MISS KATRI LAHTI (Orcid ID : 0000-0002-4024-9949)

MRS. VIRVA SAUNAVAARA (Orcid ID : 0000-0001-7858-5924)

PROF. LEENA HAATAJA (Orcid ID : 0000-0002-8057-6194)

Article type : Regular Article

Diffusion Tensor Imaging is associated with motor outcomes of very preterm born children at 11 years of age

Katri Lahti[1,2], MD; Virva Saunavaara[3,4], PhD; Petriina Munck[5], PhD; Karoliina Uusitalo[1,2], MD; Mari Koivisto[6], MSc; Riitta Parkkola[7, 8], MD, PhD; Leena Haataja[9], MD, PhD, on behalf of the PIPARI Study Group

1 Department of Pediatric Neurology, University of Turku, Turku, Finland
2 Department of Pediatric Neurology, Turku University Hospital, Turku, Finland
3 Department of Medical Physics, Turku University Hospital, Turku, Finland
4 Turku PET Centre, Turku University Hospital, Turku, Finland
5 Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland
6 Turku University Hospital, Clinical Research Centre, Turku, Finland
7 Department of Radiology, University of Turku, Turku Finland
8 Department of Radiology, Turku University Hospital, Turku, Finland
9 University of Helsinki and Helsinki University Hospital, Children's Hospital, and Pediatric Research Center, Helsinki, Finland

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.15004

Corresponding author: Katri Lahti, Department of Pediatric Neurology, University of Turku and Turku University Hospital, PO Box 52, 20521 Turku, Finland. E-mail: kaalah@utu.fi. Telephone: +358 40 82 68 287. Fax: +358 2 313 1460

Running title: Diffusion metrics and outcome of preterm children

ABSTRACT

Aim: Very preterm children born less than 32 weeks of gestation are at risk for motor difficulties such as cerebral palsy and developmental coordination disorder. This study explores the association between diffusion tensor imaging metrics at term and motor outcomes at 11 years of age.

Methods: A cohort of 37 very preterm infants (mean gestational age 29 4/7, SD 2 0/7) born in 2004-2006 in Turku University Hospital underwent diffusion tensor imaging at term. A region-of-interest analysis of fractional anisotropy and mean diffusivity was performed. Motor outcomes at 11 years of age were measured with the Movement Assessment Battery for Children – Second Edition.

Results: The diffusion metrics of the corpus callosum (genu p=0.005, splenium p=0.049), the left corona radiata (p=0.035) and the right optic radiation (p=0.017) were related to later motor performance. Mean diffusivity decreased and fractional anisotropy increased in proportion to the improving performance.

Conclusion: The diffusion metrics of the genu and splenium of the corpus callosum, the left corona radiata and the right optic radiation at term were associated with motor skills at 11 years of age. Diffusion tensor imaging should be further studied as a potential tool in recognising children at risk for motor impairment.

KEY NOTES

- This study assessed diffusion tensor imaging metrics at term age and later motor development of very preterm infants.
- The diffusion tensor metrics of the corpus callosum, corona radiata and optic radiation at term age were associated with motor performance at 11 years of age.
- The role of diffusion tensor imaging as a tool in early recognition of the preterm infants at risk for motor impairments should be further investigated.

KEY WORDS

Developmental coordination disorder, diffusion tensor imaging, motor development, Movement Assessment Battery for Children – Second Edition, very preterm infants

INTRODUCTION

Children born before the gestational age of 32 weeks are defined as extremely or very preterm children and are at a higher risk for motor impairments compared to their term-born peers (1-3). The most widely known motor deficit associated with prematurity is cerebral palsy, with an estimated prevalence of 3.6% in very preterm infants (4). In parallel with the development of the neonatal care, the motor outcomes of the very preterm infants have improved and the incidence of cerebral palsy has slightly decreased (4). Despite this positive change in severe motor deficits, the milder motor deficits, such as developmental coordination disorder (DCD), are still common in very preterm infants (2,4).

DCD is defined as a neuromotor impairment that affects both gross and fine motor functions and interferes with daily activities of life (5,6). A meta-analysis showed that the odds ratio for very preterm children having DCD compared to term born children at the age of seven to 14 years old was 6.3 (2). The impact of DCD on these children's lives was adverse. In addition to the potential problems with the daily school performance, children with DCD are known to be at a higher risk for emotional problems, such as feelings of loneliness and anxiety and lower experienced quality of life (3,5,6).

