Chapter 6

A crucial role of altered white matter integrity in motor problems of very preterm children

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Submitted

Abstract

Objective Very preterm children (<32 weeks of gestation) are characterized by impaired white matter development. This study investigates whether altered white matter tract integrity underpins the widespread motor impairments and higher incidence of developmental coordination disorder (DCD) in very preterm children at school age.

Methods Thirty very preterm born children, mean (SD) age of 8.6 (0.3) years, and 47 term born controls participated. Motor development was measured using the Movement Assessment Battery for Children. A score below the 15th percentile was used as a research diagnosis of DCD. Fractional anisotropy (FA) values were measured for 18 major white matter tracts, obtained using probabilistic diffusion tensor tractography.

Results Large-sized reductions in FA of the cingulum hippocampal tract right (*d*=0.75, p=.003) and left (*d*=0.76, p=.001), corticospinal tract right (*d*=0.56, p=.02) and left (*d*=0.65, p=.009), forceps major (*d*=1.04, p<.001) and minor (*d*=0.54, p=.02) were present in very preterms, in particular with a research diagnosis of DCD. Reduced FA values moderately to strongly related to motor impairments. A receiver operating characteristic (ROC) curve for average FA, as calculated from tracts that significantly discriminated between very preterm children with and without a research diagnosis of DCD, showed an area under curve of 0.87 (95% CI 0.74 - 1.00, p=.001).

Conclusions This study provides clear evidence that reduced FA values are strongly underpinning motor impairment and DCD in very preterm children at school age, and demonstrates that altered white matter integrity is a promising measure for an improved early diagnosis of very preterm children at risk.

Introduction

In recent years, improved perinatal care has increased survival rates of very preterm (<32 weeks of gestation) infants. However, due to disturbances in the normal maturational processes of the brain, in particular the myelination process, diffuse white matter alterations prevail in very preterm children.[1] Throughout childhood and adolescence, very preterm children have substantial impairments in motor abilities[2] and a six times higher incidence of developmental coordination disorder (DCD) than term controls.[3] Unfortunately, there is limited insight in which altered white matter tracts underlie motor impairments and the increased incidence of DCD in very preterm children, although this could potentially add to an improved (early) diagnosis of very preterm children at risk.

In the last two decades, diffusion tensor imaging (DTI) has become a frequently used, non-invasive technique to delineate white matter tracts in vivo and quantify microstructural changes not detectable on conventional magnetic resonance imaging (MRI).[4] Using DTI, fractional anisotropy (FA) can be determined based on the direction of water diffusion in the brain, which is influenced by size, organization, and number of (myelinated) axons.[5] In very preterm children, significantly reduced FA values have been reported at various stages in development, interpreted as a decrease of white matter integrity,[6-10] using methods of tract-based spatial statistics (TBSS) and region of interest analysis (ROI). However, the subtle and diffuse nature of white matter alterations in very preterm children greatly increases variability across children in the wiring of fibers from white matter tracts, restricting the ability of TBSS and ROI methods (which depend on normalized data for localizing tracts) to accurately determine functional relations for specific white matter tracts.[4] Alternatively, the method of probabilistic diffusion tensor tractography (DTT) can be used, which constructs three-dimensional white matter tracts for each individual separately. Using DTT, regions with relatively low FA values or high between-subject variability in FA values can be reliably assessed, substantially increasing power to provide insight in functional relations of reduced FA values.[4]

In this study, we aimed to elucidate the relationship between white matter tract integrity and the widespread motor impairments and increased presence of DCD in very preterm children at school age. First, we examined differences in FA values between very preterm children and term controls, and the association of differences with motor

impairments in very preterm children. Second, we investigated differences in FA values between very preterm with a research diagnosis of DCD, very preterm children free of motor impairment, and term controls free of motor impairment, to elucidate the role of white matter integrity in the etiology of DCD. Finally, we explored whether differences in FA values can be used to discriminate between very preterm children with a research diagnosis of DCD and very preterm children free of motor impairment, in order to potentially improve early diagnosis of very preterm children at risk for developing DCD. We additionally included widely used measures of brain structure volumes and cognitive functioning (Wechsler Intelligence Scales for Children, WISC-III)[11] to examine 1) the specificity of DTI outcomes as opposed to brain structure volumes, and 2) the specificity of findings for motor impairment as opposed to intellectual impairment.

