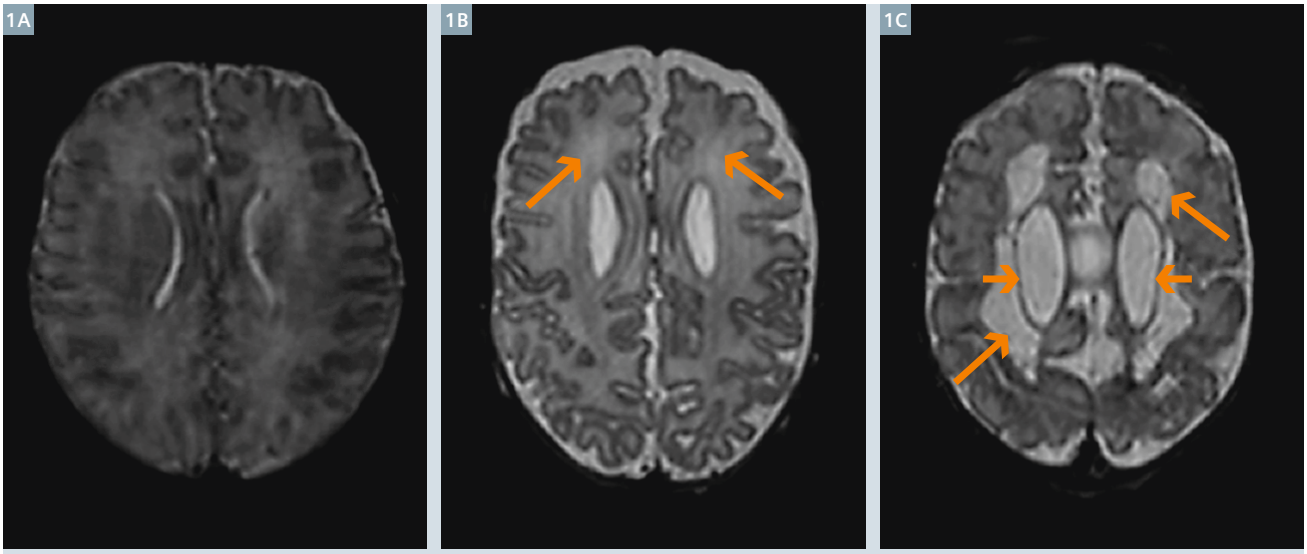
Using Diffusion MRI and Quantitative Tractography to Investigate Gender Specific Effects on the Development of White Matter after Preterm Birth at 3T

Mark E. Bastin[1]; Devasuda Anblagan[2]; Sarah Sparrow[2]; Emma Moore[2]; Rozi Pataky[3]; Chinthika Piyasena[4]; Graham Wilkinson[5]; Thorsten Feiweier[6]; Scott I. K. Semple[4,7]; James P. Boardman[2]

[1]Centre for Clinical Brain Sciences, University of Edinburgh, UK
[2]MRC Centre for Reproductive Health, University of Edinburgh, UK
[3]NHS Lothian, UK
[4]Centre for Cardiovascular Sciences, University of Edinburgh, UK
[5]Department of Paediatric Radiology, NHS Lothian, UK
[6]Siemens Healthcare, Erlangen, Germany
[7]Clinical Research Imaging Centre, University of Edinburgh, UK

