

DTI study of white matter abnormalities in children with fetal alcohol spectrum disorders

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INTRODUCTION

- Diffusion tensor imaging (DTI) yields a measure of white matter integrity [1] allowing one to study the anatomical links and fibre pathways between brain regions.
- Several DTI studies have reported white matter abnormalities in children or young adults with fetal alcohol spectrum disorders (FASD) [2-4]. Despite differences, these studies confirmed microstructural abnormalities of corpus callosum and other white matter regions.
- Previously, we found lower fractional anisotropy (FA) bilaterally in a region within the superior cerebellar peduncle in children with fetal alcohol syndrome (FAS) compared to healthy controls.
- The present study examined white matter abnormalities in cerebrum.
 - Participants were children from a prospective longitudinal cohort [5] from the Cape Coloured community in Cape Town, South Africa, which has the highest reported incidence of FASD in the world [6].
 - Detailed drinking histories [7] and extensive neurobehavioural and neurocognitive data are available for these children.

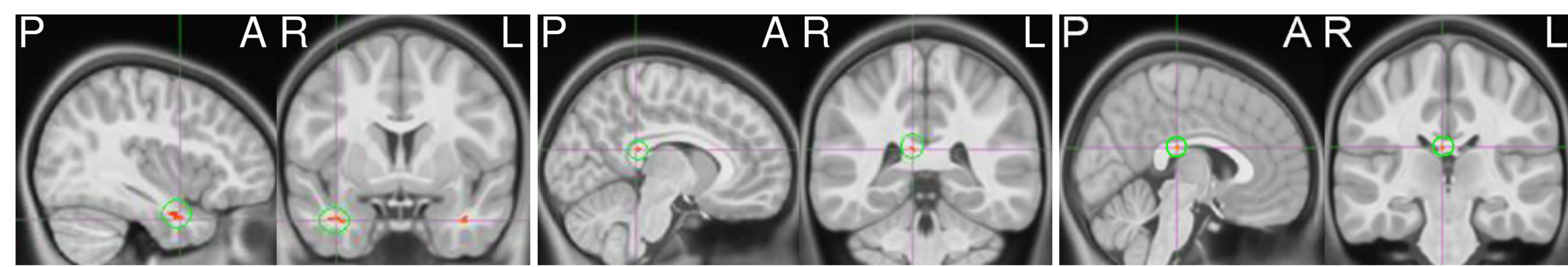
METHODOLGY

- **Participants:** 41 children with FASD (7 FAS, 19 partial FAS (PFAS), 15 nonsyndromal heavily exposed (HE)) and 13 healthy controls (Ctl) from the Cape Town Longitudinal Study [5]; mean age 10.4 ± 0.4 yrs.
- Timeline follow-back interviews [7] were conducted with the mother to record amount of alcohol consumed during pregnancy. Two interviews were administered during pregnancy and one at 1 month postpartum. Volume was recorded for each type of beverage consumed, converted to oz absolute alcohol (AA), and averaged to provide a summary measure of absolute alcohol (AA) consumed per day during pregnancy. AA/day was log transformed to reduce skewness.
- **FASD participants:** Mothers consumed at least 14 standard drinks/week or engaged in binge drinking during pregnancy.
- **Control participants:** Mothers abstained or drank < 1 standard drink/month and did not binge drink during pregnancy.
- **Diagnosis:** All children were evaluated for FAS facial dysmorphism and growth at 5 years of age by two U.S.- and one South African-based expert dysmorphologists [5]. Three groups of children were compared: FAS/PFAS, nonsyndromal HE, and Ctl.
- **DTI protocol:** All children were imaged using DTI with alternating phase encoding directions (i.e., anterior-posterior and posterior-anterior) on a 3T Allegra MRI (Siemens, Erlangen). Diffusion-weighting was performed in 30 directions, 72 slices, $1.8 \times 1.8 \times 1.8$ mm³, b=1000, 4 b=0 images.
- **Pre-processing:** Pre-processing included motion correction in FSL and susceptibility correction in Matlab. Outliers of each acquisition were examined by first calculating z-scores based on 25 and 75 percentile limits; any data points more than 3 standard deviations beyond the mean were discarded. The two DTI acquisitions were averaged and FA images were generated. Unweighted (b0) images were co-registered to their own T1-weighted structural image using linear and nonlinear co-registration algorithms in FSL. T1 images of controls were co-registered to a control image and then averaged to create a mean T1. All T1's were co-registered to this mean T1 image. The FA images were warped using the same transforms to achieve intra- and inter-subject alignment. As a final step, co-registered FA's of all subjects were averaged, after which individual FA's were co-registered to this mean FA. The cerebellum and the brain stem of the pre-processed images were extracted to define the cerebrum (FA threshold > 0.2).
- **Analyses:** Voxelwise group comparisons were performed in FSL. Children with FAS or PFAS were combined in a single group for analyses. We report results that survive cluster size correction of 197 mm³ at $p < 0.01$ [8]. Results were warped to an MNI paediatric standard image [9].

