

White Matter Microstructure in Moderate and Late Preterm Infants assessed using Tract-Based Spatial Statistics

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Target audience

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

Purpose

Infants born moderate or late preterm (MLPT, 32⁺⁰-36⁺⁶ weeks' gestation) have higher rates of neonatal health complications and poorer neurodevelopmental outcomes than infants born at term (≥ 37 weeks' gestation).¹ However, few studies have investigated the effects of MLPT birth on brain development using MRI. Diffusion-weighted MRI is currently the only method available for non-invasively studying tissue microstructure. This study aimed to: 1) compare white matter microstructure across the whole brain between MLPT infants and healthy term-born infants; 2) investigate associations between perinatal factors and white matter microstructure in MLPT infants, specifically gestational age (GA) at birth, being born small for GA (SGA) and sex. It was hypothesized that white matter microstructure would be altered in MLPT infants compared with controls, and that decreasing GA at birth and SGA would be associated with altered white matter microstructure in MLPT infants.

Methods

Participants: MLPT infants (n=199) and term-born controls (n=72) underwent MRI at approximately term-equivalent age (38-45 weeks' GA). **MRI:** MRI was performed on a 3T Siemens Magnetom Trio, Tim system (syngo MR B17). Diffusion-weighted data were acquired with echo planar imaging sequences. Parameters were: TR= 20400 ms, TE= 120 ms, FOV= 173x173 mm, matrix size= 144x144, voxel size= 1.2 mm³, b values ranging from 100 to 1200 s/mm². 45 non-collinear diffusion-weighted gradient directions were acquired in total, as well as three b= 0 s/mm² reference volumes. **Image pre-processing:** Pre-processing was performed using ExploreDTI version 4.8.2.² Diffusion-weighted data were corrected for motion and eddy current induced distortions. The weighted linear least squares tensor model was applied to generate parametric maps of the fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD) and mean diffusivity (MD). **Tract-based spatial statistics (TBSS):**³ The standard TBSS pipeline was modified for neonatal scans, to avoid using adult templates. Nonlinear registrations were used to align every control infant's FA image to every other control infant's FA image, thereby identifying the 'most representative' control FA image, which was used as a study-specific target to bring all infants' FA images into spatial alignment. Next, a mean FA image was created, skeletonised and thresholded at FA>0.2. Every infant's skeletonised data were then projected onto the mean FA skeleton. The original registrations were also applied to the AD, RD and MD data, which were subsequently projected onto the mean FA skeleton. Finally, projected data were fed into voxelwise statistical analysis. Group differences in FA, AD, RD and MD, as well as relationships between perinatal variables and FA, AD, RD and MD in MLPT infants, were investigated using non-parametric permutation based testing, with 5000 permutations per test and threshold-free cluster enhancement. A statistical threshold was set at p<0.05, corrected for voxelwise multiple comparisons and for GA at MRI.

Results

Diffusion tensor data from 185 MLPT infants and 70 controls could be analysed (data from 16 infants were excluded due to incomplete acquisitions or severe motion artefact). Compared with controls, MLPT infants were slightly younger at the time of MRI [mean difference (95% CI): -5.6 (-7.7, -2.8) days, p<0.001]. TBSS identified many voxels that had lower FA and/or higher AD, RD and MD in the MLPT infants than controls. These voxels encompassed several major white matter tracts, including the corpus callosum, corticospinal tracts and optic radiations (p<0.05, adjusted for multiple comparisons and GA at MRI, Fig. 1). The voxels that had lower FA in the MLPT infants than controls corresponded to 61% of the mean FA skeleton. The voxels that had higher AD, RD or MD in the MLPT infants than controls corresponded to 50%, 71% and 68% of the skeleton voxels respectively. There were some voxels with lower FA in male than female MLPT infants, corresponding to 17% of the skeleton. There were also some voxels with lower FA in the MLPT infants born SGA than MLPT infants born appropriate for GA, corresponding to 7% of the skeleton. There were no associations between GA at birth and diffusion tensor measures in MLPT infants.

Discussion and conclusion

Lower FA and higher AD, RD and MD within the white matter of MLPT infants compared with controls may reflect changes in white matter fiber density, diameter, coherence, membrane permeability or myelination.⁴ Thus, the current study shows that MLPT infants have widespread alterations in white matter microstructure compared with term-born infants. Additionally, this study suggests that male sex and SGA are associated with altered white matter microstructure within MLPT infants. The current study is the first to assess white matter microstructure in MLPT infants using TBSS, and suggests that MLPT infants are at higher risk of altered white matter development than previously recognised. Follow-up of MLPT infants is important to determine whether white matter microstructural alterations persist beyond infancy and are associated with neurodevelopmental outcome.

References

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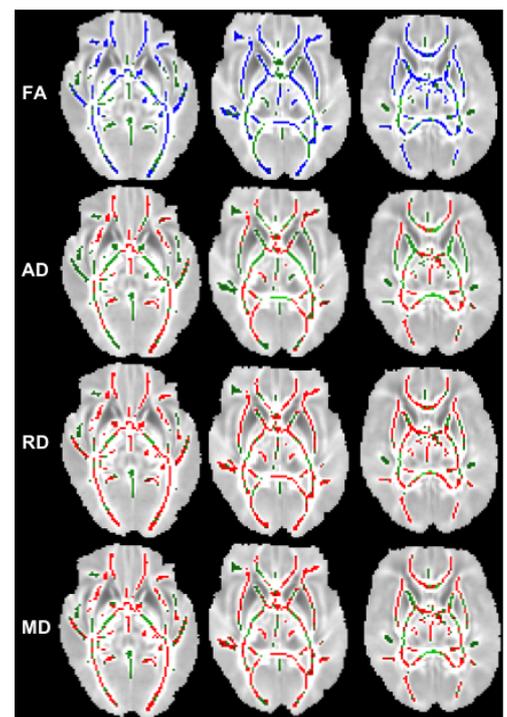


Fig. 1. Group differences in FA, AD, RD and MD. The mean FA skeleton is shown in green. Regions of lower diffusion values in MLPT infants than controls are blue; regions of higher diffusion values in MLPT infants than controls are red (p<0.05, adjusted for multiple comparisons and GA at MRI).