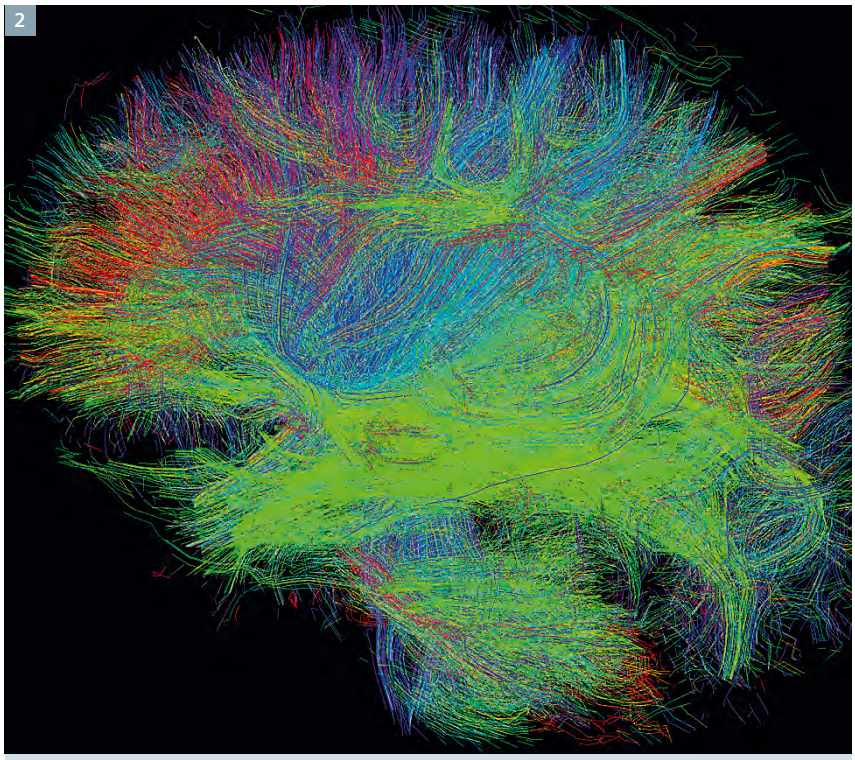
Introduction

Preterm birth is a leading cause of cognitive impairment in childhood and is associated with alterations in brain development that are apparent in the neonatal period. Brain structural changes associated with preterm birth include enlargement of the ventricular system, reduced cortical complexity and diffuse white matter signal abnormalities on structural MRI (see Figure 1 and Reference [2]). However, some of the adverse neurodevelopmental sequelae of preterm birth are gender-specific, with preterm males having a worse neurodevelopmental outcome than preterm females [6, 7, 9] and some neuroprotective strategies appearing to have gender specific effects [10]. Connectivity of developing white matter tracts is altered in association with preterm



1 T2-weighted axial images at the level of the lateral ventricles from: **(1A)** A healthy infant* born at 39^{+1} weeks with images acquired at 41^{+3} weeks post menstrual age (PMA); **(1B)** An infant born at 25^{+0} weeks with image acquisition at 42^{+4} weeks PMA; and **(1C)** An infant born at 26^{+0} weeks, with images acquired at 39^{+3} weeks PMA. **Figure 1B** shows features that are common among preterm infants at term equivalent age including enlargement of the ventricular system and extra cerebral space reduced cortical complexity and diffuse excessive high signal intensity in the white mattter (arrows) compared with (1A). **Figure 1C** shows areas of cystic periventricular leucomalacia (long arrows) distinct from the lateral ventricles (short arrows).

birth but the neural basis for differential gender effects is unknown. Diffusion MRI (dMRI) and tractography may provide further insights into the cerebral microstructural changes that accompany preterm birth by supplying quantitative biomarkers of white matter integrity in specific tracts of interest (see Figures 2 and 3, and Reference [1]). We therefore present the first application of an automatic single seed point tractography-based segmentation method, probabilistic neighbourhood tractography (PNT) [3-5], to study gender specific effects in developing white matter tracts in preterm infants*. PNT, which can segment the same fasciculus across groups of subjects and provide quantitative measures of tract integrity and shape, works by placing seed points in a neighbourhood surrounding a seed point transferred from standard space, with the tract that best matches a predefined reference tract in terms of length and shape chosen from this group of 'candidate' tracts [4].



2 Sagittal view of whole brain white matter obtained using dMRI from a healthy neonate.

Methods

Following ethics committee approval, 49 preterm infants born at post-menstrual age (PMA) of 29 ± 6 weeks were scanned on a MAGNETOM Verio 3T clinical scanner (Siemens Healthcare, Erlangen, Germany) at term equivalent age (PMA 40 ± 3 weeks) without sedation. All infants were scanned axially using a dMRI protocol consisting of 11 T2- and 64 diffusion-weighted ($b = 750$ s/mm^2) single-shot, spin-echo, echo planar imaging volumes acquired with 2 mm isotropic voxels (field-of-view 256 × 256 mm, imaging matrix 128 × 128, 50 contiguous interleaved slices with 2 mm thickness) using the 'Works-in-Progress Package for Advanced EPI Diffusion Imaging (WIP 511 E)'**. To reduce eddy current induced artefacts and shimming errors to a minimum, the bipolar+ gradient pulse scheme was selected, with manual shimming and shim box covering a region extending from the top of the head to several centimetres below the chin.

Ten fasciculi-of-interest (FOI) were identified using PNT from the dMRI data (http://www.tractor-mri.org.uk): Genu and splenium of corpus callosum, right and left projections of the arcuate, cingulum cingulate gyri (CCG), corticospinal tract and inferior longitudinal fasciculi. Using a 7 × 7 × 7 neighbourhood of seed voxels, the seed point that produced the best matching tract to the reference (defined in Montreal Neurological Institute standard space; http://www.mni.mcgill.ca) was determined using tract shape models produced from a group of adult volunteers aged 25–65 years [3]. Streamlines that did not resemble the median path of the best-matched tract were pruned automatically [5]. An experienced rater then visually assessed all best matched tracts and subjects with aberrant or truncated pathways that were not anatomically plausible representations of the FOI were excluded from further analysis. For anatomically acceptable tracts, the resulting tractography masks were applied to each subject's mean diffusivity (MD) and fractional anistropy (FA) maps to provide tract-averaged measures of these biomarkers for the 10 FOI.