Methods

Sample

Thirty very preterm born (<32 weeks) children and 47 term born controls participated. Very preterm children acted as controls in an intervention study on glutamine supplementation in the neonatal period, and all very preterm children admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam between September 2001 and July 2003 were eligible for inclusion.[12] As we found some evidence that glutamine supplementation may have influenced brain development (see chapter 10), only very preterm children of the control group of this trial were included in the current study. At 7-8 years of age, parents of 39 children were contacted and invited to participate in the current study, of which 34 children (87%) successfully completed motor and cognitive assessment at the mean (SD) age of 7.5 (0.4) years,[13] and 30 children (83%) successfully finished MRI follow-up at the mean (SD) age of 8.6 (0.3) years.[14] For each child, data were collected on birth weight in grams, gestational age in weeks, z-score of birth weight for gestational age using methods of Usher et al. (BW for GA),[15] number of serious neonatal infections, and number of other clinical complications.

Age-matched, term peers from the same classrooms or recruited by contacting other schools located in the same area as the schools attended by the very preterm children were invited to participate in the study. Controls were required to be born >37 weeks gestation

without any perinatal complications as reported by their parents. In addition, controls had to be free of motor impairment (scored above the 15th percentile for their age on the Total Motor Impairment score of the MABC), to attend regular classes, and free of behavioral and academic difficulties as reported by their teacher. In total, 47 term born peers participated in neurocognitive assessment (mean (SD) age 7.8 (0.5) years) as well as in the MRI follow-up (mean (SD) age of 8.7 (0.5) years). Socio economic status (SES) was determined by classifying the highest level of education in a household with a number ranging from one (low SES) to four (high SES).[16]

Table 1. Sample characteristics

	Very preterm (N=30)		Term controls (N=47)			Preterm DCD (N=13)		Preterm no DCD (N=17)		
	M	SD	M	SD	p[1]	M	SD	M	SD	p[1]
General characteristics										
Age at MRI scan in years	8.6	0.3	8.7	0.5	.34	8.6	0.4	8.7	0.3	.65
Socio economic status	3.1	0.7	3.3	0.8	.42	2.8	0.6	3.3	0.8	**.05**
WISC-III full-scale IQ score	93.0	18.1	106.8	15.4	**<.001**	86.8	17.0	97.7	18.0	.11
MABC Total Motor Impairment score	8.3	7.2	2.7	2.4	**.001**	14.4	7.1	3.6	1.5	**<.001**
Gender n (male/female)	13 / 17		22 / 25		.77	7 / 6		6 / 11		.31
Clinical characteristics										
Birth weight in grams	1186	336				1052	316	1289	322	**.05**
Birth weight for GA z-score	-0.44	1.41				-0.96	1.24	-0.05	1.44	.08
GA in weeks	28.9	1.7				28.5	1.7	29.3	1.7	.20
Head circumference in cm	26.6	2.6				25.5	2.6	27.4	2.3	**.04**
Head circumference for GA z-score	-0.01	1.26				-0.50	1.15	0.36	1.24	.06
HELLP syndrome, n (%)	6 (20)					4 (31)		2 (12)		.20
Prenatal corticosteroids, n (%)	27 (90)					11 (85)		16 (94)		.39
BPD, n (%)	10 (33)					6 (46)		4 (24)		.19
IVH grade I/II, n (%)	4 (13)					2 (15)		2 (12)		.77
Cystic PVL, n (%)	2 (7)					1 (8)		1 (6)		.84
ROP grade III/IV, n (%)	2 (7)					1 (8)		1 (6)		.84
Apgar score after 5 min < 6, n (%)	2 (7)					1 (8)		1 (6)		.84
Caesarean delivery, n (%)	16 (53)					8 (62)		8 (47)		.43
1 or more infections, n (%)	24 (80)					11 (85)		13 (77)		.58

