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Alterations in the optic radiations of very preterm children—Perinatal predictors and relationships with visual outcomes ☆

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ABSTRACT

Children born very preterm (VPT) are at risk for visual impairments, the main risk factors being retinopathy of prematurity and cerebral white matter injury, however these only partially account for visual impairments in VPT children. This study aimed to compare optic radiation microstructure and volume between VPT and term-born children, and to investigate associations between 1) perinatal variables and optic radiations; 2) optic radiations and visual function in VPT children. We hypothesized that optic radiation microstructure would be altered in VPT children, predicted by neonatal cerebral white matter abnormality and retinopathy of prematurity, and associated with visual impairments.

142 VPT children and 32 controls underwent diffusion-weighted magnetic resonance imaging at 7 years of age. Optic radiations were delineated using constrained spherical deconvolution tractography. Tract volume and average diffusion tensor values for the whole optic radiations and three sub-regions were compared between the VPT and control groups, and correlated with perinatal variables and 7-year visual outcome data.

Total tract volumes and average diffusion values were similar between VPT and control groups. On regional analysis of the optic radiation, mean and radial diffusivity were higher within the middle sub-regions in VPT compared with control children. Neonatal white matter abnormalities and retinopathy of prematurity were associated with optic radiation diffusion values. Lower fractional anisotropy in the anterior sub-regions was associated with poor visual acuity and increased likelihood of other visual defects.

This study presents evidence for microstructural alterations in the optic radiations of VPT children, which are largely predicted by white matter abnormality or severe retinopathy of prematurity, and may partially explain the higher rate of visual impairments in VPT children.

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1. Introduction

Children born very preterm [VPT, <32 weeks' gestational age (GA)] are at high risk of visual impairments compared with children born at term (≥37 weeks' GA) (Arpino et al., 2010), which range from relatively subtle complications such as reduced visual acuity to complete blindness (Mirabella et al., 2006). Complex visual perceptual processes that rely on the integration of visual information are also often affected (Geldof et al., 2012). Such visual impairments may contribute to learning difficulties at school (Cooke et al., 2004). Major causes of visual impairment in VPT children include retinopathy of prematurity (ROP; pathologic vascular hyperproliferation in the immature retina (Palmer et al., 2005)) and overt cerebral white matter injury affecting the visual pathways (Ricci et al., 2006). However, visual impairments have been

Abbreviations: AD, Axial diffusivity; BWSDS, Birth weight standard deviation score; CI, Confidence interval; CSD, Constrained spherical deconvolution; FA, Fractional anisotropy; GA, Gestational age; MRI, Magnetic resonance imaging; MD, Mean diffusivity; RD, Radial diffusivity; ROP, Retinopathy of prematurity; VPT, Very preterm.

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reported even in VPT children who have no history of ROP or overt cerebral injury (Kozeis et al., 2012), indicating that other factors may be associated with visual impairment in VPT children. By studying the white matter within the optic radiations, elucidation of potential neuroanatomical correlates for visual impairment in VPT children may be possible.

One method that can be utilized to study the major tracts of the white matter is constrained spherical deconvolution (CSD) based tractography. CSD is an advanced diffusion-weighted magnetic resonance imaging (MRI) analysis method that is capable of modeling multiple fiber orientations, enabling robust delineation of white matter tracts (Tournier et al., 2007). Combined with the diffusion tensor model, non-invasive estimates of the microstructure and volume of specific white matter tracts can be made. Diffusion imaging has been applied to investigate the optic radiations in preterm infants in association with visual function assessed both in the neonatal period (Bassi et al., 2008; Berman et al., 2009; Groppo et al., 2012), and 6–20 months later (Glass et al., 2010). However, it is unknown whether further maturation and development of the optic radiations later into childhood strengthen or weaken relationships with visual function. The current study extends previous studies by investigating the association between optic radiation microstructure and volume and visual function at 7 years of age, when visual system structure and function is approaching full development (Birch and O'Connor, 2001). Furthermore, it associates optic radiations with neonatal MRI-detected white matter abnormality and ROP. It also extends previous studies by including a term-born control group, having access to a large sample size, and utilizing advanced CSD based tractography. The specific aims of the current study were to: 1) compare the microstructure and volume of the optic radiations between VPT children and controls at 7 years of age; 2) investigate relationships between perinatal variables and optic radiation structure in VPT children, particularly ROP and MRI-detected white matter abnormality; and 3) determine the relationship between optic radiation structure in VPT children and visual function assessed contemporaneously. It was hypothesized that: 1) optic radiation structure would be altered in VPT children compared with controls; 2) neonatal white matter abnormality and ROP would be associated with altered optic radiation structure in VPT children; and 3) altered optic radiation structure would be associated with visual impairments in VPT children.