Comprehensive magnetic resonance imaging (MRI) at term equivalent age has been shown to be a good predictor of cerebral palsy, but less is known about the possible association between MRI results and DCD (7). A previous study has shown an association between term age volumetric measurements of total brain tissue, the cerebrum and basal ganglia, including the thalamus and the scores on Movement Assessment Battery for Children – Second Edition (MABC-2) at 11 years (8). In a systematic literature review, Peters et al concluded that the neuropathophysiology of DCD is highly likely to involve several brain regions (9). They also summarised that in children with perinatal adversities, there might be an association between DCD and abnormalities in the periventricular white matter of the brain.

Diffusion tensor imaging (DTI) has been suggested as a potential tool for recognising children at risk for DCD. The two commonly used DTI metrics are fractional anisotropy and mean diffusivity. It is known that DTI metrics measure the changes in signal amplitude created by the diffusion of the water molecules (10,11). Water molecule diffusion is affected by myelination, axon density and diameter, membrane permeability and the level of organisation of axons inside a voxel (12). Changes in these features in white matter can cause sensitive, but not specific changes in fractional anisotropy and mean diffusivity (12,13). Elevation in the level of organization is seen, for example, during maturation of the white matter tracts (13). However, in some regions of the

brain there are exceptions, such as with regions with crossing fibres. In central parts of large and parallel white matter tracts, high fractional anisotropy values and low mean diffusivity values might indicate higher maturation. However, the evidence that is available regarding the correlation between the DTI metrics and brain development is disputed (9,12).

Previous studies have shown associations between DTI metrics in several regions of white matter at term age and the motor development of very preterm born children up to four years of age. In general, these studies have suggested that the higher the fractional anisotropy and the lower the mean diffusivity, the better the motor performance. In these studies, the DTI metrics of the corpus callosum, posterior limb of the internal capsule and corticospinal tracts have been reported to associate with motor development (14-17). However, there is also one study reporting no associations between DTI metrics and motor outcomes measured with the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) at two years of corrected age (18).

Studies focusing on very preterm children and the potential association between DTI metrics at term age and later motor development at school-age are scarce. In this study, our aim was to assess whether DTI metrics at term age are associated with motor development at 11 years of age in very preterm children. We hypothesised that later motor coordination skills would be associated with the DTI metrics of the corticospinal tract, visual tract and interconnective pathways of the corpus callosum measured at term age.

MATERIALS AND METHODS

Subjects

This study was a part of the Development and Functioning in Very Low Birth Weight Infants from Infancy to School Age (PIPARI) study, which has been conducted at the Turku University Hospital in Turku, Finland since 2001. The PIPARI study infants were born in 2001–2006, but this part of study only included children born in 2004–2006 due to an upgrade of the MRI scanner. All children in the cohort were either born before 37 weeks' gestation and with a birthweight of ≤1,500g or born before 32 weeks' gestation regardless of the birth weight. To allow comparison with other similar studies we excluded infants born at a gestational age ≥32 weeks.

The other inclusion criteria for this study at term were at least one of the parents spoke Finnish or Swedish with the child, 1.5 T MRI was performed at term-equivalent age and DTI was performed

at term age. At 11 years of age, Touwen neurological assessment was performed to exclude other differential diagnosis and motor performance assessed with the MABC-2 to diagnose DCD.

Infants were excluded from the study for the following reasons: infant death during the neonatal period or follow-up; major congenital anomalies or recognised syndromes, including clinical suspicions of one; or cerebral palsy. Infants were likewise excluded if they lived outside the hospital district, if they were born outside of the hospital or if families refused to participate. Further criteria for exclusion were a missing DTI or one that did not fulfil the qualitative criteria due to artefacts. The flow chart of participants is shown in Figure 1.

The study protocol was approved by the Ethics Review Committee of the Hospital District of Southwest Finland. All families provided written informed consent after receiving oral and written information. At the age of 11, the children also provided their own assent.

MRI at term age

Imaging was performed on a 1.5-T Gyroscan Intera CV Nova Dual MRI system (Philips, North Holland, The Netherlands) with a SENSE head coil. 3M Disposable Ear Plugs (3M, São Paolo, Brazil) and Wurth Hearing Protector (Wurth, Nieder-Österreich, Austria) were used as ear protection.

The MRI was conducted at term-equivalent age during postprandial sleep without any pharmacological sedation. A pulse oximeter was routinely used during scans. If necessary, a physician attended the examination to monitor the infant.