Note. [1]Chi-square and t-tests. BPD = bronchopulmonar dysplasia; DCD = developmental coordination disorder; GA = gestational age; HELLP = hemolysis elevated liver enzymes and low platelets; IVH = intraventricular haemorrhage; IQ = Intelligence quotient; MABC = Movement Assessment Battery for Children; MRI = Magnetic Resonance Imaging; PVL = periventricular leukomalacia; ROP = retinopathy of prematurity. WISC = Wechsler Intelligence Scales for Children. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05).

Procedure

All parents completed written informed consent prior to the study, explaining the nature of the experimental procedures. The study was approved by the medical ethical committee of the VU University Medical Center. Neurocognitive assessment took place at the VU University Amsterdam by qualified and trained testers. MRI follow-up took place at

the VU Medical Center, where a simulation scanner was used for subjects to get comfortable with the scanner environment and procedures.[17]

MRI acquisition and processing

Structural MRI images were acquired using a 1.5 Tesla MRI-scanner, equipped with an 8-channel phased-array head coil (Siemens Sonata, Erlangen, Germany). Anatomical 3D T1-weighted images were obtained in the sagittal plane with an MPRAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) sequence (TR=2730 ms, TE=3.7 ms, TI=1000 ms, flip angle=7˚, with 1x1 mm in-plane resolution and slice thickness of 1 mm). We used techniques supplied by the FSL software package version 4.1 (FMRIB Analysis group, Oxford, UK[18]) to extract all brains (BET-tool) and to automatically segment white matter and grey matter using the FAST-tool. The cerebellum and subcortical structures, including the thalamus, hippocampus, putamen and globus pallidum, were automatically segmented using the FIRST-tool. In addition, total striatum was calculated by adding putamen and globus pallidum volumes.

DTI acquisition and processing

DTI images were collected during one acquisition with single shot echo planar imaging consisting of four volumes without directional weighting, and 24 volumes with 24 non-collinear gradient directions (b-value=750 s/mm2, TR=7500 ms, TE=85 ms, with a 2.5x2.5 mm in-plane resolution and slice thickness of 2.5 mm). DTI analysis was performed using the FMRIB's Diffusion Toolbox (FDT) as implemented in the FSL software package.[18] After Eddy current and motion correction, all volumes for each child were visually inspected for the presence of artifacts. If an artifact was present within a volume, this volume was removed for this child. After that, analyses were conducted using default settings of bedpostx from FDT. To reconstruct the 18 major white matter tracts as described by Mori et al.[19] using probabilistic diffusion tensor tractography, we defined the seeding regions of tracking in line with the protocol of Wakana, which has a high reproducibility and reliability.[20] Using brain atlases supplied by the FSL software package, seeding regions were transformed into subject space, and tracts were delineated in subject space. The 18 paths (see Figure 2) included the bilateral cingulum gyrus tract (CGT), cingulum hippocampal tract (CHT), corticospinal tract (CST), inferior fronto-occipital tract (IFOT), inferior longitudinal

fasciculus (ILF), superior longitudinal fasciculus (SLF), anterior thalamic radiation (ATR), uncinate fasciculus (UF), the forceps major (Fmajor), and the forceps minor (Fminor). Finally, path tracing with probtrackx from FDT was performed,[21] using a total of 5000 permutations for each voxel of a seeding region. Path tracing was performed from one seeding region towards another, and vice versa. To minimize the possibility that voxels were erroneously considered to be part of a tract, a threshold that a minimum of 1% of all traced fibers within a tract passed a single voxel, was used. For each of the 18 major white matter tracts, we derived the mean FA value for every child.

