White matter microstructural changes in 6-year-old children who are HIV-exposed uninfected in a South African birth cohort – A Diffusion Tensor Imaging Study

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Introduction

Earlier findings from the DCHS cohort study have described altered white matter (WM) integrity using diffusion-weighted and diffusion tensor Magnetic Resonance Imaging (DWI/ DTI), in 2–6-week-old children who are HIV-exposed and uninfected (CHEU).

Purpose

To investigate white matter microstructural integrity in 6-year-old CHEU in the DCHS birth cohort in order to improve current understanding of the impact of HIV exposure on white matter integrity and the neurodevelopmental trajectory of CHEU.

Methods

Data collection

- A total of 228 6-year-olds underwent MRI scanning between August 2018 and July 2022, as part of a longitudinal nested neuroimaging study, of which 129 children (43 CHEU; 86 CHUU) met inclusion criteria and had usable DWI scans.
- The neurocognitive and behavioural data collected included the Weschler Preschool and Primary Scale of Intelligence (WPPSI), and the Child Behaviour Checklist (CBCL).
- DWI scan pre-processing was conducted using TORTOISE software, and diffusion parameters were extracted using the FMRIB Software Library Diffusion Toolbox and Tract-Based Spatial Statistics pipeline

Data analysis

- Multivariate analysis of variance (MANOVA) models were conducted to assess group differences in diffusion parameters, adjusting for age at scanning, sex, height and prenatal.
- An exploratory partial correlation analysis controlling for HIV-exposure was also conducted, assessing the association of tract diffusion parameters with cognition, as measured using the Weschler Preschool and Primary Scale of Intelligence (WPPSI), and behaviour, as measured using the Child Behaviour Checklist (CBCL).

Results

Table 2 : Group differences in DTI Metrics , Diffusion parameters by CHEU status

				Group[1]			Group[2]			Group[3]			Group[4]		
Region	**Hemisphere**	**Tract type**	**Effect in CHEU**	**P value**	**Effect size**	**Power**	**P value**	**Effect size**	**Power**	**P value**	**Effect size**	**Power**	**P value**	**Effect size**	**Power**
Inferior cerebellar peduncle	Right	Brain stem	Lower MD	0.024	0.040	0.623	0.062	0.028	0.463	0.041	0.033	0.535	0.050	0.031	0.503
			Lower AD	0.024	0.040	0.622	0.076	0.025	0.426	0.059	0.029	0.474	0.084	0.024	0.409
			Lower RD	0.026	0.038	0.606	0.060	0.028	0.469	0.037	0.035	0.551	0.040	0.034	0.538
	Left	Brain stem	Lower MD	0.233	0.011	0.221	0.343	0.007	0.157	0.254	0.011	0.206	0.197	0.014	0.251
			Lower AD	0.181	0.014	0.267	0.318	0.008	0.169	0.244	0.011	0.213	0.221	0.012	0.230
			Lower RD	0.266	0.010	0.199	0.360	0.007	0.149	0.263	0.010	0.200	0.189	0.014	0.258
Anterior Limb of internal capsule	Right	Projection	Lower MD	0.020	0.042	0.645	0.138	0.017	0.316	0.135	0.018	0.320	0.205	0.013	0.244
			Lower AD	0.065	0.026	0.454	0.276	0.010	0.192	0.295	0.009	0.181	0.499	0.004	0.103
	Left	Projection	Lower MD	0.225	0.012	0.227	0.720	0.001	0.065	0.752	0.001	0.061	1.000	0.000	0.050
			Lower AD	0.704	0.001	0.067	0.470	0.004	0.111	0.399	0.006	0.134	0.095	0.023	0.386
Posterior limb of internal capsule	Right	Projection	Lower MD	0.012	0.049	0.716	0.064	0.027	0.427	0.065	0.027	0.455	0.132	0.018	0.324
			Lower AD	0.005	0.060	0.805	0.044	0.032	0.525	0.049	0.031	0.506	0.155	0.017	0.295
			Lower RD	0.025	0.039	0.614	0.096	0.022	0.384	0.093	0.023	0.390	0.142	0.018	0.311
	Left		Lower MD	0.691	0.001	0.068	0.844	0.000	0.054	1.000	0.000	0.050	0.572	0.003	0.087
			Lower AD	0.276	0.009	0.192	0.702	0.001	0.067	0.755	0.001	0.061	0.766	0.001	0.060
			Lower RD	1.000	0.000	0.050	0.659	0.002	0.072	0.737	0.001	0.063	0.553	0.003	0.091
Pontine crossing tract	-	Projection	Lower MD	0.016	0.045	0.678	0.114	0.020	0.352	0.144	0.017	0.308	0.285	0.009	0.187
			Lower RD	0.049	0.030	0.507	0.124	0.019	0.337	0.135	0.018	0.320	0.133	0.018	0.323