The MRI protocol included DTI and conventional T1-weighted and T2-weighted turbo spin echo as well as T1 inversion recovery sequences. The diffusion-weighted images were acquired using single-shot echo-planar imaging. Repetition time / echo time was 2,264 / 68 ms. The axial slice thickness was 5mm, with a gap between slices of 1mm. A 200mm^2 field of view was used. The data was reconstructed to a voxel size of 0.78mm × 0.78mm. The number of signal averages was two. Parallel imaging was used with an echo-planar imaging factor of 47. Fat suppression was done using spectral presaturation with inversion recovery. The total scan duration was 14 minutes 54 seconds, during which DTI was completed for two minutes 24 seconds. The sequence was imaged with b-values 0 s/mm^2, 600 s/mm^2 and 1200 s/mm^2. For both high b-values (600 s/mm^2 and 1200 s/mm^2) 15 diffusion encoding gradient directions were collected. One b0 image was acquired. In the analysis, only the data collected using b-values of 0 s/mm^2

and 600 s/mm^2 were used due to the high diffusivity of the white matter of preterm infants imaged at term age. A B-value 600 s/mm^2 was chosen to optimize the contrast-to-noise ratio (19).

The infants were assigned to three groups according to the most severe pathological finding on the MRI: normal findings, minor brain pathologies and major brain pathologies. Normal findings were defined as normal brain anatomy with a width of cerebral cortical cerebrospinal fluid space ≤ 4 mm in the frontal lobes. Minor brain pathologies were regarded as intraventricular haemorrhages of grades 1–2, caudothalamic cysts or a cerebral cortical cerebrospinal fluid space width of the frontal lobes of 4–6mm. Major brain pathologies were defined as intraventricular haemorrhages grades 3 or 4, haemorrhage of the brain parenchyma, white matter cysts, abnormal signal on T1-weighted or T2-weighted images in the cortex, the basal ganglia, the thalamus, the cerebellum or the internal capsule, abnormal shape of the corpus callosum or cerebral cortical cerebrospinal fluid space width of the frontal lobes ≥ 6 mm or ventriculitis. Ventriculitis was defined as high signal intensity of the ependyma of the ventricles on T1-weighted images. Possible haemorrhages were diagnosed on both T1-weighted and T2-weighted images. The performing neuroradiologist (R.P.) was blinded to the clinical status of the infant.

Fractional anisotropy and mean diffusivity values were measured from the genu and splenium of the corpus callosum, the posterior part of the internal capsule, the corona radiata, the optic radiation and the colliculus inferior using manually drawn regions-of-interest (Figure 2). Symmetrical structures were analysed bilaterally. The chosen trajectories were known to be clearly definable in the anatomical images and to only have a limited amount of crossing tracts that could interfere with the measurements. The size and placement of the regions-of-interests was defined based on the anatomical structures.

Data was processed using manufacturer software PRIDE V4 Fiber Tracking 4.1 beta 4 (Philips Medical Systems, Best, The Netherlands). The program used an automatic processing line resulting in the finalized colour-encoded fractional anisotropy maps. The program made the DTI fitting automatically. Data with motion artefacts was excluded. No additional pre-processing was carried out. The region-of-interests were drawn on a specific slice. Misregistrations between slices did therefore not impact our analyses. A detailed description of the regions-of-interests has been previously reported (20). The intra-observer reproducibility for the regions-of-interest analyses was shown to be excellent in all studied structures and to be fair to excellent in all studied areas except the colliculus inferior. Reproducibility data in this cohort has previously been published in Lepomäki et al (20).

MABC-2 at 11 years of age

Motor performance was assessed using the MABC-2 (21). MABC-2 consists of three different domains: manual dexterity, aiming and catching and balance. These domains form the total score of the assessment. A total raw score of 56, equalling a standard score of five (5th percentile), is diagnostic for DCD when other causes for motor impairment, such as cerebral palsy or neuromuscular disorders, are excluded. Children scoring 57–67 in total and/or a standard score of six (> 5th to 15th percentile) are at risk of having a motor difficulty. A test score of 67 or greater and a standard score of seven or above (> 15th percentile) indicate normal motor development. Age band three (11 to 16 years) of the test manual was used and the test was scored according to the norms of 11-year-old children. An appropriate visus correction was controlled for by an ophthalmologist during the visit.