Measures of motor and cognitive functioning

Motor functioning was assessed using the Movement Assessment Battery for Children.[22] The MABC contains eight subtests covering three different subscales. The Total Motor Impairment score was calculated by combining scores on all three subscales, ranging from 0 to 40. Children received a research diagnosis of DCD when they scored at or below the 15th percentile for their age on the Total Motor Impairment score of the MABC.[23] Normally, higher scores indicate poorer motor performance. However, for reasons of clarity, we mirrored outcome scores of the correlational analyses such that lower scores indicated poorer motor performance.

Cognitive functioning was estimated by Full Scale IQ score, as measured by a short-form of the WISC-III, including the subtests Vocabulary and Block Design.[11] This short form composite score has satisfactory reliability (r=.91) and correlates highly (r=.86) with Full Scale IQ.[24]

Statistical Analyses

All statistical analyses were performed using SPSS 17.0 (SPSS Inc, Chicago, USA), and motor and cognitive measures were normalized using a van der Waerden transformation.[25] To study differences in mean FA values of white matter tracts, brain structure volumes, and white matter tract volumes between very preterm children (free of motor impairment and with a research diagnosis of DCD) and term controls, ANOVAs were performed with group as fixed factor, and SES as covariate (see Results). Associations between mean FA values of white matter tracts, brain structure volumes, and functional outcomes were explored using Pearson correlations. To explore the discriminative abilities of differences in FA values, a

Receiver Operating Characteristic (ROC) curve was determined for average FA value as calculated from those tracts that significantly discriminated between both groups. Effect-sizes (Cohen's *d*) were determined with values of 0.20, 0.50, and 0.80 considered small, medium, and large effects, respectively.[26] Testing was performed two-sided, and α was set at .05.

Results

Sample

Sample characteristics are shown in Table 1. Except for SES between very preterm children with or without a research diagnosis of DCD (p=.05), no differences were found between groups in general characteristics. Subsequently, SES was included as covariate in all analyses investigating the effects of DCD status. Furthermore, there was a significantly lower birth weight (p=.05) and smaller head circumference (p=.04) in children with a research diagnosis of DCD. As expected, very preterm children had significantly poorer Total Motor Impairment scores as measured by the MABC (*d*=1.27, p<.001), and lower full-scale IQ scores as measured using the WISC-III (*d*=0.80, p=.001), than term peers. For all included children, on average 96.6% of all volumes were found to be suitable for DTI analyses.

Brain differences and functional associations

Differences in mean FA values and brain structure volumes between very preterm children and term controls are shown in Table 2. Poorer Total Motor Impairment scores were associated with reduced white matter volume (*r*=.43, p=.02), thalamic volume (*r*=.55, p=.002), and FA values of various tracts (range *r*=.40-.67) of very preterm children (Table 2). Lower estimated full-scale IQ scores were associated with reduced FA values of the right SLF (*r*=.51, p=.004), left SLF (*r*=.41, p=.02), and reduced grey matter volumes (*r*=.39, p=.03).

The impact of DCD status on brain differences

Differences in FA values and brain structure volumes between very preterm children with a research diagnosis of DCD, very preterm children free of motor impairment, and term controls (free of motor impairment), are shown in Table 3. For all FA values and brain structure volumes, significant differences were present between the three groups, except for the right CGT (p=.42), left CGT (p=.46), the right SLF (p=.07), and the right UF (p=.15).

Table 2. FA values, brain structure volumes, and functional correlations of 18 investigated white matter tracts in very preterm children and term controls at school age

