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Identification and interpretation of microstructural abnormalities in motor pathways in adolescents born preterm

Samuel Groeschel [a,*,1], J-Donald Tournier [b,1], Gemma B. Northam [c], Torsten Baldeweg [c], John Wyatt [d], Brigitte Vollmer [e,f], Alan Connelly [b]

[a] University Children's Hospital Tübingen, Germany
[b] Florey Institute of Neuroscience and Mental Health, Melbourne, Australia
[c] UCL Institute of Child Health, London, UK
[d] UCL Hospitals, London, UK
[e] Karolinska Institutet, Stockholm, Sweden
[f] University of Southampton, Southampton, UK

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ABSTRACT

There has been extensive interest in assessing the long-term effects of preterm birth on brain white matter microstructure using diffusion MRI. Our aim in this study is to explore diffusion MRI differences between adolescents born preterm and term born controls, with a specific interest in characterising how such differences are manifested in white matter regions containing predominantly single or crossing fibre populations. Probabilistic high angular resolution tractography together with large deformation spatial normalisation were used to objectively investigate diffusion tensor parameters at regular intervals along fibre tracts of 45 adolescents born before 33 weeks of gestation and 30 term-born typically developing adolescents.

Diffusion parameters were significantly different between preterms and controls at several levels along the cortico-spinal, thalamo-cortical and transcallosal pathways. Within the predominantly single fibre regions of the corpus callosum and internal capsule, in the preterms mean diffusivity (MD) was found to be increased while fractional anisotropy (FA) was decreased compared to controls. In contrast, however, where these pathways traversed the centrum semiovale, FA and MD were both significantly increased. The major contributor to reduced FA in preterms in predominantly single fibre regions was the increased radial eigenvalue (i.e. increased radial diffusivity). In predominantly crossing-fibre regions, the tensor eigenvalues are not meaningful, and the observed increase in FA is likely to be due to a decrease in anisotropy in one of the contributing fibre bundles. Similar differences (although less pronounced) were observed after excluding preterms with radiological signs of preterm brain injury from the sample.

In summary, white matter microstructure was found to be altered in motor pathways in adolescents born preterm. Disruption of white matter (WM) microstructure in a single fibre region with resulting higher radial diffusivity leads to lower FA, whereas selective disruption of one fibre population in a crossing fibre region is observed to lead to higher FA. These findings challenge the common simplistic interpretation of FA as a measure of WM tract integrity.

Introduction

Infants born preterm are at high risk for brain injury and altered brain development (Volpe, 2009). In recent years, a number of in vivo magnetic resonance imaging (MRI) studies have focused on the assessment of preterm brain injury in the neonatal period as well as its long-term effects in childhood and adolescence (for review see e.g. (Ment et al., 2009)). Diffusion tensor imaging (DTI) has been shown to be particularly useful and highly sensitive to detect and quantify microstructural changes associated with preterm brain injury (see e.g. (Anjari et al., 2007; Arzoumanian et al., 2003)). As survivors of preterm birth frequently have impairments of motor function ranging from minor motor difficulties to cerebral palsy, characterising microstructural changes in motor pathways using DTI has become a major interest.

However, this remains challenging, due primarily to limitations of the DTI method itself. The tensor model describes only one principal direction per voxel and anisotropy indices can therefore only be interpreted as being related to "white matter integrity" in voxels containing fibres with a single orientation. Due to the low spatial resolution of diffusion images, partial volume effects are inevitable, and many

* Corresponding author at: Department of Paediatric Neurology and Developmental Medicine and Experimental Paediatric Neuroimaging, University Children's Hospital, Hoppe-Seyler-Strasse 1, 72076 Tübingen, Germany. Fax: +49 7071 295473.
E-mail address: samuel.groeschel@med.uni-tuebingen.de (S. Groeschel).
[1] Equal contribution.

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voxels will contain multiple fibre populations. A recent study estimates that, using typical imaging parameters, crossing fibres can be detected in 90% of voxels in the white matter (WM) (Jeurissen et al., 2013). In such voxels, the diffusion tensor will be strongly biased, which makes interpretation of derived measures such as fractional anisotropy (FA), radial and axial diffusivity difficult (Jones, 2010; Tournier et al., 2011; Wheeler-Kingshott and Cercignani, 2009). This is especially problematic for the study of preterm brain injury, which is primarily located in the periventricular white matter and frequently extends throughout the centrum semiovale, which has particularly complex crossing-fibre characteristics.

Another challenge is to ensure the reproducibility of measurement locations across subjects. Studies on preterm children have generally measured diffusion parameters in regions of interest (ROI), most often within the posterior limb of the internal capsule (PLIC) (i.e. the cortico-spinal tract (CST)), but also in the centrum semiovale. The disadvantage of this approach is the subjectivity of the ROI definition, often based on visual inspection of maps of the parameters (e.g. FA) to be measured. Other studies have used the whole CST, delineated using deterministic DTI-based tractography, as a ROI for measuring diffusion parameters and reported this approach to be more sensitive than ROI-measurements (Murakami et al., 2008). Whole brain voxel-wise analysis methods may provide a more objective approach (Anjari et al., 2007; Counsell et al., 2008; Eikenes et al., 2011; Lee et al., 2011; Mullen et al., 2011; Nagy et al., 2003), but suffer from reduced statistical power due to the very large number of multiple comparisons performed. While these problems are reduced using skeleton-based methods such as Tract Based Spatial Statistics (TBSS, (Smith et al., 2006)), specificity to certain structures is low and the projection of data onto the skeleton may bias the results (Jones and Cercignani, 2010).