Statistical analysis

Continuous variables were characterised using means, standard deviations and minimum and maximum values or medians and minimum and maximum values. MABC-2 scores, DTI metrics and gestational age were used as continuous variables. In the case of categorical variables, frequencies were used. MRI findings and small for gestational status were used as categorical variables. Univariate associations between the MABC-2 standard scores and the DTI metrics were studied using regression analysis. Multiple regression analysis was used to study the associations between MABC-2 standard scores and DTI metrics while controlling for gestational age at birth, small for gestational age status and findings in the brain MRI. The statistical analyses were performed using a 9.4 version of SAS (SAS Institute Inc., North Carolina, USA) for Windows. *P* values of < 0.05 were considered statistically significant.

RESULTS

A total of 132 infants fulfilling the gestational age and weight criteria were born in the catchment area of Turku University Hospital, in Turku, Finland during 2004-2006. Of these children, 34 were excluded, 16 died and 45 of the infants were not assessed in either or both age points (Figure 1). A total of 37 preterm infants (27 boys, 73.0%) were included in this study, of whom 34 were right handed and three left handed. One of the girls could not perform the balance domain of MABC-2 due to a post-surgical state. The neonatal child-related, neonatal care-related and brain MRI characteristics of these children are shown in Table 1. The mean diffusivity and fractional

anisotropy values of all regions-of-interests are shown separately for all children and children with DCD in Table 2.

Motor performance at 11 years of age

A total of 36 children were able to perform all the tasks in the MABC-2. The median standard scores of the three domains were: manual dexterity 8.0 (range 4-12), aiming and catching 9.0 (3-15) and balance 9.0 (2-14). The median standard score for the complete test was 8.5 (2-12). The median percentiles were 25 (2-75), 37 (1-95), 37 (0.5-91) and 31 (0.5-75) respectively. DCD diagnosis criteria was met by eight children (22.2%), who scored five or less in standard scores, which equals a total score ≤ 56 and fifth percentile or below. Scoring six in standard scores equalling a total score of 57-67, six (16,7%) children met the criteria to be considered at risk for motor deficits. A standard score above 7 (> 67 total score), which equals > 15th percentile and a normal motor development was reached by 22 (61.1%) children. Normal motor development was seen in 22 (61.1%) children, which was defined as a standard score of seven or above (> 67 total score), which equals > 15th percentile and a normal motor development.

Associations between DTI metrics and MABC-2

The mean diffusivity of the genu of the corpus callosum (p=0.005) and the fractional anisotropies of the splenium of the corpus callosum (p=0.049), the left corona radiata (p=0.035) and the right optic radiation (p=0.017) were associated with the motor performance in the MABC-2. The mean diffusivity values associated negatively and fractional anisotropy values positively with the motor outcomes. The correlation plots between the DTI metrics and motor scores are shown in Figure 3.

The associations between the outcome measurements and the genu, corona radiata and optic radiation results also remained significant in the multivariate analysis. In the multivariate model, the mean diffusivity value of the left corona radiata showed a statistical significance (p=0.030). Table 3 shows the estimates and p values of the associations between the mean diffusivity and fractional anisotropy values of the MABC-2 scores in both a univariate and a multivariate model.

DISCUSSION

This study showed an association between the DTI metrics of the corpus callosum, genu and splenium, left corona radiata and right optic radiation measured at term age and motor outcomes at 11 years. Associations between the outcomes and the imaging results of the genu of the

corpus callosum, corona radiata and optic radiation also remained significant in a multivariate analysis that took into account gestational age, small for gestational age status and brain pathology. High fractional anisotropy and low mean diffusivity of white matter was associated with better motor performance.

Our study was in line with the previous studies reporting findings in very preterm infants at 18–24 months of age including outcomes measured with the BSID-II, BSID-III, Amiel-Tison neurological examination, Gross Motor Function Classification System (GMFCS) and Peabody Developmental Motor Scales – Second Edition (14-17). Areas associated with motor development in the present study were also associated with motor development in these previous studies with a shorter follow-up period. In addition, the left precuneus, right superior occipital gyrus and right hippocampus have been suggested to predict motor development in very low birth weight infants at 18–24 months (22). In contrast, Kidowaki et al found no association between the DTI metrics at term and motor development measured with a Japanese public health screening tool at three years of age (n=13). The outcome measurement used in our study and the one used by Kidowaki et al are not comparable since a structured motor examination was used in this study (23).