	Very preterm (N=30)		Term controls (N=47)				WISC-III		MABC[2]	
	M	SD	M	SD	Effect size	p[1]	*r*	p	*r*	p
White matter tracts FA value										
Cingulum gyrus tract – right	.244	.028	.249	.018	0.22	.31	.10	.61	.19	.31
Cingulum gyrus tract – left	.258	.033	.261	.019	0.12	.60	.03	.86	.17	.36
Cingulum hippocampal tract – right	.237	.018	.252	.021	0.75	**.003**	.22	.24	.30	.11
Cingulum hippocampal tract – left	.226	.021	.241	.019	0.76	**.001**	.18	.34	.40	**.03**
Corticospinal tract – right	.387	.016	.396	.016	0.56	**.02**	.32	.09	.46	**.01**
Corticospinal tract – left	.383	.018	.394	.016	0.65	**.009**	.32	.08	.47	**.009**
Forceps major	.341	.024	.366	.024	1.04	**<.001**	.13	.51	.49	**.006**
Forceps minor	.376	.028	.389	.021	0.54	**.02**	.16	.41	.53	**.002**
Inferior fronto-occipital tract – right	.350	.020	.352	.012	0.13	.66	.15	.43	.65	**<.001**
Inferior fronto-occipital tract – left	.354	.020	.363	.012	0.58	**.02**	.24	.21	.54	**.002**
Inferior longitudinal fasciculus – right	.343	.022	.341	.017	0.10	.71	.12	.54	.48	**.007**
Inferior longitudinal fasciculus – left	.332	.021	.339	.019	0.35	.10	.17	.37	.45	**.01**
Superior longitudinal fasciculus – right	.324	.031	.321	.025	0.11	.68	.51	**.004**	.47	**.01**
Superior longitudinal fasciculus – left	.327	.031	.335	.021	0.32	.19	.41	**.02**	.52	**.003**
Anterior thalamic radiation – right	.319	.020	.324	.015	0.29	.22	.34	.07	.48	**.007**
Anterior thalamic radiation – left	.330	.020	.336	.015	0.35	.19	.35	.06	.67	**<.001**
Uncinate fasciculus – right	.267	.018	.271	.019	0.21	.33	.25	.19	.31	.09
Uncinate fasciculus – left	.267	.017	.274	.019	0.38	.08	.21	.26	.56	**.001**
Brain structure volumes in cm[3]										
Grey matter	705.4	63.3	736.8	49.5	0.57	**.02**	.39	**.03**	.32	.08
White matter	466.5	49.2	494.8	48.7	0.58	**.02**	.19	.32	.43	**.02**
Cerebellum	105.7	9.5	113.3	11.7	0.70	**.004**	.19	.31	.14	.46
Thalamus	14.6	1.5	16.0	1.1	1.17	**<.001**	.25	.19	.55	**.002**
Hippocampus	6.9	0.6	7.4	0.8	0.75	**.002**	.26	.17	.27	.15
Striatum	20.7	2.2	22.4	1.8	0.88	**<.001**	.23	.22	.23	.22

Note. [1]Brain structure volume analyses adjusted for total brain volume. [2]Lower scores indicate poorer motor performance. FA = Fractional Anisotropy; MABC = Movement Assessment Battery for Children; WISC-III = Wechsler Intelligence Scale for Children, third edition. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05). Effect sizes are depicted as Cohen's *d*.

Results of the post-hoc analyses are included in Table 3, and consistently indicate larger reductions in FA values and brain structure volumes in very preterm children with a research diagnosis of DCD. Reduced FA values and brain structures volumes were also present between very preterm children free of motor impairment and term controls for the Fmajor (*d*=0.69, p=.02), the right CHT (*d*=0.65, p=.02), the cerebellum (*d*=0.58, p=.04), thalamus (*d*=0.87, p=.007), hippocampus (*d*=0.56, p=.05), and striatum (*d*=0.85, p=.007).

Diagnostic value of white matter integrity for DCD status

A ROC curve was determined for average FA value, as calculated from those tracts that significantly discriminated between very preterm children with a research diagnosis of

Table 3. Brain structure volumes and FA values of 18 investigated white matter tracts of very preterm children and term controls specified by DCD status

