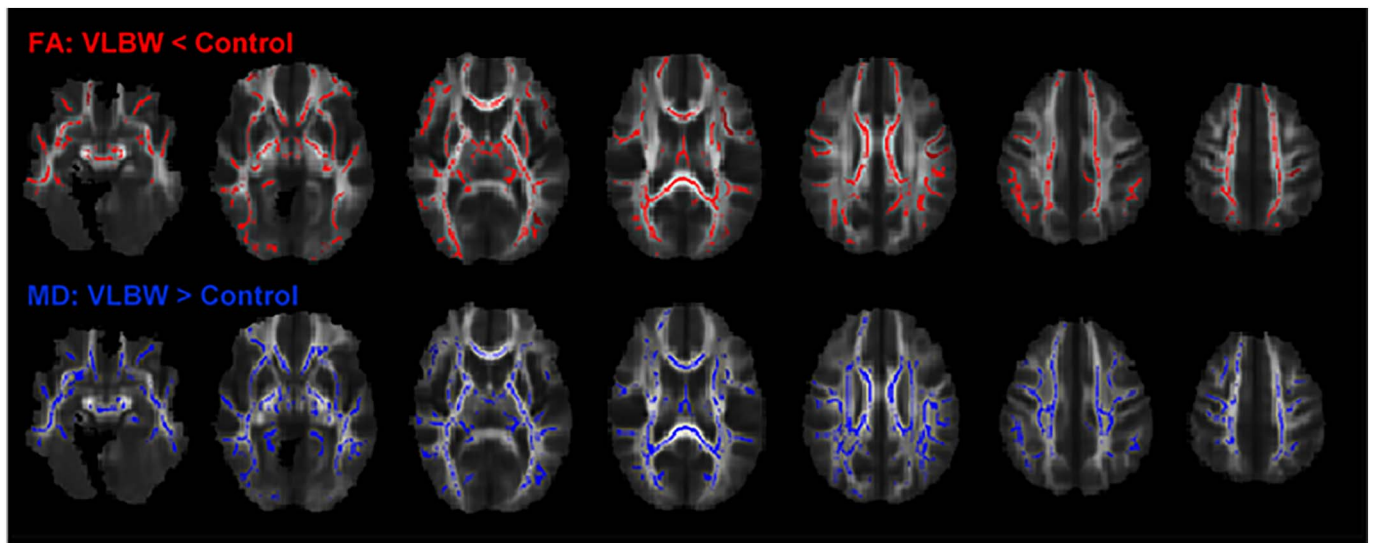


Fig. 4. TBSS analysis demonstrated significantly lower fractional anisotropy (red) and higher mean diffusivity (blue) in the VLBW group compared with the control group ( $p < 0.05$ , nonparametric permutation test, corrected for multiple comparisons, sex and age at MRI). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

motor function and DTI at the same time (Jurcoane et al., 2016; van Kooij et al., 2012). Furthermore, a large variety of motor assessments were used, possibly affecting the associations with FA. The former studies have also used various tractography and whole-brain voxel-based methods, thereby incorporating a different selection and extent of the white matter studied. Probabilistic tractography is likely to be more sensitive to the effects of crossing fibres on FA than TBSS, as also regions with low FA are included in the analyses.

In our study, TBSS was used to test for voxel-wise group differences in diffusion measures of white matter tracts in the whole brain. The finding of reduced FA and increased MD in all major white matter tracts in VLBW young adults compared with controls is in line with earlier findings in this cohort at age 15 and 20 years (Eikenes et al., 2011; Vangberg et al., 2006), as well as other studies of preterm born individuals at different ages (Li et al., 2014; Meng et al., 2016). The reduction of FA was caused by a significant increase in RD, possibly indicating reduced and aberrant myelination or poor axonal packing (Beaulieu, 2002; Song et al., 2005). Hence, these alterations may be related to the “encephalopathy of prematurity”, involving diffuse periventricular leukomalacia with a disturbed maturation of myelin-producing oligodendrocytes and injury of axons and subplate neurons (Volpe, 2009). However, other explanations for reduced anisotropy, like decreased fibre organization and increased membrane permeability, may not be excluded (Beaulieu, 2002).

Strengths of this study are the long-term follow-up of the two study groups, which were recruited at birth and equivalent in terms of maternal age and parental socioeconomic status. The groups have been followed prospectively with comprehensive multidisciplinary clinical, cognitive and MRI assessments at different ages. At 23 years, motor assessments were performed by experienced examiners and manual ROIs were drawn by the same researcher, all of whom were blinded to neonatal history and clinical outcome, thus reducing the risk of information bias. Only participants from the 14-year follow-up were invited, potentially increasing the risk of selection bias due to loss to follow-up from the original cohort. However, we found no differences in clinical characteristics at birth or motor skills at 14 years between those who participated and those who did not participate or were not invited to follow-up at 23 years in either of the groups. Due to the limited sample size, we chose not to correct for multiple comparisons for the association and tractography analyses to avoid potential type II errors. By using linear regression to examine associations between motor function and FA, both the VLBW and control group are included

in the analysis, thereby increasing statistical power. The main findings were consistent, indicating that they were not due to chance.

#### 4.1. Conclusion

Our findings showed that individual variability in motor function has structural correlates in VLBW young adults. Motor function was associated with FA only in crossing fibre regions of the CST and CC in the VLBW group, indicating that other tracts crossing the CST and CC are causing this association and/or that the vulnerable periventricular white matter in the centrum semiovale affect motor function. As poorer fine motor function was associated with higher FA, our results show that higher FA does not always indicate better function. Furthermore, VLBW young adults still showed widespread white matter alterations by TBSS, demonstrating that white matter abnormalities persist into young adulthood.

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