Rose et al reported a strong relationship between low neonatal fractional anisotropy in the posterior limb of the internal capsule and an abnormal later motor outcome defined using gait evaluation and the GMFCS. Low fractional anisotropy was defined as a value less than one SD below the mean fractional anisotropy value of the children in the study. In contrast, among very preterm children with normal fractional anisotropy no correlation with the motor outcome was found. Accordingly, they concluded that DTI might provide a tool for predicting the severity of the motor impairment (24). Skranes et al reported an association between low MABC fine motor scores and low fractional anisotropy in the internal and external capsule and superior fasciculus at the age of 15 in a group of 34 adolescents born with a very low birth weight and 47 controls (25). Our study also supported the finding of an association between the fractional anisotropy in parts of the corticospinal tract and later motor performance. Our study suggested that the association could be seen already at term age.

An association was also found between the optic radiation and motor outcomes in our study. In a study by Sripada et al, a poorer visual-motor performance seen in a group of very low birth weight born young adults was associated with not only a thinner cortex and reduced cortical surface areas in several regions, but also reduced fractional anisotropy in several association tracts. The lower fractional anisotropy of the optic radiation was associated with poorer copying scores in the Beery-Buktenica Developmental Test of Visual-Motor Integration-V (26). Our results could

thereby reflect the visual dimension of the performed motor tasks, especially the fine manipulation tasks (21). Indeed, visual information mediated via the optic radiation is also significantly involved in gross motor functioning.

Skranes et al also showed that the fractional anisotropy values and myelination of the white matter tracts in very low birth weight born adolescents were still deviant compared to term-born controls even at the age of 15 years (25). This might reflect the high occurrence of minor motor problems in preterm infants compared to the general population (2).

Most of the significant associations between DTI and motor performance found in this study were fractional anisotropy values. Previous studies have shown that the fractional anisotropy values of the motor tracts increase over time in line with the maturation of the brain (11,27). Interestingly, Zwicker et al did not find any group differences in the fractional anisotropy values of the corticospinal tract in a small pilot study including seven children with DCD and nine typically developing children aged 8–10 years. Instead, they found a correlation between the mean diffusivity of the corticospinal tract and posterior thalamic radiation and MABC-2 scores. They stated that the correlation was mainly driven by axial diffusivity. However, our study relied on DTI metrics at term and Zwicker et al report DTI metrics at school age. Hence these studies cannot be directly compared. However, even though our results differed in terms of the DTI metric with best correlation, both studies supported the underlying role of brain microstructure in the development of DCD (28).

The limitation in interpreting the results of this and previous studies lie in DTI as a technique. DTI metrics are quantitative parameters based on the diffusion of water molecules. DTI metrics are highly sensitive but not specific to any changes in underlying structures. Accordingly, any conclusions regarding underlying structures have to be taken with caution.

A concern of this study are motion artefacts, which were the most common reason why DTI analysis could not be performed. The DTI data was collected at term age of this patient cohort as a part of a long-term follow-up project between 2004 - 2006. All typical DTI pre-processing steps such as motion correction, eddy current or susceptibility corrections were not in standard use at that time and thereby they were not used in this study. The lack of presently available pre-processing steps makes our data more prone to blurred DTI metrics. This is a major limitation of the study since subject motion correction ensures reliable DTI metrics.

A relatively small number of participants was also a limitation in this study. We applied the region-of-interest method, which allowed us to minimise the impeding partial volume effect as much as

possible. This method also allowed for analysis on an individual level, while the other widely used method – tract based spatial statistics – can only be used for group comparisons.

Besides its role as a potential method for providing supportive correlative measurable values, DTI analysis already functions as a base for the connectome analysis of the brain (29). Several methodological motor structural connectome studies in the population of preterm born children with a short follow-up period have already been published (30). This analysis may offer additional information about the brain plasticity in preterm infants and provide a possible diagnostic tool in the future.

CONCLUSION

This study suggests that the DTI metrics of the corpus callosum, corona radiata and optic radiations are associated with later motor development in the population of very preterm children. Studies with larger samples are needed to delineate the clinical value of DTI analysis in estimations of motor outcome in very preterm infants.