	Preterm DCD (N=13)		Preterm no DCD (N=17)		Controls (N=47)			
	M	SD	M	SD	M	SD	p[1]	Post-hoc contrasts
White matter tracts FA value								
Cingulum gyrus tract – right	.239	.034	.247	.022	.249	.018	.42	
Cingulum gyrus tract – left	.250	.029	.264	.035	.261	.019	.46	
Cingulum hippocampal tract – right	.235	.019	.238	.018	.252	.021	**.01**	Preterm DCD, Preterm no DCD < Controls
Cingulum hippocampal tract – left	.219	.023	.231	.018	.241	.019	**.003**	Preterm DCD < Controls
Corticospinal tract – right	.379	.018	.393	.012	.396	.016	**.005**	Preterm DCD < Preterm no DCD, Controls
Corticospinal tract – left	.377	.020	.388	.016	.394	.016	**.03**	Preterm DCD < Controls
Forceps major	.329	.021	.350	.023	.366	.024	**<.001**	Preterm DCD < Preterm no DCD < Controls
Forceps minor	.362	.025	.387	.026	.389	.021	**.004**	Preterm DCD < Preterm no DCD, Controls
Inferior fronto-occipital tract – right	.338	.016	.360	.018	.352	.012	**.001**	Preterm DCD < Preterm no DCD, Controls
Inferior fronto-occipital tract – left	.342	.012	.364	.020	.363	.012	**<.001**	Preterm DCD < Preterm no DCD, Controls
Inferior longitudinal fasciculus – right	.331	.021	.351	.018	.341	.017	**.02**	Preterm DCD < Preterm no DCD
Inferior longitudinal fasciculus – left	.321	.021	.340	.017	.339	.019	**.03**	Preterm DCD < Preterm no DCD, Controls
Superior longitudinal fasciculus – right	.310	.028	.334	.029	.321	.025	.07	
Superior longitudinal fasciculus – left	.310	.028	.340	.027	.335	.021	**.007**	Preterm DCD < Preterm no DCD, Controls
Anterior thalamic radiation – right	.309	.020	.327	.016	.324	.015	**.008**	Preterm DCD < Preterm no DCD, Controls
Anterior thalamic radiation – left	.318	.016	.340	.018	.336	.015	**.003**	Preterm DCD < Preterm no DCD, Controls
Uncinate fasciculus – right	.261	.023	.271	.013	.271	.019	.15	
Uncinate fasciculus – left	.257	.014	.274	.016	.274	.019	**.02**	Preterm DCD < Preterm no DCD, Controls
Brain structure volumes in cm^3								
Grey matter	688.8	71.7	718.0	54.8	736.8	49.5	**.03**	Preterm DCD < Controls
White matter	452.1	51.0	477.4	46.3	494.8	48.7	**.04**	Preterm DCD < Controls
Cerebellum	104.2	10.1	106.9	9.1	113.3	11.7	**.02**	Preterm DCD, Preterm no DCD < Controls
Thalamus	13.9	1.7	15.1	1.1	16.0	1.1	**<.001**	Preterm DCD < Preterm no DCD < Controls
Hippocampus	6.7	0.8	7.0	0.5	7.4	0.8	**.01**	Preterm DCD, Preterm no DCD < Controls
Striatum	20.5	2.6	20.8	1.9	22.4	1.8	**.002**	Preterm DCD, Preterm no DCD < Controls

Note. [1]ANOVA results adjusted for socio economic status and total brain volume for differences in brain structure volumes, and adjusted for socio economic status for differences in FA values. DCD = developmental coordination disorder. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05).

DCD and very preterm children free of motor impairment, which included the right CST,Fmajor, Fminor, right IFOT, left IFOT, right ILF, left ILF, left SLF, right ATR, left ATR, and left UF (Figure 1). The ROC curve area was 0.87 (95% CI 0.74 - 1.00, p=.001). Odds ratios for having 1.50 SD, 0.34 SD, or 0.15 SD lower average FA values in very preterm children with a research diagnosis of DCD as compared to very preterm children free of motor impairment were 36.00 (95% CI 3.47 – 373.18, p=.003), 13.20 (95% CI 2.11 – 82.50, p=.006), and 22.00 (95% CI 2.27 – 212.86, p=.008), respectively.