RESULTS

Voxelwise Analysis

- Lower FA was seen in alcohol-exposed children compared to controls in left and right inferior longitudinal fasciculus, right splenium of corpus callosum and right body of corpus callosum. (Table 1).



L/R inferior longitudinal fasciculus R splenium of corpus callosum R body of corpus callosum
Figure 1. Regions with lower FA in children from the FAS/PFAS group compared to controls

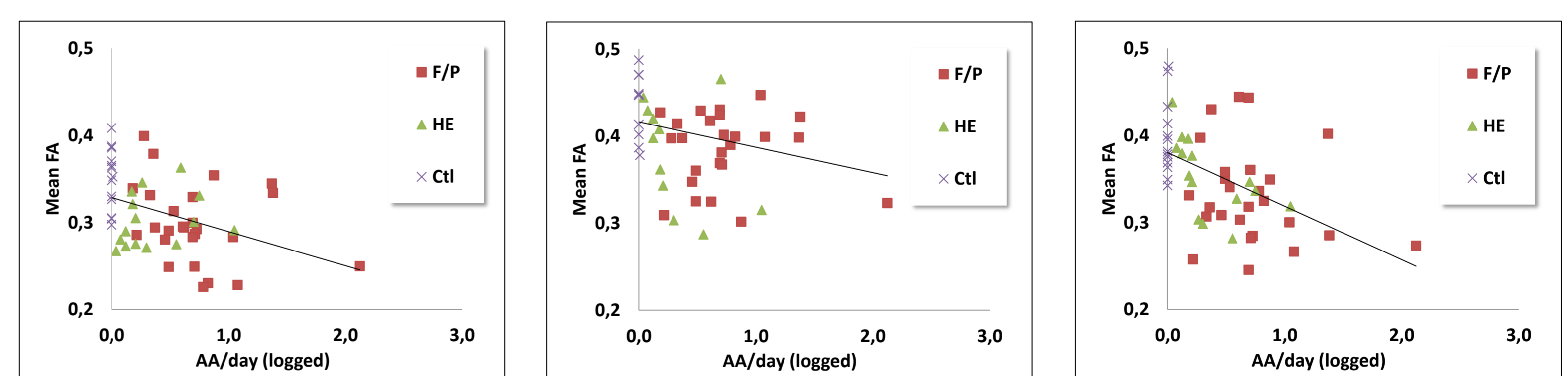
Table 1. Cluster size and peak coordinates (in MNI paediatric standard space [9]) of regions with lower FA in children with either the FAS/PFAS or HE group compared to controls, as well as correlations of absolute alcohol consumed per day across pregnancy (AA/day) with mean FA in ROIs in these regions.

Regions	Groups	Size (mm ³)	Peak coordinate (mm)			r (AA/day)
			x	y	z	
L inferior longitudinal fasciculus	FAS/PFAS	198	-37	2	-30	-0.35**
R inferior longitudinal fasciculus	FAS/PFAS	282	43	-3	-30	-0.39**
	HE	342	39	-10	-19	-0.16
R splenium of corpus callosum	FAS/PFAS	217	8	-39	18	-0.35**
	HE	247	18	-42	9	-0.16
	HE	243	14	-33	23	-0.13
R body of corpus callosum	FAS/PFAS	208	4	-25	21	-0.49***

** $p < 0.01$, *** $p < 0.001$

ROI Analysis

- Mean FA was determined in a $2 \times 2 \times 2$ mm³ region of interest (ROI) around the peak coordinate within each cluster. We examined the correlation ounces absolute alcohol consumed per day averaged across pregnancy (AA/day) with mean FA in these ROIs.
- Mean FA decreased with increasing alcohol exposure (AA/day) in all regions where children in the FAS/PFAS group exhibited lower FA (all $r_s < -0.35$, $p_s < 0.01$) (Figure 2).



R inferior longitudinal fasciculus $r = -0.39$ R splenium of corpus callosum $r = -0.35$ R body of corpus callosum $r = -0.49$

Figure 2. Relation of absolute alcohol consumed per day across pregnancy to mean FA in ROIs in the right inferior longitudinal fasciculus, right splenium of corpus callosum and right body of corpus callosum

CONCLUSIONS

- Prenatal alcohol exposure is associated with lower FA in left and right longitudinal fasciculus, right splenium of corpus callosum and right body of corpus callosum. These data are consistent with findings of abnormalities in splenium of corpus callosum reported in several previous studies [2-4] and with a report by Lebel et al. [2] of FA abnormalities in inferior longitudinal fasciculus.
- Significant correlations between mean FA and alcohol exposure in ROIs in these regions suggest dose-dependent impairment in these regions.

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