Reduced FA, increased MD and increased radial diffusivity are often interpreted in terms of reduced "integrity" of a tract, in part based on information from DTI studies in animal models (Song et al., 2002, 2003). However, in the centrum semiovale, the interpretation of WM anisotropy measurements becomes difficult. Anisotropy as characterised by the tensor model in these crossing fibre regions can be very low in the normal brain despite high "density" and "integrity" of the fibre bundles present (Jones, 2010). Methods that preferentially include higher FA regions (including for example TBSS and DTI-based tractography) may exclude these regions from the analysis (by applying a FA-thresholded skeleton or by using FA thresholds in the tracking algorithm respectively). Perhaps for the reasons outlined above, previous studies have reported conflicting results in such regions. Some have shown increases in FA in the centrum semiovale in children born preterm, and have interpreted this as "accelerated WM development" (Gimenez et al., 2008); others have found no changes in FA (Cheong et al., 2009), and some have reported decreased FA (Anjari et al., 2007; Hüppi et al., 1998, 2001).

The objective of the present study is to investigate diffusion parameters at many levels along a number of motor pathways in adolescents born preterm. In line with the understanding that injury to the immature (preterm) brain leads to long-lasting and widespread effects on brain microstructure (Kostović et al., 2011; Volpe, 2009), we investigate in addition to the cortico-spinal tract other structures involved in the motor system, i.e. the cortico-thalamic pathways to (and from) the somatosensory and premotor cortex, as well as callosal pathways connecting primary motor, somatosensory and premotor areas.

Our approach is to measure diffusion parameters along pathways identified using fibre tracking based on diffusion-weighted MRI; the latter is performed using high angular resolution diffusion imaging (HARDI) data in conjunction with Constrained Spherical Deconvolution (CSD) (Tournier et al., 2007) to define the local fibre orientations, and a probabilistic tracking algorithm. While it is expected that microstructural alterations in motor fibres as a consequence of preterm brain injury are present at adolescence, and can be detected by measuring DTI parameters, our main hypothesis is that any abnormalities detected in DTI parameters will be different in single fibre regions than in crossing fibre regions, making interpretation of diffusion parameters highly dependent on the underlying fibre architecture.

Methods

Subjects

Forty-five adolescents born very preterm (born between 1989 and 1994; age median 16.3 years [min 12.3, max. 19.7], 16 males) were studied (Table 1). They are part of a large cohort of very preterm infants born before 33 weeks of gestation and treated in a single level III unit. Thirty term-born healthy subjects of similar age (median 15.7 years [min 13.6, max. 18.4], 14 males) were studied as a control group. The study was approved by the local ethics committee, and written informed consent was obtained for data acquisition and analysis.

Image acquisition

Images were acquired on a 1.5 Tesla Siemens Avanto Scanner (Erlangen, Germany). Conventional T2-weighted images were acquired using an axial multislice sequence (repetition time [TR] = 4920 ms, echo time [TE] = 101 ms, field of view = 220 mm, slice thickness = 4 mm, slices = 25, matrix size = 384 × 384). Three-dimensional data sets were acquired using a T1-weighted 3-dimensional fast low angle shot (3D-FLASH) sequence (TR = 11 ms, TE = 4.94 ms, flip angle = 15°, field of view = 256 mm, matrix size = 256 × 256, voxel size = 1 × 1 × 1 mm), and a 3D T2-weighted fluid attenuated inversion recovery sequence (TR = 6000 ms, TE = 353 ms, TI = 2200 ms, flip angle = 150°, field of view = 256 mm, matrix = 256 × 256, voxel size = 1 × 1 × 1 mm).

The diffusion-weighted (DW) sequence consisted of a high angular resolution twice-refocused echo planar imaging (EPI) sequence (b = 3000 s/mm^2, 60 DW directions, TE/TR = 128/7700 ms, 112 × 112 matrix, FOV = 235 × 235 mm, slice thickness = 3 mm, voxel size = 2.1 × 2.1 × 3 mm, 37 contiguous slices). Of the original 80 datasets, 5 diffusion MRI datasets were excluded due to artefacts (ventriculo-peritoneal shunt n = 1, severe motion n = 4), leaving 45 preterm datasets and 30 data sets from term born controls in the final sample.

Visual assessment of T1 and T2-weighted images

T2-weighted, FLAIR and 3D T1-weighted images were visually assessed by an experienced paediatric neuroradiologist using a scoring protocol, which paid particular attention to signs of preterm brain injury such as periventricular signal abnormalities on T2-weighted images (radiological sign of gliosis), reduction of periventicular WM, and ventricular dilatation. Twenty (44.4%) preterms had normal MRI, signal abnormalities on T2-weighted images only were seen in 3, and WM reduction/ventricular dilatation in 20 preterms (n = 18 mild/moderate, n = 2 severe WM reduction). In one preterm subject, high signal was seen in the external capsule on the right, which was categorised as an incidental finding. Lesions were bilateral in the majority of the cases (n = 18). All MRIs of the controls included in the analyses were normal on visual inspection.

DTI preprocessing

Diffusion tensor images were calculated using a log-linear least-squares fit (Basser et al., 1994). From the diffusion tensor image, derived tensor parameters were calculated, including: mean diffusivity (MD); fractional anisotropy (FA) (Basser and Pierpaoli, 1996); parallel (or axial) diffusivity $\lambda_{parallel} = \lambda_1$ (the principal eigenvalue); and perpendicular (otherwise known as 'transverse' or 'radial') diffusivity $\lambda_{perpendicular} = (\lambda_2 + \lambda_3) / 2$ (the average of the two