Figure 1. ROC curve for detecting DCD status using a cut-off score (in standard deviation) of FA value in very preterm children

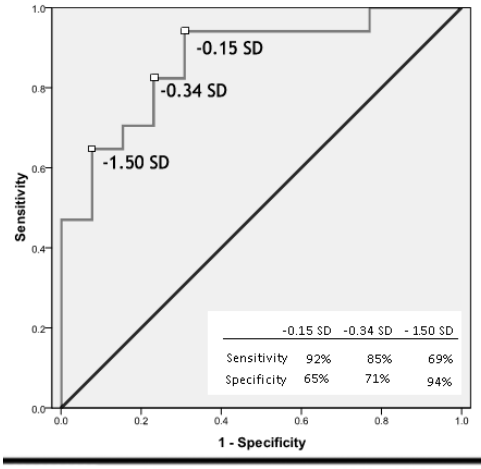
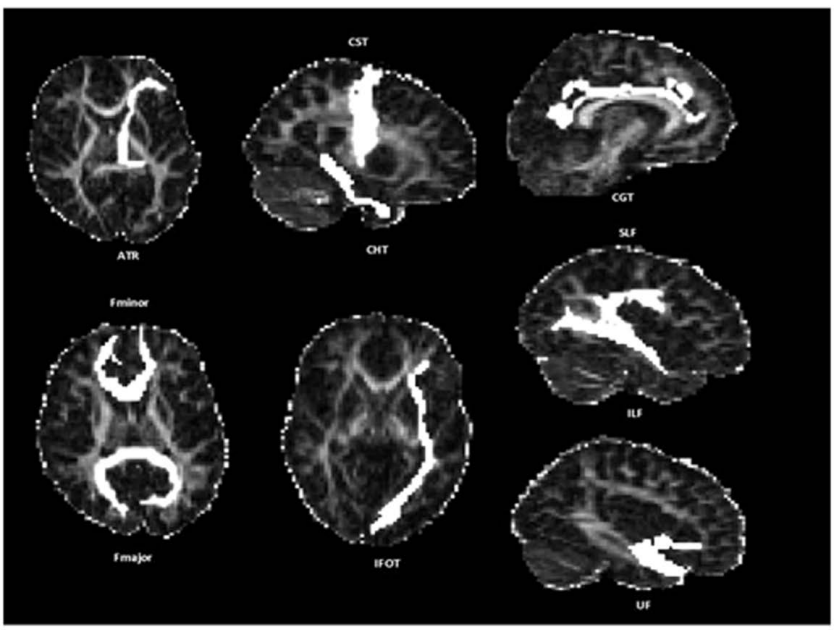


Figure 2. Overview of white matter tracts as determined using the Wakana protocol



Note. All tracts are derived from one individual for illustration purposes. ATR = Anterior thalamic radiation; CGT = Cingulum gyrus tract; CHT = Cingulum hippocampal tract; ILF = Inferior longitudinal fasciculus; SLF = superior longitudinal fasciculus; UF = Uncinate fasciculus.

Discussion

By using both probabilistic DTT and volumetric MRI, we found medium to large-sized reductions of white matter integrity (as indicated by lower FA values) in the majority of white matter tracts and brain structure volumes in very preterm children as compared to term controls at school age. Reduced white matter integrity for major white matter tracts was most prominent in very preterm children with a research diagnosis of DCD, as compared to both very preterm children free of motor impairment and term controls. Finally, we demonstrate that white matter integrity can potentially be a powerful tool to diagnose very preterm children at risk for adverse motor development and DCD at school age.

