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Fixel-based analysis reveals alterations is brain microstructure and macrostructure of preterm-born infants at term equivalent age

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ABSTRACT

Preterm birth causes significant disruption in ongoing brain development, frequently resulting in adverse neurodevelopmental outcomes. Brain imaging using diffusion MRI may provide valuable insight into microstructural properties of the developing brain. The aim of this study was to establish whether the recently introduced fixel-based analysis method, with its associated measures of fibre density (FD), fibre bundle cross-section (FC), and fibre density and bundle cross-section (FDC), is suitable for the investigation of the preterm infant brain at term equivalent age. High-angular resolution diffusion weighted images (HARDI) of 55 preterm-born infants and 20 term-born infants, scanned around term-equivalent age, were included in this study (3 T, 64 directions, b = 2000 s/mm^2). Postmenstrual age at the time of MRI, and intracranial volume (FC and FDC only), were identified as confounding variables. Gestational age at birth was correlated with all fixel measures in the splenium of the corpus callosum. Compared to term-born infants, preterm infants showed reduced FD, FC, and FDC in a number of regions, including the corpus callosum, anterior commissure, cortico-spinal tract, optic radiations, and cingulum. Preterm infants with minimal macroscopic brain abnormality showed more extensive reductions than preterm infants without any macroscopic brain abnormality; however, little differences were observed between preterm infants with no and with minimal brain abnormality. FC showed significant reductions in preterm versus term infants outside regions identified with FD and FDC, highlighting the complementary role of these measures. Fixel-based analysis identified both microstructural and macrostructural abnormalities in preterm born infants, providing a more complete picture of early brain development than previous diffusion tensor imaging (DTI) based approaches.

1. Introduction

Preterm birth occurs at a critical time during brain development. Exposure to the extra-uterine environment causes disturbances in the balance of developmental processes of apoptosis, synaptogenesis, and myelination (Volpe, 2009). Infants born prematurely are therefore at an increased risk of motor, cognitive, and behavioural problems (Allen et al., 2011; Saigal and Doyle, 2008). Earlier identification of infants at high risk of developing adverse outcomes would enable earlier, targeted intervention.

Diffusion magnetic resonance imaging (MRI) can provide unique insights into the microstructural development of the brain. Diffusion tensor imaging (DTI) is the most commonly used diffusion MRI method in neonates. Typical measures obtained from DTI include fractional anisotropy (FA), mean diffusivity (MD; sometimes also referred to as apparent diffusion coefficient, ADC), and axial and radial diffusivity. During early brain development, ongoing processes of fibre organisation, membrane proliferation, and (pre-)myelination are thought to impact the DTI measures (Dubois et al., 2008). Indeed, previous studies have shown that DTI measures vary across the lifespan (Hasan et al., 2008; Lebel et al., 2012), with rapid increases in FA and decreases in MD over the first few weeks and years of life (Braga et al., 2015; Kidowaki et al., 2016; Kersbergen et al., 2014; Nossin-Manor et al., 2013; Akazawa et al., 2015). Furthermore, regional patterns of brain development can be observed with DTI (Rose et al., 2014; Wu et al., 2017).

A major limitation of DTI, however, is its inability to resolve crossing fibres. It has been shown previously that between 63 and 90%

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Table 1
Acquisition parameters.

Contrast	Sequence	Details
T2	HASTE	Acquired in axial, coronal, and sagittal; TR/TE 2000/101 ms; in-plane resolution 0.56 × 0.56 mm; slice thickness 4.8 mm
T2 (quantitative)	Multi-echo TSE axial	TR/TE1/TE2/TE3 10,580/27/122/189 ms; in-plane resolution 0.70 × 0.70 mm; slice thickness 2 mm
T1	MPRAGE	TR/TE/TI 2100/3.18/1500 ms; resolution 1.3 × 1.25 × 1.25 mm
T1	TSE axial	TR/TE 1490/12 ms; in-plane resolution 0.7 × 0.7 mm; slice thickness 2 mm
Perfusion	EPI axial	TR/TE/TI1/TI2 3427.5/21/700/1800 ms; in-plane resolution 4.0 × 4.0 mm; slice thickness 5 mm
Field map	GRE axial	TR/TE1/TE2 488/4.92/7.38 ms; in-plane resolution 2.5 × 2.5 mm; slice thickness 3.25 mm
Diffusion (DTI)	EPI axial	TR/TE 9500/130 ms; 30 directions; b = 1000 s/mm^2; in-plane resolution 1.75 × 1.75 mm; slice thickness 2 mm
Diffusion (HARDI)	EPI axial	TR/TE 9500/130 ms; 64 directions; b = 2000 s/mm^2; in-plane resolution 1.75 × 1.75 mm; slice thickness 2 mm

of white matter voxels in the adult human brain contain crossing fibres (Jeurissen et al., 2013). High angular resolution diffusion weighted imaging (HARDI), in conjunction with advanced models of reconstruction, can be used to overcome this limitation by estimating multiple fibre orientations within each voxel. Today, HARDI is still primarily used to improve the delineation of white matter pathways using tractography, and only rarely to examine local microstructural features in preterm-born infants (Eaton-Rosen et al., 2015; Shi et al., 2016; Gao et al., 2016).

