A Preliminary DTI-based Tractography Study of Newborns with Prenatal Alcohol Exposure

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INTRODUCTION

Prenatal alcohol exposure (PAE) has serious consequences for brain development and cognitive function. To our knowledge, no DTI-tractography studies of PAE newborns have been performed.

In this preliminary study, DTI and tractography were used to analyze WM development in newborns whose mothers were recruited during pregnancy as part of the Cape Town Longitudinal FASD Study [1]. The incidence of heavy drinking during pregnancy and fetal alcohol related disorders in the local Cape Coloured (mixed ancestry) population is among the highest in the world [2]; this is the first nonsedated newborn neuro-MR study conducted in Cape Town, SA. Data were investigated for WM traits, via DTI parameters, T1 and proton density (PD), and comparisons were made with age-matched healthy controls (HCs) from the same communities.

METHODS

This preliminary group includes 13 nonsedated newborns: 7 PAE and 6 HCs (characteristics in Table 1; mothers only differed in education and in alcohol consumption). A timeline follow-back maternal interview was administered antenatally to ascertain alcohol use during pregnancy [3]. Women averaging ≥1oz absolute alcohol (AA)/day (≈2 standard drinks/day), or ≥2 binges (5 standard drinks/occasion) were invited to participate. Women initiating antenatal care who drank <0.5 oz AA/day and did not binge drink were recruited as controls. Exposed newborns were born to mothers who drank >8 standard drinks/occasion around time of conception.

Scanning was performed on a 3T Siemens Allegra using a custom-built, 170.9mm (inner diameter) circularly polarized birdcage RF coil. Two DWI sets were acquired using opposite phase encoding directions with a twice-refocused SE-EPI sequence: TR/TE 9500/86ms; 72 slices; 2x2x2mm^3; 30 DW gradients, b=1000s/mm^2; 5 b=0 scans. Data were inspected for motion and dropout slices, with individual volumes discarded (>20 DWIs remained in all cases), and were motion corrected using FSL and susceptibility-distortion corrected [4-5]. Using Z-scores based on 25 and 75 %ile limits, points outside mean±3SD were discarded. Tensors, uncertainty and probabilistic tractography (FA>0.1, max. prop. angle 60deg, 5000 Monte Carlo repetitions) were calculated via FATCAT in AFNI [6-7].

Wholebrain structural properties were investigated. Next, spheres were used to create sets of regions of interest (ROIs) to investigate changes due to PAE in selected areas of WM in the brain: A) along the corpus callosum (CC) [8] (ROIs shown in Fig. 1, left panel); B) cortico-cortical development in each hemisphere, (projection and association fibers; Fig. 1, right panel) [2,9]. Spheres were mapped across subjects. HC-PAE group differences were examined via *t*-tests, *F*-tests using general linear modelling (GLM) and repeated measures MANCOVAs (RM-MANCOVAs).

RESULTS

The relative fractions of brain volume with FA>0.1 (standard proxy for WM regions in newborns) were similar across groups, with mean/SD values of 0.41/0.05 for HC and 0.42/0.05 for PAE.

Table 1: Sample characteristics

	HC ($n=6$)	PAE ($n=7$)	t or χ^2
Infant characteristics			
Gender (% male)	66.7	71.4	0.03
GA at birth (weeks)	38.8 (2.4)	38.1 (2.3)	0.51
GA at scan (weeks)	41.8 (2.6)	41.3 (3.1)	0.30
Age at scan (weeks)	3.0 (2.0)	3.1 (2.0)	0.17
Maternal characteristics			
Age at delivery	24.3 (4.3)	28.3 (5.6)	1.43
Parity	1.2 (1.2)	2.3 (1.6)	1.41
Education (years)[a]	10.2 (0.8)	8.1 (1.5)	2.81*
Marital status (% married)	33.3	14.3	0.66
Pregnancy smoking (cig./day)	4.2 (3.1)	5.5 (5.1)	0.54
Pregnancy alcohol consumption			
At conception			
oz AA/day	0.02 (0.1)	1.7 (1.6)	2.45*
oz AA/occasion	0.2 (0.5)	3.2 (1.7)	4.23**
Drinking days/week	0.1 (0.4)	2.9 (2.1)	3.07*
Across pregnancy			
oz AA/day	0.02 (0.04)	1.4 (1.4)	2.32*
oz AA/occasion	0.2 (0.5)	4.1 (1.4)	6.36**
Drinking days/week	0.1 (0.2)	2.2 (2.0)	2.70*

Values given as: mean (SD). GA = gestational age. AA = absolute alcohol (1 oz AA ≈ 2 standard drinks). $^*p<0.05$. $^{**}p<0.001$. [a]Value missing for one HC mother.

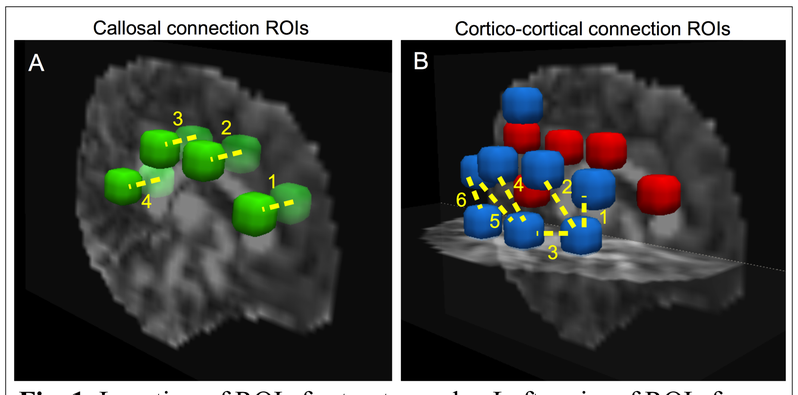

Fig. 1. Location of ROIs for tractography. Left: pairs of ROIs for trans-callosal connections (green). Right: ROIs for projection (red) and association (blue) fiber connections (and similar for opposite hemisphere). Schematic connections are shown and numbered for each (yellow). ROIs were mapped among subjects.