In general, our findings indicate that the widespread reductions in white matter integrity in very preterm children are particularly associated with their motor impairments as compared to term controls. Interestingly, we found evidence that multiple white matter tracts are involved in motor performance, demonstrating that motor impairments of very preterm children at school age are not related to white matter alterations affecting one tract specifically. Furthermore, next to grey matter volume, poorer cognitive performance appears to be specifically associated with reduced white matter integrity of the right SLF and the left SLF, connecting the temporal, occipital, and parietal cortices with the frontal cortex. This confirms the findings of previous studies showing relations between white matter integrity and cognitive functioning in very preterm children.[6,7,9,10,27-29]

Our findings demonstrate that major differences in white matter integrity were present between very preterm children with a research diagnosis of DCD and very preterm children free of motor impairment, but not between very preterm children free of motor impairment and term controls, indicating that the frequently described diffuse white matter alterations may generally be limited to the subgroup of very preterm children with a research diagnosis of DCD. Neonatal white matter development comprises a cascade of events including the development of subplate neurons, axons, and pre-oligodendrocytes, which are negatively affected by multiple factors including the presence of serious neonatal infections and complications such as bronchopulmonar dysplasia, with accompanying excitotoxicity and ischemic events.[1] Interestingly, the subgroup of very preterm children with a research diagnosis of DCD is characterized by a relatively lower birth weight, shorter gestation, and smaller head circumference at birth (Table 1), suggesting a particular

vulnerability of this subgroup of very preterm children for the disturbances in neonatal white matter development. Indeed, negative associations between lower birth weight, shorter gestation, smaller head circumference, and adverse motor outcomes throughout childhood have been reported.[30,31] Differences in cerebellar volume, thalamic volume, hippocampal volume, striatal volume, and FA values of the bilateral CHT and the Fmajor were found between very preterm children free of motor impairment and term controls, suggesting that especially these brain structures are vulnerable for the adverse effects on brain development of very preterm birth per se. Indeed, alterations in these brain structures are frequently reported in very preterm children throughout childhood and adolescence,[32,33] and may play a crucial role in the widespread subtle impairments observed in these children, regardless of DCD status.

Importantly, using average white matter integrity in very preterm children at school age, our findings indicate that a powerful discrimination can be made between very preterm children with a research diagnosis of DCD and very preterm children free of motor impairments. However, differences in average white matter integrity between very preterm children with and without a research diagnosis of DCD are potentially amplified throughout childhood, given that children with impaired motor abilities may tend to avoid or limit their exposure to situations putting high demands on the brain's motor system, giving rise to the question whether the discriminative abilities of average white matter integrity are replicable early in development. Nevertheless, several studies have found that differences in FA values at younger ages were predictive for motor functioning later in childhood.[34-37] These findings suggests that average white matter integrity in very preterm children is a promising measure for improving early diagnosis of adverse motor outcome and DCD in very preterm children, and await further replication using longitudinal prospective study designs.

This study has some limitations which need to be taken into account. First, this study included term controls free of motor impairment, but did not include term controls with a research diagnosis of DCD. Future studies may be conducted to investigate whether similar findings can be found in term controls with a research diagnosis of DCD as compared to term controls free of motor impairment. Second, some studies showed poorer functional outcomes and FA values in males as compared to females,[6] or illustrated gender differences regarding the relation between white matter integrity and functional outcomes.[36] However, including gender as additional covariate did not alter any of the results. In addition, males

and females were equally distributed among all groups included in our analysis, limiting the influence of potential gender effects on our findings. Finally, although the Total Motor Impairment score of the MABC represents an adequate and frequently used selection criterion for defining the presence DCD in children at school age,[23] some differences may be present between children with a research diagnosis and a clinical diagnosis of DCD.

This study provides clear evidence for medium to large-sized reductions in white matter integrity of the majority of white matter tracts in very preterm children as compared to term controls at school age, which were moderately to strongly related with motor impairment. Interestingly, although diffuse white matter alterations are frequently described for the whole group of very preterm children, our findings suggest that reduced white matter integrity in very preterm children are prominent for very preterm children with a research diagnosis of DCD, but generally limited to subcortical volumes, the bilateral CHT, and the Fmajor, for very preterm children free of motor impairment. Furthermore, given the discriminative abilities of average white matter integrity between very preterm children with a research diagnosis of DCD and very preterm children free of motor impairment, using DTI at follow-up can be a promising future direction for successfully improving early diagnosis of very preterm children at risk for motor impairments and DCD at school age.

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