Tract-Based Spatial Statistics Analysis of Diffusion Tensor Data in Very Preterm 7 year-olds

Claire E Kelly[1], Deanne K Thompson[1,2], Alexander Leemans[3], Chris Adamson[1], Jian Chen[1], Terrie E Inder[4], Jeanie LY Cheong[1,5], Lex W Doyle[1,5], and Peter J Anderson[1,6]

[1]Murdoch Childrens Research Institute, Melbourne, VIC, Australia, [2]Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia, [3]Image Sciences Institute, University Medical Center Utrecht, Utrecht, Netherlands, [4]Brigham and Women's Hospital, Boston, MA, United States, [5]Royal Women's Hospital, Melbourne, VIC, Australia, [6]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia

Target audience

Researchers involved in applications of MRI methods, paediatric researchers, clinicians.

Purpose

Very preterm birth (<32 weeks' gestation) places infants at high risk of cerebral white matter injury.[1] Diffusion-weighted MRI is currently the only method available for studying white matter microstructure non-invasively. This study aimed to: 1) compare white matter microstructure across the whole brain between very preterm children and children born at term (≥37 weeks' gestation) using Tract-Based Spatial Statistics (TBSS) analysis of diffusion tensor measures; 2) investigate possible associations between perinatal factors and white matter microstructure in very preterm children. It was hypothesised that white matter microstructure in major white matter tracts would be altered in very preterm children compared with controls, and that perinatal complications would be associated with altered white matter microstructure in very preterm children.

Methods

Participants: Participants were 150 very preterm children (born <30 weeks' gestation and/or <1250 g birthweight) and 35 term-born controls who underwent MRI at 7 years of age. **MRI**: MRI was performed with a 3T scanner on a Siemens Magnetom Trio, Tim system. Diffusion-weighted data were acquired with echo planar imaging sequences. Parameters were: TR= 12000 ms, TE= 96 ms, FOV= 250 x 250 mm, matrix size= 144 x 144, voxel size= 1.7 mm^3. 25 non-collinear diffusion-weighted gradient directions were acquired with *b*-values ranging up to 1200 s/mm^2. **Image pre-processing:** ExploreDTI version 4.8.2 was used for motion and eddy current distortion correction, and generation of diffusion tensor maps [fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD)].[2] **TBSS:** The TBSS methods used in this study have been detailed previously.[3] Briefly: 1) all participants' FA data were aligned to 1 mm^3 MNI152 standard space using nonlinear registrations; 2) a mean FA image was created, skeletonised and thresholded at FA>0.3; 3) each participant's aligned FA data were projected onto the mean FA skeleton; 4) the original nonlinear registrations were applied to the AD, RD and MD data, which were subsequently projected onto the mean FA skeleton; 5) projected data were fed into voxelwise statistical analysis. **Statistical analysis**: Non-parametric permutation based testing, with 10,000 permutations per test and threshold-free cluster enhancement, was used to investigate group differences in FA, AD, RD and MD, and relationships between perinatal variables and FA, AD, RD and MD in the very preterm children (gestational age at birth, birthweight standard deviation score, sex, postnatal corticosteroid exposure, qualitative neonatal brain abnormality score on structural MRI,[4] and postnatal infection). The perinatal variables were investigated separately, as well as in combined models to assess their associations with diffusion tensor measures independent of the other perinatal variables. Statistical thresholds were set at $p<0.05$, controlled for voxelwise multiple comparisons and for corrected age at MRI. Results were localised to white matter tracts using the John Hopkins University White Matter Tractography atlas.

Results

There were regions of higher AD and RD, and some regions of lower FA, in the very preterm children compared with controls (Table 1). No MD differences were found between groups. There were many voxels where higher neonatal MRI abnormality scores correlated with lower FA and higher AD, RD and MD in the very preterm children, even after adjusting for the other tested perinatal variables (Figure 1). The correlations between higher neonatal MRI abnormality scores and lower FA and higher AD, RD and MD corresponded to 33%, 16%, 43% and 40% of the skeleton voxels respectively. There were regions where decreasing GA at birth, decreasing birthweight standard deviation score, female sex and postnatal infection were associated with lower FA and/or higher diffusivity in very preterm children, however these regions were relatively small, not continuous over major white matter tracts and weakened after adjusting for the other tested perinatal variables (data not shown).

