NeuroImage: Clinical 16 (2017) 268–275

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

White matter microstructure of 6-year old children born preterm and full term

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ARTICLE INFO

Keywords:
Diffusion tensor imaging
White matter
Prematurity
Development
Tractography

ABSTRACT

Aim: We previously observed a complex pattern of differences in white matter (WM) microstructure between preterm-born (PT) and full-term-born (FT) children and adolescents age 9–17 years. The aim of this study was to determine if the same differences exist as early as age 6 years.

Method: We obtained diffusion MRI (dMRI) scans in children born PT at age 6 years (n = 20; 11 males) and FT (n = 38; 14 males), using two scanning protocols: 30 diffusion directions (b = 1000 s/mm^2) and 96 diffusion directions (b = 2500 s/mm^2). We used deterministic tractography and analyzed fractional anisotropy (FA) along bilateral cerebral WM pathways that demonstrated differences in the older sample.

Results: Compared to the FT group, the PT group showed (1) significantly decreased FA in the uncinate fasciculi and forceps major and (2) significantly increased FA in the right anterior thalamic radiation, inferior fronto-occipital fasciculi, and inferior longitudinal fasciculi. This pattern of group differences resembles findings in the previous study of older PT and FT participants. Group differences were similar across dMRI acquisition protocols.

Interpretation: The underlying neurobiology driving the pattern of PT-FT differences in FA is present as early as age 6 years. Generalization across dMRI acquisition protocols demonstrates the robustness of group differences in FA. Future studies will use quantitative neuroimaging techniques to understand the tissue properties that give rise to this consistent pattern of WM differences after PT birth.

1. Introduction

Cerebral white matter injury after preterm birth is associated with long-term, adverse neurodevelopmental outcomes (Hintz et al., 2015; Allen, 2008; Aylward, 2005). In the past, many children born preterm (PT) had cystic lesions visualized readily on cranial ultrasound and clinical MRI scans (Gupta et al., 2016; Inder et al., 1999a). Advances in neonatal medicine have reduced the rates of cystic injuries, (Gano et al., 2015) but have not eliminated noncystic white matter injury and subsequent white matter dysmaturity (Volpe, 2009; Back et al., 2007). Such injuries are difficult to detect and quantify on cranial ultrasound or conventional (T1 or T2) MRI scans. Non-cystic injuries may lead to impaired brain growth that can be detected with volumetric analyses; however, these techniques are not widely used in clinical settings (Mathur et al., 2010; Inder et al., 1999b; de la Monte et al., 1990).

Over the past 15 years, diffusion magnetic resonance imaging (dMRI) has emerged as the method of choice for detecting and quantifying white matter microstructure in health and illness (Anjari et al., 2007; Arzoumanian et al., 2003). Tractography is an algorithmic approach applied to dMRI data, which is considered a sensitive method for identifying long-range white matter pathways (tracts) in individual participants (Yeatman et al., 2012). Microstructural properties of these tracts can be quantified by calculating fractional anisotropy (FA), a scalar value that indexes the degree of directional preference of water diffusion at each voxel within the tract (Basser and Pierpaoli, 1996). FA can be decomposed into axial diffusivity (AD) and radial diffusivity (RD), which quantify the speed of water diffusion along the principal and perpendicular diffusion directions, respectively (Feldman et al., 2010). Because bundles of axons constrain water diffusion in a directional fashion, water diffusion has greater directional preference within white matter than in cerebral spinal fluid or in gray matter; FA is higher in white matter than in other tissue compartments. FA increases with increased myelination and high axonal density (Basser and Pierpaoli, 1996). FA decreases with larger axonal diameter and increased

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http://dx.doi.org/10.1016/j.nicl.2017.08.005
Received 28 June 2017; Received in revised form 4 August 2017; Accepted 7 August 2017
Available online 08 August 2017

numbers of crossing fibers within each voxel in the brain (Jeurissen et al., 2013; Assaf and Pasternak, 2008). The value of FA in any given voxel reflects the relative contributions of these neurobiological factors.

Studies have used dMRI tractography in infants born preterm at- and near- term equivalent ages to assess white matter microstructure in the aftermath of PT birth and to explore associations of early white matter properties with neurodevelopmental outcomes (Pannek et al., 2014; Hasegawa et al., 2011; Adams et al., 2010; Liu et al., 2010; Berman et al., 2005). However, few dMRI tractography studies of PT-born neonates had a FT comparison group (Kaur et al., 2014; Ball et al., 2013; Thompson et al., 2011). These studies comparing PT and FT-born neonates find evidence for early impairments in white matter microstructure in PT children: FA was increased in FT compared to PT neonates in the corpus callosum, uncinate fasciculus, inferior fronto-occipital fasciculus and cingulum (Kaur et al., 2014; Thompson et al., 2011). A lack of studies with a longitudinal design make it unclear whether early white matter differences in the newborn period change with experience, or if new differences emerge as a consequence of ongoing developmental delays.

