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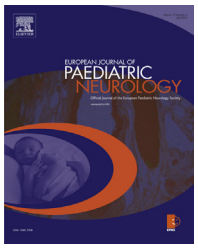

Original article

A crucial role of altered fractional anisotropy in motor problems of very preterm children

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ABSTRACT

Background: Very preterm children (<32 weeks of gestation) are characterized by impaired white matter development as measured by fractional anisotropy (FA). This study investigates whether altered FA values underpin 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 (mean [SD] age 8.7 [0.5] years) 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. FA values, as measure of white matter abnormalities, were determined 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 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. In addition, outcomes demonstrate that altered white matter FA values can potentially be used to discriminate between very preterm children at risk for motor impairments, although future studies are warranted.

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1. 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) and associated negative outcomes[4,5] than term controls.[3] Unfortunately, there is limited insight in which altered white matter tracts underly motor impairments and the increased incidence of DCD in very preterm children, although understanding the aetiology may eventually benefit (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).[6] 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.[7] In very preterm children, significantly reduced FA values have been reported at various stages in development, interpreted as altered white matter functioning,[8–12] 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 fibres 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.[6] 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.[6]

In this study, we aimed to elucidate the relationship between white matter tract FA values 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. Second, we investigated associations between motor impairment and FA values of those white matter tracts discriminating between very preterm children and term controls. Third, 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 whether altered FA values underpin the increased incidence of DCD in very preterm children. 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. We additionally included widely used measures of brain structure volumes and cognitive functioning (Wechsler Intelligence Scales for Children, WISC-III)[13] 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.

2. Methods

2.1. 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.[14] Description of baseline characteristics of the original sample has been previously reported.[14] At 7–8 years of age, parents of all 39 children who survived the neonatal period and acted as controls in the intervention study were 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,[15] and 30 children (83%) successfully finished MRI follow-up at the mean (SD) age of 8.6 (0.3) years.[16] 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),[17] number of serious neonatal infections (including sepsis, meningitis, pyelonephritis, pneumonia, and arthritis), and number of other clinical complications. There were no differences in birth weight, gestational age, z-score of BW for GA, and age between the 30 participating children and the nine non-participating children in MRI follow-up.

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 (scores above the 15th percentile for their age on the Total Motor Impairment score of the MABC), to attend regular classes, and free of behavioural 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 1 (low SES) to 4 (high SES).[18]

2.2. 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