ACKNOWLEDGEMENTS

The members of the multi-disciplinary PIPARI Study Group: Annarilla Ahtola, Mikael Ekblad, Satu Ekblad, Eeva Ekholm, Leena Haataja, Mira Huhtala, Jere Jaakkola, Max Karukivi, Pentti Kero, Riikka Korja, Katri Lahti, Helena Lapinleimu, Liisa Lehtonen, Tuomo Lehtonen, Marika Leppänen, Annika Lind, Hanna Manninen, Mari Koivisto, Mira Mattson, Jonna Maunu, Petriina Munck, Laura Määttänen, Pekka Niemi, Anna Nyman, Pertti Palo, Riitta Parkkola, Liisi Ripatti, Päivi Rautava, Katriina Saarinen, Virva Saunavaara, Sirkku Setänen, Matti Sillanpää, Suvi Stolt, Päivi Tuomikoski-Koiranen, Timo Tuovinen, Karoliina Uusitalo, Anniina Väliaho and Milla Ylijoki. Sarah Holdren, language editing.

ABREVIATIONS

BSID-II and -III; Bayley Scales of Infant and Toddler Development Second and Third Edition

DCD; Developmental coordination disorder

DTI; Diffusion tensor imaging

GMFCS; Gross motor function classification scale

MABC and MABC-2; Movement Assessment Battery for Children First and Second Edition

MRI; Magnetic resonance imaging

CONFLICTS OF INTEREST

The authors do not have any conflicts of interest to declare.

FUNDING

This study was supported by the Foundation for Pediatric Research and Arvo and Lea Ylppö foundation.

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FIGURE LEGENDS

Fig 1. Inclusion-exclusion criteria

Fig 2. The manually drawn regions-of-interest from which the fractional anisotropy and mean diffusivity values were measured. The regions-of-interests with significant associations are highlighted with arrows: B) the genu of the corpus callosum anteriorly, the optic radiation posteriorly, C) splenium of the corpus callosum and D) the corona radiata.

Fig 3. The regression models for MABC-2 standard scores and diffusion tensor imaging metrics of the regions-of-interests that were significant in the univariate analysis. Mean diffusivity is shown in $x10^{-3}mm^2s^{-1}$.

Table 1. Neonatal characteristics

Background variables	
Gestational age in weeks	
Mean, (SD), [min, max]	29 4/7, (2 0/7), [24 5/7, 31 6/7]
Birth weight in grams	
Mean, (SD), [min, max]	1315.3, (360.3), [620.0, 2120.0]
Head circumference in cm	
Mean, (SD), [min, max]	27.37, (2.33), [22.50, 32.00]
Apgar-scores, 5 min	
Mean, (SD), [min, max]	7.53, (1.71), [2.00, 10.00]
Antenatal steroids	
Yes / no (data missing)	36 / 1 (0)
Postnatal steroids	
Yes / no (data missing)	1 / 36 (0)
Umbilical artery pH ≥ 7	
Yes / no (data missing)	36 / 0 (1)
Caesarean section	
Yes / no (data missing)	24 / 13 (0)
Preeclampsia	
Yes / no (data missing)	11 / 26 (0)
Absent or reversed flow in the umbilical artery	
Yes / no (data missing)	4 / 13 (20)
SGA status (less than z score -2)	
Yes / no (data missing)	9 / 28 (0)
Bronchopulmonary dysplasia	
Yes / no (data missing)	3 / 34 (0)
Necrotizing enterocolitis	