Previous evidence has shown that dMRI can be sensitive to microstructural differences in white matter in the absence of gross structural injuries in adolescents born preterm (Travis et al., 2015a; Groeschel et al., 2014; de Kieviet et al., 2014; Inder et al., 1999a). Three dMRI studies used tractography as the analytic method. However, the findings have been inconsistent. One study comparing PT and FT children at age 8 years consistently found decreased FA in the PT group in six tracts: bilateral cingulum hippocampal tracts, bilateral corticospinal tracts, forceps major and forceps minor (de Kieviet et al., 2014). By contrast, a second study of adolescents born PT compared to FT at age 16 years demonstrated mixed findings: decreased FA in segments of the corpus callosum and corticospinal tract, and increased FA in the superior longitudinal fasciculus, thalamo-cortical pathway, anterior thalamic radiation and segments of the corpus callosum (Groeschel et al., 2014). A third study compared PT and FT children at age 9–17 years and found, again, a mixed pattern of results: PT participants had decreased FA in segments of the uncinate fasciculi (UF), forceps major (FMajor) and right inferior fronto-occipital fasciculus (IFOF), and increased FA in segments of the anterior thalamic radiations (ATR), inferior fronto-occipital fasciculi and inferior longitudinal fasciculi (ILF) (Travis et al., 2015a). Though the age range of participants was broad, there was no association between age and FA (Travis et al., 2015a). The differences in findings across these three studies may relate to differences between the samples (*e.g.*, in age composition) or to differences between the scan protocols and analytic approaches applied in each study. In the current study, we set out to examine patterns of differences in the tract properties of PT and FT born children as early as age 6 years, using methods previously applied in PT and FT at age 9–17 years (Travis et al., 2015a).

We hypothesized that FA differences detected at late childhood to adolescence (Travis et al., 2015a) would be detected at age 6 years, based on the lack of associations with age within the older sample. We specifically expected to find decreased FA in PT compared to FT in segments of the UF, FMajor and IFOF, and increased FA in segments of the ATR, IFOF and ILF in the PT compared to the FT sample. We assessed white matter microstructure using two different acquisition protocols to examine the robustness of the findings.

2. Material and methods

2.1. Participants

Participants were enrolled in a longitudinal study investigating the neural basis of reading in children born preterm, for which children were recruited from the San Francisco Bay Area from 2012 to 2015. For the analyses presented in this study, PT birth was defined as gestational age (GA) < 31 weeks and FT birth was defined as GA > 37 weeks. This definition was employed to equate the mean GA of the PT and FT samples to those in Travis et al. (Travis et al., 2015a). Gestational age was used as the estimate of newborn immaturity and not birth weight because methods for estimating gestational age have improved and because birth weight is comprised of both gestational age and intrauterine growth rate and is therefore less specific for estimating immaturity than gestational age. Only children who completed both dMRI acquisition protocols at age 6 years (see below) were included in the current study. PT children were recruited from the High-Risk Infant Follow Clinic at Lucile Packard Children's Hospital Stanford, local parent groups and surrounding communities. FT children were recruited through online parent groups, postings in local school newsletters and letters to families who had participated in past research studies in affiliated research laboratories at Stanford University. Exclusion criteria for all participants included congenital anomalies, mother's self-reported use of illicit drugs or alcohol during pregnancy, active seizure disorder, hydrocephalus or sensorineural hearing loss. Diagnosis of cerebral palsy (CP) was not an exclusion criterion. One PT participant had mild CP. The experimental protocol was approved by the Stanford University Institutional Review Board #IRB-22233. A parent or legal guardian provided informed written consent and participants were compensated for participation.

Characteristics assessed in this sample included ethnicity and socioeconomic status (SES), as measured using a modified 4-Factor Hollingshead Index (Supplementary material). Intellectual abilities (IQ) were assessed using the Wechsler Abbreviated Scale of Intelligence (WASI-II). Handedness was measured using the Edinburgh Handedness Inventory.

2.2. Diffusion MRI acquisition and analyses

MRI data were acquired on a 3 T Discovery MR750 scanner (General Electric Healthcare, Milwaukee, WI, USA) equipped with a 32-channel head coil (Nova Medical, Wilmington, MA, USA) at the Center for Cognitive and Neurobiological Imaging at Stanford University (www.cni.stanford.edu). All subjects were scanned for research purposes and without the use of sedation. For each subject, we collected a high-resolution T1-weighted anatomical image using a 5-min inversion recovery (IR)-prep 3D fast-spoiler gradient (FSPGR) sequence collected in the sagittal plane (0.9-mm cubed voxel size), and two separate diffusion-weighted sequences. Protocol 1 consisted of a 30-direction diffusion-weighted scan ($b = 1000$ s/mm^2) and Protocol 2 consisted of a 96-direction diffusion-weighted scan ($b = 2500$ s/mm^2). Imaging parameters, data preprocessing steps and analysis of motion are described in the Supplementary material for both acquisition protocols (see Supplementary material).

In order to maximize sensitivity while taking into account considerable individual variability, particularly at this early stage in brain development, our approach used individual tract identification in the native space of each child. We also quantified diffusivity properties along the length of the tract rather than rely on less sensitive mean values. Methods for performing deterministic tractography, fiber tract identification, segmentation and quantification were implemented using the Automated Fiber Quantification (AFQ; https://github.jyeatman/AFQ) software package and MATLAB and are described in detail in Supplementary material. These procedures were directly comparable to those employed by Travis et al. (Travis et al., 2015a). Bilateral pathways for analysis were selected *a priori* based on evidence of significant unilateral or bilateral group differences in the separate cohort of older PT and FT children and adolescents (Travis et al., 2015a). Fig. 1 shows the analyzed tracts: left (L) and right (R) UF, FMajor, ATR, IFOF and ILF.