Discussion and conclusion

Very preterm 7 year-olds have altered white matter microstructure within several white matter tracts compared with controls. Such microstructural alterations at 7 years of age are largely predicted by qualitative MRI-detected brain abnormalities in the newborn period, independent of other perinatal complications. TBSS based on diffusion tensor data provides a sensitive method for studying whole brain white matter microstructure in very preterm children.

References

1. Volpe J J. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009;8(1):110-124.

2. Leemans A, Jeurissen B, Sijbers J, et al. ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. In: 17th Annual Meeting of Intl Soc Mag Reson Med. 2009: p. 3537. Hawaii, USA.

3. Smith S M, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage. 2006;31(4):1487-1505.

4. Kidokoro H, Neil J J, and Inder T E. New MR Imaging Assessment Tool to Define Brain Abnormalities in Very Preterm Infants at Term. Am J Neuroradiol. 2013. 10.3174/ajnr.A3521.

Table 1. Diffusion differences between the very preterm children (VPT) and controls (C).

Diffusion parameter	Direction	# of voxels	Center of gravity (mm)			*p*-value	White matter tract
			x	y	z		
FA	C>VPT	210	-27.2	13.5	-4.9	0.04	Inferior fronto-occipital fasciculus, left
	C>VPT	140	15.4	-28.5	14.6	0.04	Anterior thalamic radiation, right
	C>VPT	137	-33.3	-12.0	-9.0	0.04	Uncinate fasciculus, left
	C>VPT	99	-4.4	-24.0	-10.7	0.04	Anterior thalamic radiation, left
	C>VPT	75	33.0	-7.9	-11.3	0.04	Inferior fronto-occipital fasciculus, right
	C>VPT	33	10.6	-22.6	5.82	0.04	Anterior thalamic radiation, right
	C>VPT	10	-12.4	-21.8	1.3	0.048	Anterior thalamic radiation, left
	VPT>C	71	28.8	-14.1	34.5	0.04	Superior longitudinal fasciculus, right
AD	VPT>C	6230	-0.5	-26.9	-15.6	0.006	Anterior thalamic radiation, left & right
	VPT>C	4013	26.2	-21.6	21	0.003	Superior longitudinal fasciculus, right
	VPT>C	1788	-24.7	-23.2	27.4	0.01	Corticospinal tract, left
	VPT>C	24	19.7	-91.4	3.04	0.049	Forceps major
	VPT>C	19	23.4	-82.9	6.32	0.049	Inferior fronto-occipital fasciculus, right
RD	VPT>C	6960	-6.2	-12.0	-2.05	0.03	Anterior thalamic radiation, left
	VPT>C	3726	-9.4	-27.6	20	0.03	Forceps major and minor
	VPT>C	483	32.0	-3.3	-10.5	0.04	Inferior fronto-occipital fasciculus, right

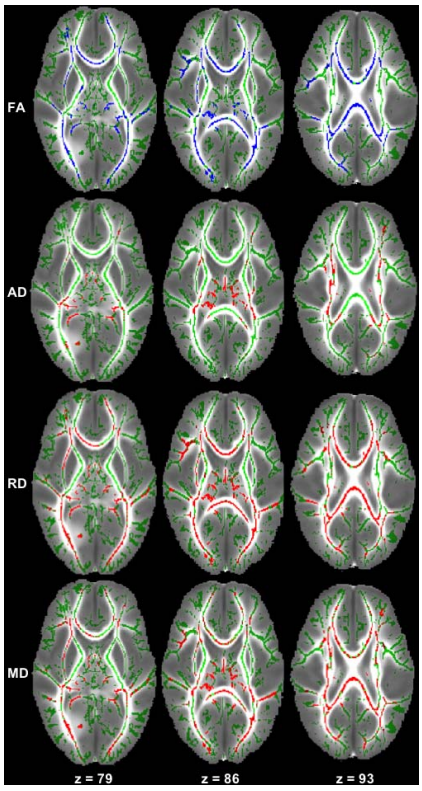

Fig. 1. Negative (blue) and positive (red) associations between qualitative neonatal MRI abnormality score and diffusion measures in very preterm children ($p<0.05$, adjusted for multiple comparisons, corrected age at MRI and other perinatal variables) overlaid on the mean FA skeleton (green) and mean FA image.