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Brain microstructural development at near-term age in very-low-birth-weight preterm infants: An atlas-based diffusion imaging study

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ABSTRACT

At near-term age the brain undergoes rapid growth and development. Abnormalities identified during this period have been recognized as potential predictors of neurodevelopment in children born preterm. This study used diffusion tensor imaging (DTI) to examine white matter (WM) microstructure in very-low-birth-weight (VLBW) preterm infants to better understand regional WM developmental trajectories at near-term age.

DTI scans were analyzed in a cross-sectional sample of 45 VLBW preterm infants (BW ≤ 1500 g, GA ≤ 32 weeks) within a cohort of 102 neonates admitted to the NICU and recruited to participate prior to standard-of-care MRI, from 2010 to 2011, 66/102 also had DTI. For inclusion in this analysis, 45 infants had DTI, no evidence of brain abnormality on MRI, and were scanned at PMA ≤40 weeks (34.7–38.6). White matter microstructure was analyzed in 19 subcortical regions defined by DiffeoMap neonatal brain atlas, using threshold values of trace <0.006 $mm^2 s^{-1}$ and FA >0.15. Regional fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) were calculated and temporal–spatial trajectories of development were examined in relation to PMA and brain region location.

Posterior regions within the corona radiata (CR), corpus callosum (CC), and internal capsule (IC) demonstrated significantly higher mean FA values compared to anterior regions. Posterior regions of the CR and IC demonstrated significantly lower RD values compared to anterior regions. Centrally located projection fibers demonstrated higher mean FA and lower RD values than peripheral regions including the posterior limb of the internal capsule (PLIC), cerebral peduncle, retrolenticular part of the IC, posterior thalamic radiation, and sagittal stratum. Centrally located association fibers of the external capsule had higher FA and lower RD than the more peripherally-located superior longitudinal fasciculus (SLF). A significant relationship between PMA-at-scan and FA, MD, and RD was demonstrated by a majority of regions, the strongest correlations were observed in the anterior limb of the internal capsule, a region undergoing early stages of myelination at near-term age, in which FA increased ($r = .433$, $p = .003$) and MD ($r = -.545$, $p = .000$) and RD ($r = -.540$, $p = .000$) decreased with PMA-at-scan. No correlation with PMA-at-scan was observed in the CC or SLF, regions that myelinate later in infancy.

Regional patterns of higher FA and lower RD were observed at this near-term age, suggestive of more advanced microstructural development in posterior compared to anterior regions within the CR, CC, and IC and in central compared to peripheral WM structures. Evidence of region-specific rates of microstructural development was observed. Temporal–spatial patterns of WM microstructure development at near-term age have important implications for interpretation of near-term DTI and for identification of aberrations in typical developmental trajectories that may signal future impairment.

Abbreviations: VLBW, very-low-birth-weight; GA, gestational age; PMA, postmenstrual age; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; CR, corona radiata; ACR, anterior corona radiata; SCR, superior corona radiata; PCR, posterior corona radiata; CC, corpus callosum; IC, internal capsule; ALIC, anterior limb of the internal capsule; PLIC, posterior limb of the internal capsule; CereP, cerebral Peduncle; RLC, retrolenticular part of internal capsule; PTR, posterior thalamic radiation; SS, sagittal stratum; EC, external capsule; SLF, superior longitudinal fasciculus; StriaT, stria terminalis.

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Introduction

At near-term age, the brain undergoes rapid growth and microstructural development (Brody et al., 1987; Dubois et al., 2006; Huang et al., 2006; Kinney et al., 1988; Nossin-Manor et al., 2013; Oishi et al., 2011). Abnormalities identified during this period have been recognized as potential predictors of neurodevelopment in children born preterm (Aeby et al., 2013; Arzoumanian et al., 2003; Mukherjee et al., 2002; Rose et al., 2007, 2009; Thompson et al., 2012; van Kooij et al., 2011, 2012; Woodward et al., 2012). Advances in neonatal medicine have improved survival rates and outcome among preterm infants, however, 40–50% of very preterm infants experience neurodevelopmental impairments, including cerebral palsy, developmental coordination disorder, as well as cognitive and language delays (Spittle et al., 2011; Williams et al., 2010). At term-equivalent age, prematurity has been found to be associated with reduced cerebral volume and WM immaturity compared to term-born neonates (Hüppi et al., 1998; Inder et al., 2005; Lee et al., 2012; Rose et al., 2008; Thompson et al., 2006, 2013). However, little is known about the effect of timing, location, and severity of WM injury on neurodevelopment and future function. Near-term neuroimaging holds potential for establishing early biomarkers for future impairment to guide early intervention at a time of optimal neuroplasticity and rapid musculoskeletal growth.

