High b-value HARDI analysis in neonates scanned at term-equivalent age reveals correlation between apparent white matter fibre density and immaturity at birth

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Introduction: Preterm birth is associated with poor neurodevelopmental performance, a problem that is becoming increasingly important as modern medicine has significantly reduced both the overall mortality and the gestational age at which premature children can survive. Diffuse white matter injury is frequently observed in infants who are born preterm. A number of studies have shown significant correlations of tensor-derived metrics such as fractional anisotropy (FA) with gestational age[1]. However, in crossing fibre regions such correlations are difficult to interpret due to the limitations of the DTI model. In this study, we investigate the effect of gestational age on a new direction-specific measure, termed the apparent fibre density (AFD)[2], using a high *b*-value, high angular resolution diffusion imaging (HARDI) acquisition.

Methods: Research Ethics Committee approval was granted for this study. HARDI data (64 non-collinear directions with a b value of 2500 s/mm^2, TE/TR= 62/10 000ms using 80mT/m gradients, Philips 3T MRI scanner) were obtained in 31 infants (28 infants born preterm, median gestational age 30 weeks, and 3 healthy term-born controls). Median age at scan was 43 weeks post-menstrual age. One dataset was excluded due to excessive motion artefact on visual inspection.

AFD analysis: Pre-processing involved bias field correction and intensity normalisation[2]. FODs were computed using Constrained Spherical Deconvolution[3] using MRtrix[4]. Individual FOD images were non-linearly registered to a population-specific FOD template, with AFD modulation applied in the final transform[2]. AFD samples were taken along 200 uniformly distributed directions within each voxel, and anisotropic smoothing was performed[2]. A GLM correlation of AFD with gestational age (GA) was performed across subjects for each 'dixel' (we define the term 'dixel' to denote a particular direction within a particular voxel), with post-menstrual age as a covariate of no interest. Multiple comparison correction was performed using threshold-free cluster enhancement (TFCE)[5], with clusters formed using dixel neighbours defined in both space and orientation[2]. Corrected p-values were assigned to each dixel using permutation testing (5000 permutations)[6]. To visualise significant dixels, one million streamlines were generated using the iFOD2 probabilistic tractography algorithm[7] on the population-specific FOD template. Every point along each streamline was colour-coded according to the associated dixel TFCE t-value, and non-significant streamline points were excluded from the visualisation ($p > 0.05$).

Results: Fig. 1 shows regions where statistically significant positive correlations were found between AFD and GA at birth. No significant negative correlations were found. The changes observed were bilateral, with many major fibre tracts implicated, including: corpus callosum (CC) (particular splenium and genu), optic radiations (OR), cortico-spinal tracts (CST) (including lateral projections), anterior commissure (AC), caudate (CN), and external capsule (EC). Changes were also observed in other tracts, although only in isolated regions (*p*-values in these tracts were borderline significant); these include: uncinate fasciculus (UF), fornix (FX), cingulum bundle (CB) (including hippocampal projections), arcuate fasciculus (AF), and inferior frontal occipital fasciculus (IFOF).

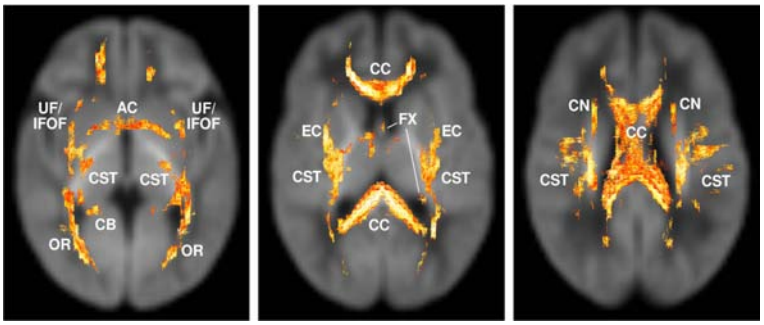

Figure 1: results of the apparent fibre density (AFD) analysis, shown on a series of axial slices, overlaid on the template average image. Significant correlations between gestational age and AFD were identified in a number of locations and directions (post-menstrual age was included as a covariate of no interest. **CC:** corpus callosum, **OR:** optic radiations, **CST:** cortico-spinal tracts, **AC:** anterior commissure, **CN:** caudate, **EC:** external capsule, **UF:** uncinate fasciculus, **FX:** fornix, **CB:** cingulum bundle, **IFOF:** inferior frontal occipital fasciculus.

To highlight the advantage of the AFD analysis, Fig 2 shows a close up of a significant region in the CST, where the crossing fibres from the superior longitudinal fasciculus (SLF) can be observed in the FOD glyphs. The AFD analysis identified significant correlations with apparent fibre density only in the direction of the CST, as can be appreciated from the colour-coded streamlines display. No significant changes were observed in the SLF, with the exception of patchy changes in the AF.

Discussion and Conclusion: Significant positive correlations between AFD and immaturity at birth were observed in most major white matter tracts in our cohort of children scanned at term-equivalent age. The overall pattern is similar to previous findings using DTI-derived measures[1]. A major advantage of AFD is that in many regions where two tracts cross, the AFD analysis identified distinct correlations along directions corresponding to one or both tracts, making the interpretation of observed changes much more straightforward than when using voxel-wise scalar measures. These findings suggest that AFD may provide additional information regarding white matter development than that obtained using DTI alone and has the potential to serve as an early imaging biomarker of preterm white matter injury,

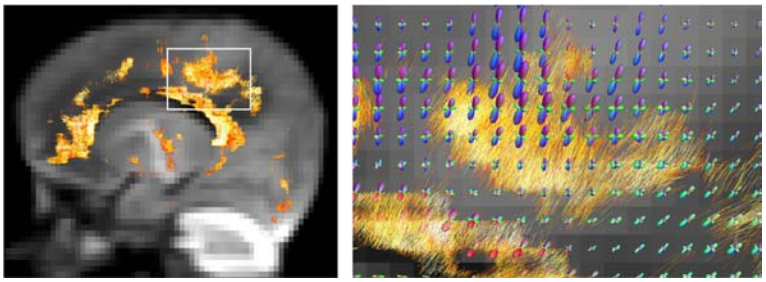

Figure 2: A close-up of a significant region identified in the CST, in an area where it crosses with the SLF. Left: a sagittal section through the template average image, highlighting the region of interest shown in the right-hand side. Right: the average fibre orientation distribution across all subjects is shown within each voxel, as a glyph with amplitude proportional to the apparent fibre density. Significant dixels (i.e. a direction within a voxel) are shown as color-coded streamlines, with hotter colours indicating lower *p*-values (thresholded at $p < 0.05$). In this region, correlations with AFD are only observed along the direction of the CST, with no involvement of the SLF.

References: [1]Ball et al., Neuroimage 53, 94–102 (2010). [2]Raffelt et al., Neuroimage 59, 3976–3994 (2012). [3]Tournier et al., NeuroImage 35, 1459–1472 (2007). [4]Tournier et al., Int. J. Imag. Sys. Technol. 22, 53–66 (2012). [5]Smith & Nichols, Neuroimage 44, 83–98 (2009). [6]Nichols et al., Proc. OHBM 14 (2008). [7]Tournier et al., Proc. ISMRM 18, 1670 (2010).