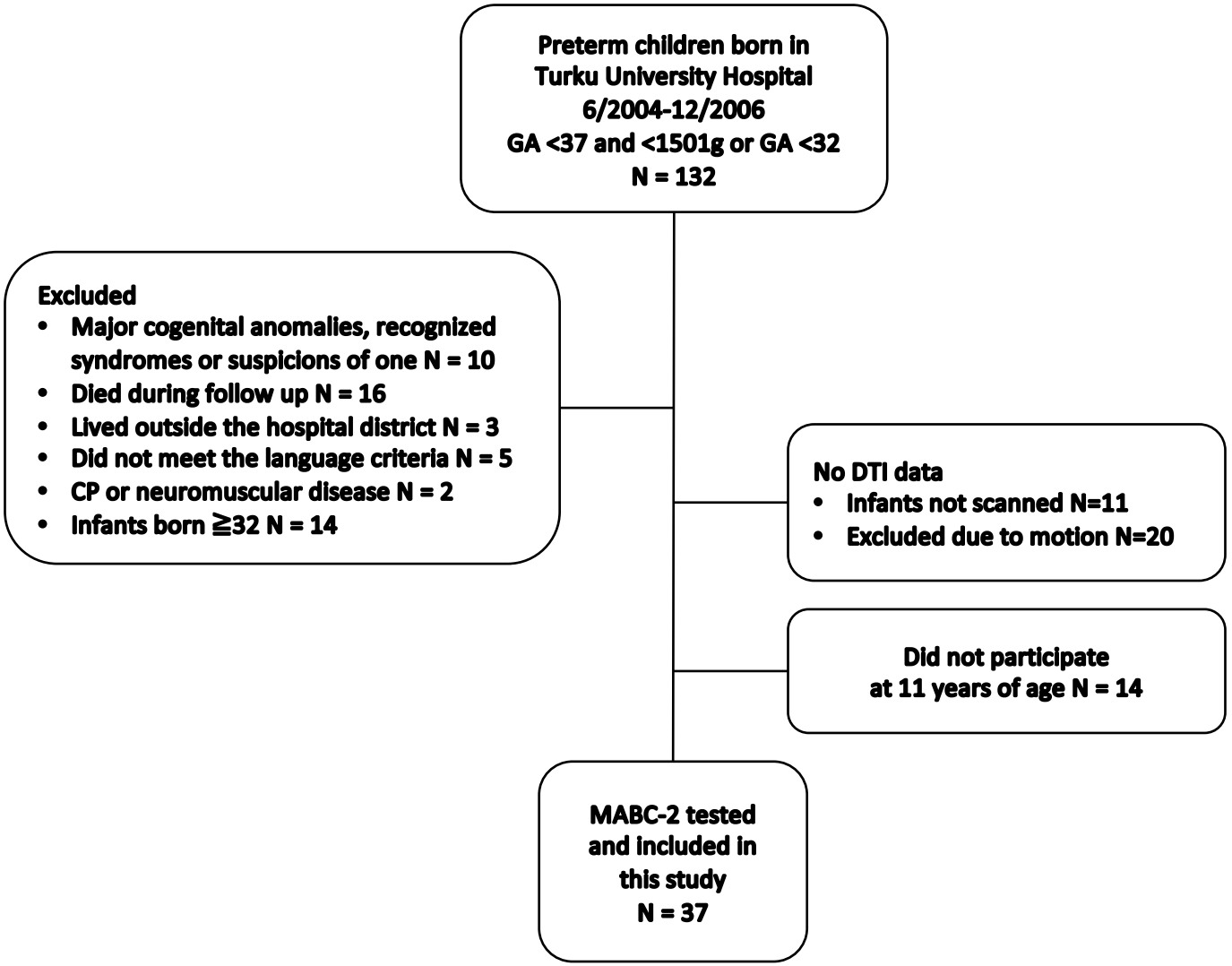
Yes / no (data missing)	2 / 33 (2)
Gestational age at MRI in weeks	
Mean, (SD), [min, max]	40 1/7, (0 5/7), [39 2/7, 44 1/7]
MRI findings	
Normal	23
Minor	4
Major	10

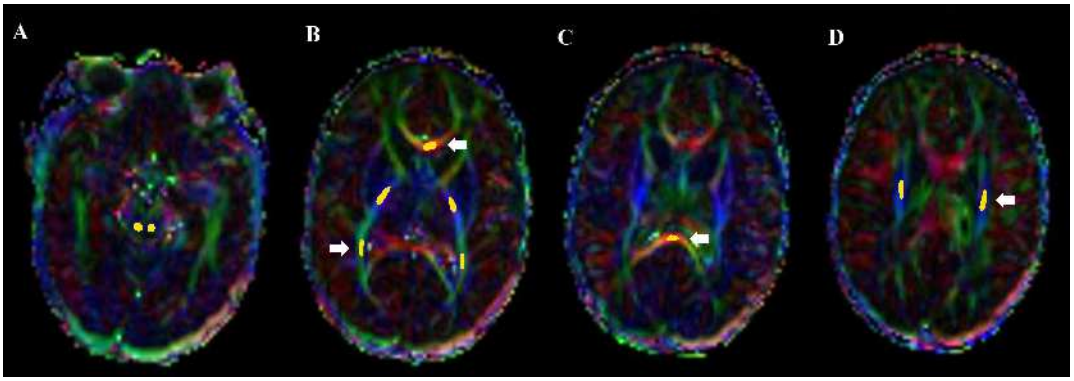
Region-of-interest	FA		MD ($x10^{-3}mm^2s^{-1}$)	
	All	DCD	All	DCD
Corpus callosum, genu	0.45, (0.08)	0.43, (0.13)	1.41, (0.13)	1.48, (0.13)
Corpus callosum, splenium	0.52, (0.10)	0.46, (0.15)	1.44, (0.35)	1.56, (0.48)
Posterior part of capsula interna, right	0.47, (0.06)	0.48, (0.03)	1.02, (0.07)	1.02 (0.06)
Posterior part of capsula interna, left	0.50, (0.06)	0.52, (0.04)	1.03, (0.07)	1.02, (0.07)
Colliculus inferior, right	0.38, (0.05)	0.37, (0.06)	1.03, (0.08)	1.01, (0.08)
Colliculus inferior, left	0.39, (0.05)	0.37, (0.07)	1.01, (0.08)	0.97, (0.05)
Corona radiata, right	0.41, (0.08)	0.40, (0.08)	1.09, (0.10)	1.10, (0.08)
Corona radiata, left	0.40, (0.08)	0.36, (0.06)	1.11, (0.12)	1.13, (0.08)
Optic radiation, right	0.37, (0.05)	0.33, (0.06)	1.36, (0.23)	1.38, (0.32)
Optic radiation, left	0.37, (0.05)	0.35, (0.06)	1.34, (0.22)	1.34, (0.23)