Brain MRI is commonly assessed in very-low-birth-weight (VLBW) preterm infants prior to discharge from the NICU and offers an opportunity for early prognosis. To date, structural MRI has been only partially successful at detecting risk for neurodevelopmental problems later in life (Benini et al., 2012; Kidokoro et al., 2011). Diffusion tensor imaging (DTI) allows quantitative analysis of brain microstructure based on patterns of water diffusion (Basser and Pierpaoli, 1996; Counsell et al., 2002; Hüppi et al., 1998; Pierpaoli et al., 1996) and has shown promise for early prognosis of developmental outcome (Arzoumanian et al., 2003; Rose et al., 2007, 2009). As the brain develops, brain water content decreases, extracellular spaces diminish in size, and intra- and intercellular microstructures become more complex and organized. New barriers to water mobility form, such as axonal cell membranes, dendrites, and development of WM structural coherence and myelination that restrict water diffusion (Dubois et al., 2008; Kinney et al., 1994; Nossin-Manor et al., 2013). Scalars obtained from DTI can assess brain development and maturation and include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) (Pierpaoli et al., 1996). FA reflects the degree of diffusion anisotropy within a voxel, and is determined by fiber diameter and density, myelination, extracellular diffusion, inter-axonal spacing, and intra-voxel fiber-tract coherence. AD, a measure of diffusivity along the primary axis of diffusion within a voxel, is thought to reflect fiber coherence, and structure of axonal membranes (Song et al., 2002). RD, the mean of the diffusivities perpendicular to the primary axis of diffusion, is thought to represent degree of myelination (Chen et al., 2011; Song et al., 2002). MD is a calculation of average diffusion along the three main axes, relative to the primary direction of diffusion (AD). In neonates, FA has been found to increase, while MD, AD, and RD decrease, with age in WM regions, likely due to increased fiber organization, axonal coherence, and preliminary myelination (Aeby et al., 2009; Dubois et al., 2008; Mukherjee et al., 2002; Partridge et al., 2004; Shim et al., 2012).

Previous post-mortem and in-vivo fetal imaging studies in humans and histochemical imaging studies in animals suggest that early brain development follows an organized pattern (Bockhorst et al., 2008; Brody et al., 1987; Rajagopalan et al., 2012; Vasung et al., 2010; Yakovlev and Lecours, 1967; Yoshida et al., 2013). Specifically, post-mortem anatomical study of human brain development at 12–22 weeks using 7.0 T MR identified the germinal matrix in the periventricular zone as early as 12 weeks GA (Meng et al., 2012). Huang et al. (2009) used DTI for post-mortem anatomical study of brain development from 13 to 22 weeks GA, and identified centrally located brainstem WM tracts, including the lower corticospinal tract (CST) and limbic fibers in the fornix and stria terminalis, at 13 weeks. During the second trimester, commissural, projection, and some association tracts were identified; the corpus callosum (CC) and internal capsule (IC) were visible at approximately 15 weeks. Association fibers of the sagittal stratum (SS) and external capsule (EC) were identified at 13–15 weeks. The cerebral peduncle (CereP) and IC developed earlier than more peripheral regions that extended into the corona radiata (CR) at 19–20 weeks (Huang et al., 2009).

As neurogenesis and neurodevelopment proceed, recently formed neurons migrate from the centrally-located germinal matrix to outer aspects of the cortical plate, producing the "inside out" order of cortical layers (Rakic, 1988). Cortical thickening and deepening of sulci continue during the second and third trimesters (Zhang et al., 2011, 2013) and the underlying intermediate zone matures into WM that contains afferent and efferent axons (Rakic, 1988). Proliferation and migration of oligodendrocytes, formed in centrally-located germinal matrix, ensheath axons and form myelin (Liu et al., 2013), influencing temporal–spatial patterns of WM development.

During the first two years of life, regional WM has been found to develop in a central-to-peripheral direction (Gao et al., 2008). Within specific regions such as the IC and CC, myelination has been reported to progress primarily from posterior-to-anterior direction with fronto-cortical brain regions the last to myelinate (Deoni et al., 2011; Geng et al., 2012; Kinney et al., 1988; Löbel et al., 2009; van der Knaap and Valk, 1990; Yoshida et al., 2013). DTI analysis of WM in full-term infants demonstrated progressive increase in FA and decrease in MD, AD, and RD with age (Gao et al., 2008; Geng et al., 2012; Yoshida et al., 2013).

In this study we use DTI to examine patterns of regional WM microstructure development in a cross-sectional sample of preterm infants with no evidence of brain injury on MRI, to better understand temporal–spatial trajectories of WM development at near-term age. Atlas-based DTI was used in order to quantify the developmental status of brain regions at near-term age, including WM microstructure and relative volume, using a semi-automated approach with potential clinical applications (Oishi et al., 2011, 2013). We hypothesized that posterior regions within WM structures will show evidence of earlier microstructural development relative to anterior portions, and that centrally-located WM projection fibers will demonstrate evidence of earlier development than peripherally-located projection and association fibers.

Methods

Neonatal scans were obtained from 102 VLBW neonates, representing 76% of eligible participants admitted to Lucile Packard Children's Hospital (LPCH) and scanned between 1/1/10–12/31/11. Parents of all infants with GA $\leq$32 weeks, BW $\leq$1500 g, with no evidence of genetic disorders or congenital brain abnormalities were approached prior to scheduled standard-of-care MRI and consent was obtained for this IRB-approved study. Infants with no evidence of congenital brain abnormalities on MRI were included. 66 of 102 had successful DTI scans, collected at the end of the MRI scans, which are performed as standard-of-care at LPCH for all VLBW preterm infants at near-term age. 45 were scanned before 40 weeks PMA and had no evidence of brain abnormalities as reported by the clinical neuroradiologist and confirmed by a second neuroradiologist X.S.

MRI data acquisition

Brain MRI scans performed on 3T MRI (GE Discovery MR750, GE 8-Channel HD head coil) at LPCH, included T1, T2-weighted scans and diffusion-weighted scans (b = 1000 s/mm^2). The DTI was based on diffusion-weighted, single-shot, spin-echo, echo-planar imaging sequence of 25 directions, with slice thickness of 3 mm, matrix size of 128 × 128, and 90° flip angle. Two repetitions (~5 min each) were collected. Diffusion-weighted sequences were collected at the end of the