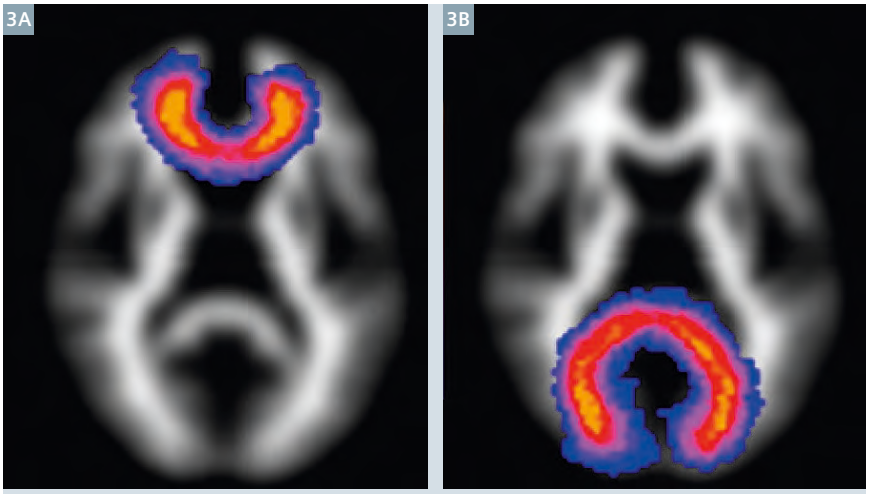
Results

Figure 3 shows an example of the tract segmentation for a subset of 12 subjects for genu and splenium of corpus callosum, and indicates the close spatial correspondence of the segmented pathways for these two tracts.

The gender effect for tract-averaged FA and MD for the 10 FOI in each subject were assessed using an independent samples t-test. Tract-averaged FA values of the left CCG were significantly increased in male infants ($p = 0.05$), while MD of the left CCG were significantly increased in female infants ($p < 0.04$). To assess the effect of PMA at birth and PMA at scanning on these dMRI biomarkers, a general linear univariate model based on one between-subject variable was performed for FA and MD in the 10 FOI. Two important covariates were included in all analyses: PMA at birth and PMA at scanning. Track averaged MD of the left CCG was significantly increased ($p < 0.03$) in female infants (1551 ± 285 μm^2/s) compared to male infants (1397 ± 858 μm^2/s).

Discussion

These pilot data show for the first time that quantitative measurements of dMRI biomarkers can be made in the preterm brain from high angular resolution dMRI data using PNT at 3T. These values are comparable to other studies using tractography methods, and demonstrate increased MD and reduced FA in the CCG of female preterm infants compared with male equivalents. Of particular interest is the fact that the method is able to identify successfully a range of fasciculi using reference tracts obtained from the adult brain. This approach may be useful for studying sexual dimorphism early in human development. We are currently investigating whether the use of reference tracts from infants further improves this study, and whether the tract shape parameter R (the absolute goodness-of-fit of the best match tract to the reference) provides additional useful information about brain structure that can be used to assess cerebral development in preterm birth and potential therapeutic interventions.



3 Group maps of **(3A)** genu and **(3B)** splenium generated by transforming the best match tract for each subject into MNI standard space.

Acknowledgements

This work was funded by Theirworld and was carried out in collaboration with Siemens Healthcare. The authors would like to thank Craig Buckley for his valuable participation and support.

* Siemens disclaimer: MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures. This disclaimer does not represent the view of the authors, nor the view of the guest editor of this issue. It is solely for regulatory reasons.

** WIP, the product is currently under development and is not for sale in the US and other countries. Its future availability cannot be ensured.

References

1 Ball G, et al. Cortex. 2013 Jun; 49(6): 1711-21.
2 Boardman JP, et al. (2010) Neuroimage 52:409-414.
3 Bastin ME, et al. (2010) Neuroimage 51:1-10.
4 Clayden JD, et al. (2007), IEEE Trans Med Imaging 26: 1555-1561.
5 Clayden JD, et al. (2011), J Stat Software 44 (8): 1-18.
6 Edwards D. (2004) J Pediatr 145(6):723-724.
7 Kapellou O, et al. (2006) PLoS Med 3(8): e265.
8 Mackay DF, et al. (2010) PLoS Med 7(6): e1000289.
9 Marlow N, et al. (2005) N Engl J Med 352: 9-19.
10 Ment LR, et al. (2004), J Pediatr 145 (6): 832-834.

Contact

Mark Bastin, DPhil
Reader in Medical Imaging
Centre for Clinical Brain Sciences
University of Edinburgh
Western General Hospital
Crewe Road, Edinburgh,
EH4 2XU, UK
Phone: +44 (0) 131 537 2511
Mark.Bastin@ed.ac.uk