2. Materials and methods

2.1. Participants

A prospective observational cohort of 227 children born <30 weeks' GA or <1250 g (which we will call the "VPT" group, acknowledging that it is different from the usual use of "VPT" as <32 weeks' GA) and 46 healthy term controls (born ≥ 37 weeks' GA) was recruited from the Royal Women's Hospital in Melbourne between July 2001 and December 2003. 2 VPT infants died and 1 was subsequently found to have a congenital abnormality, leaving 224 VPT children eligible. Children with congenital abnormalities or chromosomal disorders were also excluded. A total of 198 VPT children and 43 controls were followed-up at age 7 years. Of those who were followed-up, 160 VPT children and 36 controls underwent MRI, but 22 of these either did not have full diffusion datasets acquired or scans were unusable due to movement artifact. Thus the final number of children in the current study was 174 (64% of those recruited), including 142 VPT and 32 controls. Perinatal characteristics were similar between VPT participants who contributed optic radiation data and non-participants, with the exception of postnatal corticosteroid exposure (participants − 5.7%; non-participants −13.8%, $p = 0.03$).

The study was approved by the Royal Children's Hospital Human Research Ethics Committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all parents/caregivers prior to inclusion in the study. Perinatal data were obtained by chart review at the time of hospital discharge.

2.2. Magnetic resonance imaging

At term-equivalent age, T_1 and T_2 weighted images were acquired on a 1.5 T scanner. Infants were immobilized in a vacuum fixation beanbag and scanned while sleeping, without sedation. A cerebral white matter abnormality score (range 0–17) was graded qualitatively, as previously described and validated (Kidokoro et al., 2013).

At 7 years of age, MRI was performed without anesthesia or sedation on a 3 T scanner. T_1 weighted three-dimensional rapid gradient-echo images were acquired: TR, 1900 ms; TE, 2.27 ms; matrix, 256 × 256; FOV, 210 × 210 mm; 0.8 mm^3 isotropic voxels. Intracranial volumes were obtained from the T_1 weighted images using 'FreeSurfer' software (Buckner et al., 2004). Given that overall head size has been shown to influence white matter diffusion tensor values due to differential partial volume effects (Takao et al., 2011), intracranial volumes were used to control for partial volume effects or other white matter microstructural differences related to head size.

Two sets of echo-planar diffusion-weighted images were acquired; one with 25 non-collinear gradient directions and b-values ranging up to 1200 s/mm^2 (TR, 12000 ms; TE, 96 ms; matrix, 144 × 144; FOV, 250 × 250 mm; 1.7 mm^3 isotropic voxels), and another with 45 gradient directions and a b-value of 3000 s/mm^2 (TR, 7400 ms; TE, 106 ms; matrix, 104 × 104; FOV, 240 × 240 mm; 2.3 mm^3 isotropic voxels). The $b = 1200$ s/mm^2 data were processed using 'ExploreDTI' software (Leemans et al., 2009). Data were corrected for motion and eddy current induced distortions, incorporating re-orientation of the B-matrix. The diffusion tensor model was fitted, generating axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and fractional anisotropy (FA) maps. CSD was applied to the $b = 3000$ s/mm^2 diffusion-weighted data using 'MRtrix' software (Tournier et al., 2012), creating a map of fiber orientation distributions in each voxel. A maximum harmonic order of 6 was used.

2.3. Fiber tractography

Probabilistic tractography was performed based on CSD's fiber orientation distributions. A seed region of interest was placed on an axial slice depicting the transition from the posterior limb of the internal capsule to the cerebral peduncle. The seed was positioned immediately lateral to the lateral geniculate nucleus within the white matter of the optic radiation at the apex of the arc around the lateral ventricles (Fig. 1A), as described previously (Ciccarelli et al., 2003). A target region of interest was positioned on a coronal slice encompassing the entire white matter cross-section of the optic radiation, just anterior to the primary visual cortex (Fig. 1B) (Berman et al., 2009). A maximum fiber orientation distribution amplitude of 0.2 was specified, and tracts were constrained to pass in one direction from the seed to target region of interest (Fig. 1C). Binary tract images were produced by counting the number of streamlines per voxels, and discarding voxels containing <6/1000 streamlines to reduce the likelihood of including aberrant fibers in the tract volume.

Diffusion metrics vary along the optic radiations due to variations in fiber density and geometry, partial volume effects and locations of injury (Berman et al., 2009; Yeatman et al., 2012). Therefore, the tracts were divided into three equal sub-regions by cutting the tracts one-third and two-thirds of the way from their most anterior to most posterior points (Fig. 1D, E and F).

Diffusion values (FA, RD, AD, MD) within the whole optic radiations and sub-regions were obtained by averaging values from the co-registered $b = 1200$ s/mm^2 diffusion tensor maps within the binary tract images. Diffusion values were obtained from the co-registered $b = 1200$ s/mm^2 maps rather than directly from the $b = 3000$ s/mm^2 maps because: 1) diffusion tensor values, particularly MD, vary according

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