In the current work, we employ a recently developed statistical analysis technique for HARDI data, termed fixel based analysis (FBA; (Raffelt et al., 2016)). A “fixel” describes the different fibre bundles (with different orientations) that may be present within a voxel (Raffelt et al., 2015). Akin to DTI, where each voxel contains information about local FA, MD, and other measures, each fixel carries microstructural (or macrostructural) information which, in contrast to DTI voxels, is specific to the fibre orientation in question. The fixel metrics fibre density (FD), fibre-bundle cross-section (FC), and a combined measure of fibre density and cross-section (FDC) were introduced by Raffelt et al. (2016).

These metrics are thought to provide insight into the different mechanisms that can lead to an alteration in a connection's ability to relay information. A reduction in the total number of axons, according to Raffelt et al. (2016), can manifest in 3 different ways: a) through changes in tissue microstructure (i.e. fewer axons per voxel, however occupying the same spatial extent), b) through changes in tissue macrostructure (i.e. the same number of axons per voxel, however occupying a decreased spatial extent), and c) through a combination of the former two (i.e. fewer axons per voxels occupying a decreased spatial extent). Changes in tissue microstructure (case a) are reflected in the measure fibre density (FD), which is a surrogate marker of the intra-axonal restricted compartment of a fibre bundle. In contrast, fibre-bundle cross-section (FC) refers to the cross-sectional area that is occupied by a fibre bundle, and measures changes in local tissue *macrostructure* (case b). During early brain development, both tissue microstructure and macrostructure change markedly and in conjunction (case c), which can be assessed using the combined measure of fibre density and bundle cross-section (FDC).

Our aim was to establish the utility of FBA in preterm-born infants scanned at term equivalent age (TEA). We investigated (i) whether FD, FC, and FDC are correlated with postmenstrual age (PMA) at the time of MRI and gestational age (GA) at birth; (ii) whether differences in preterm-born infants compared to term-born infants in these measures can be observed; and (iii) whether these differences are more pronounced in the presence of mild macroscopic brain abnormality.

2. Materials and methods

2.1. Participants

Participants for this study were selected from a larger project investigating neurodevelopmental outcomes following very preterm birth (George et al., 2015). Preterm infants born at < 31 weeks completed gestation, admitted to the Royal Brisbane and Women's Hospital Neonatal Intensive Care Unit between January 2013 and April 2016 were eligible for recruitment. Infants were excluded if known genetic or chromosomal abnormality was present, their parents or caregivers did not speak English, or they lived > 200 km from the hospital. A reference sample of healthy term-born infants was also recruited. Term-born infants were eligible if they were born between 38 and 41 weeks gestation following an uncomplicated pregnancy and delivery, had a birth weight above the 10th percentile, were not admitted to the neonatal intensive or special care units, and had a normal neurological examination at the time of the MRI.

The study was approved by the Human Ethics Research Committees at the Royal Brisbane and Women's Hospital (HREC/12/QRBW/245) and The University of Queensland (2012001060).

2.2. MRI

Magnetic Resonance Imaging was performed using a 3 T Siemens TIM Trio (Siemens, Erlangen, Germany). Infants were scanned during natural sleep without sedation, using an MR compatible incubator with a dedicated 8-channel neonatal head coil (Lammers LMT, Lübeck, Germany). Neuroimaging was performed around 30 weeks post-menstrual age and again term equivalent age, and included T1- and T2-weighted structural imaging, multi-echo T2-weighted imaging for estimation of quantitative T2, perfusion imaging, diffusion tensor imaging (DTI; 30 directions, b = 1000 s/mm^2), high angular resolution diffusion weighted imaging (HARDI; 64 directions, b = 2000 s/mm^2), and a field map to assist in the correction of susceptibility distortions on the diffusion images. Acquisition parameters are detailed in Table 1. If signal dropouts were observed during the acquisition of the DTI or HARDI data, acquisition was repeated in the same session when possible. For the current analysis, only structural and HARDI data acquired around term equivalent age were used.

2.3. Scoring of structural images

Structural images were scored by a child neurologist with training in MRI radiology (SF) using the semi-quantitative scoring system of Kidokoro et al. (2013) with modified cut-points for regional measurements (George et al., 2017). The scoring system assesses the domains of white matter, cortical grey matter, deep grey matter, and cerebellum. Scores for a subset of infants included in this study have been presented previously (George et al., 2017). For the current study, only infants with a global score ≤ 3 (indicating none or minimal brain abnormality) were included. The preterm infant group was further subdivided into groups of infants with a global score of 0 (indicating no abnormality in any of the domains), and a global score of 1–3 (indicating mild-to-moderate brain abnormality in at least one of the domains).

2.4. Diffusion image processing

Diffusion data were visually inspected, and datasets were excluded if they contained spike artefacts. Volumes containing motion between