Effect size showing partial eat[2] value

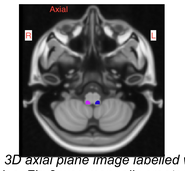
[1]Unadjusted model with maternal HIV only

[2]Adjusted basic model with age at scanning and sex covariates

[3]Adjusted model with age at scanning, sex and height covariates

[4]Final adjusted model with age at scanning, sex, height and prenatal smoking covariates

Figure 2 Inferior cerebellar peduncle location shown with WM tract atlas labels



The fig.2 Image depicts a 3D axial plane image labelled with the left and right inferior cerebellar peduncles. Fig.2 was manually created using FMRIB Software Library (FSL) softwareThe right inferior cerebellar peduncles is demonstrated by a purple overlay on orthogonal slices through the brain. While the left inferior cerebellar peduncles is indicated by a blue overlay on orthogonal slices through the brain

Results

Participant characteristics

There were no significant differences in the mean values for all the anthropometric measurements and gestation delivery for CHEU compared to CHUU controls. Only prenatal smoking was significantly different between CHEU compared to CHUU controls ($p < 0.001$).

Scan success

Of the 228 children who were invited for brain imaging at 6 years, 79.8% had successful scans. A total of 131 (71.9%) of the children with acquired DTI scans had usable good quality scans.

Group differences

The CHEU group demonstrated lower Axial Diffusivity (AD) in the right posterior limb of the internal capsule, as well as lower mean diffusivity (MD) and radial diffusivity (RD) in the right inferior cerebellar peduncle compared to the CHUU group. Findings held on adjustment for covariates, but not False Discovery Rate correction.

Partial correlation analysis

AD in the right posterior limb of internal capsule was negatively correlated with the WPPSI_similarities score, and positively correlated with CBCL externalising summary and CBCL_aggressive behaviour subscale. Right posterior limb of internal capsule MD and RD correlated with the somatic complaint's subscale score. Separately, AD and MD in the right inferior cerebellar peduncles positively correlated with the aggressive behaviour subscale.

Discussion

Although not surviving FDR correction, empirical study found group differences in in diffusion parameters in the right inferior cerebellar peduncles and between CHEU and CHUU, at 6 years. Consistent with findings in the DCHS cohort in neonates.

Group differences in the right posterior internal capsule between CHEU and CHUU, suggest that the internal capsule may be another region in addition to the cerebellar region impacted by HIV exposure.

Interpretation of these study findings requires great caution because some regions of the brain are more matured than others in the developing brain.

Discussion

The cerebellar regions WM tracts exhibit less specificity during the neonatal period because the cerebellar pathway is rapidly developing in the first 3 years of life and then slows down.

Both our study findings at 6 years and previous findings during the neonatal periods described WM alterations in cerebellar peduncles implicated in neurodevelopmental deficits in motor skills.

In the exploratory partial correlation analysis, there was a mixture in the directionality of the relationships, where some results were positive correlated while others were negative.

Brain development after 2 years of age is often characterised by reorganisation and remodelling of major networks which were previously established during rapid brain development in the neonatal period. Less is known in early life about the interpretation of the direction of effect of diffusion parameters and the directionality of the relationship between diffusion parameters and cognitive and behavioural assessment scores.

The sample size for the cross-sectional empirical study was small. Given the challenges related to movement during scanning and artefacts, sample size limitations are almost uniformly an issue in paediatric neuroimaging studies.

Conclusion

The cerebellar findings are consistent with previous cohort findings in neonates, suggesting a possible persistence of WM changes which could also have an impact on behavioural outcomes given exploratory correlational analysis findings

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