Table 2. The mean values and standard deviations of the DTI metrics fractional anisotropy (FA) and mean diffusivity (MD) in all children and in children with DCD.

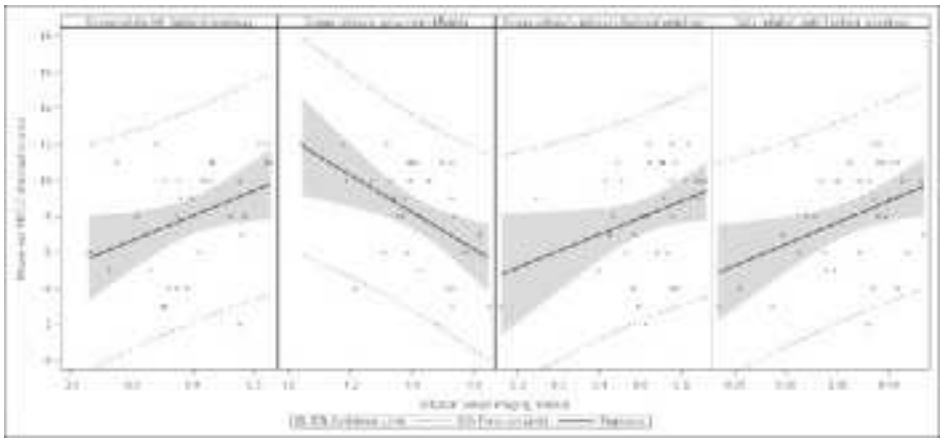
Region-of-interest	Mean diffusivity				Fractional anisotropy			
	Univariate		Multivariate		Univariate		Multivariate	
Corpus callosum, genu	**-1.029**	*0.005*	**-1.217**	*0.002*	**0.494**	*0.433*	**0.705**	*0.347*
Corpus callosum, splenium	**-0.154**	*0.274*	**-0.109**	*0.491*	**0.921**	*0.049*	**0.883**	*0.076*
Posterior part of capsula interna, right	**-0.630**	*0.407*	**-0.698**	*0.369*	**0.419**	*0.651*	**0.405**	*0.688*
Posterior part of capsula interna, left	**-0.998**	*0.147*	**-1.078**	*0.126*	**0.233**	*0.803*	**0.139**	*0.889*
Colliculus inferior, right	**0.006**	*0.993*	**-0.222**	*0.738*	**0.896**	*0.379*	**0.805**	*0.459*
Colliculus inferior, left	**0.459**	*0.458*	**0.401**	*0.539*	**1.162**	*0.260*	**0.970**	*0.381*
Corona radiata, right	**-0.667**	*0.231*	**-0.962**	*0.094*	**0.787**	*0.258*	**1.080**	*0.130*
Corona radiata, left	**-0.843**	*0.068*	**-1.003**	*0.030*	**1.382**	*0.035*	**1.655**	*0.014*
Optic radiation, right	**-0.880**	*0.681*	**-0.059**	*0.804*	**2.388**	*0.017*	**3.023**	*0.006*
Optic radiation, left	**-1.459**	*0.512*	**-0.079**	*0.733*	**1.067**	*0.243*	**1.657**	*0.098*

Table 3. The **estimates** when the DTI metric increases by 0.1, and the p values of the associations between the mean diffusivity and fractional anisotropy values of the MABC standard scores, both as a univariate and a multivariate model. Significant values are highlighted.





apa_15004_f2.tif



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