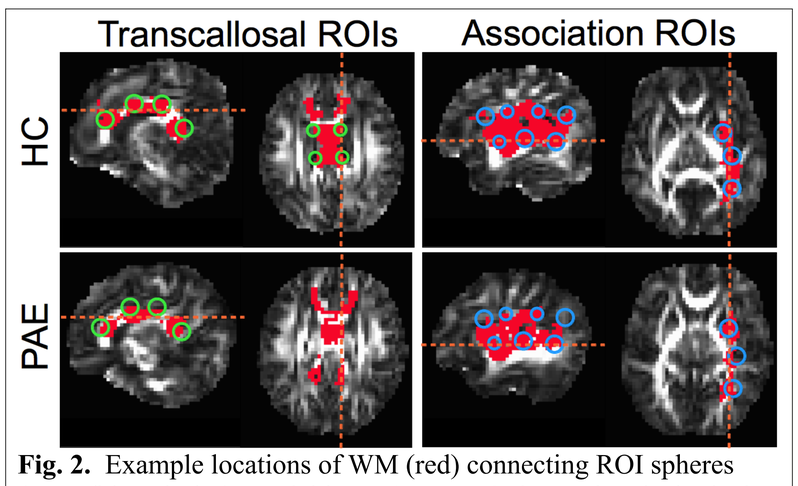

Fig. 2. Example locations of WM (red) connecting ROI spheres (green/blue circles) overlaid on FA maps. Only one hemispherical network is shown for the association case (right). Slice planes are shown (orange, dashed).

WM regions were found connecting several ROIs. Those were selected for further analysis which appeared symmetrically in all subjects: for A, four sets; and for B, six sets in each hemisphere (reference locations and numbers in Fig. 1). Examples of WM locations found with probabilistic tractography are shown in Fig. 2.

A comparison of mean DTI parameter values for the HC and PAE groups are shown in Table 2 for the CC WM and for each of the L and R association regions. MD and L1 were consistently higher in HC, while PD lower. T1 was approx. equal or higher in HC. HC FA was significantly lower in the L association region.

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Table 2: DTI parameter comparisons

Param.		CC WM		Association WM			
		HC	PAE	HC-L	PAE-L	HC-R	PAE-R
FA	μ	0.238	0.220	0.188	0.201*	0.194	0.206
	σ	0.031	0.034	0.025	0.026	0.030	0.024
MD	μ	1.415	1.361	1.337	1.259**	1.355	1.265**
	σ	0.123	0.080	0.128	0.107	0.152	0.115
RD	μ	1.230	1.196	1.209	1.128**	1.221	1.130**
	σ	0.120	0.081	0.125	0.101	0.149	0.109
L1	μ	1.785	1.690*	1.594	1.522*	1.624	1.535*
	σ	0.145	0.103	0.138	0.127	0.168	0.136
Nv	μ	345.500	256.143**	252.778	259.071	277.111	271.048
	σ	83.079	109.131	96.755	171.296	186.364	180.391
T1	μ	3699.627	3640.433	3272.999	3220.849	3705.813	3495.622*
	σ	443.177	396.111	259.343	312.229	370.868	383.113
PD	μ	6970.720	7825.458*	6666.801	7472.173**	7025.500	7775.463*
	σ	1279.773	1352.678	1261.747	1244.405	1292.829	1298.708

Nv = number of voxels. Statistical comparison of means using (unpaired) t-test: $^*p<0.05$. $^{**}p<0.01$.

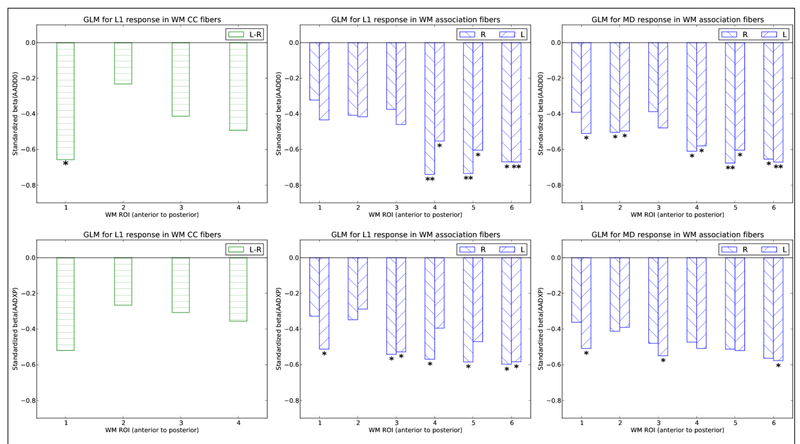

Fig. 3. Effects of AA/occasion at conception (top) and AA/day across pregnancy (bottom) on L1 and MD measures in each ROI. Column 1 shows results in the CC; Cols. 2-3, in the association fibers (ROIs in Fig. 1A and 1B, respectively). *p<0.05; **p<0.01.

Relations between DTI parameters and alcohol measures were compared via GLM-derived *F*-tests. Standardized beta values for AA/occasion at conception and AA/day across pregnancy from models including GA as an additional regressor are shown in Fig. 3. As expected, GA effects (not shown) were significant in many cases, but were independent of and did not alter alcohol effects. RM-MANCOVAs did not show significant interaction effects between region and GA or gender.

CONCLUSIONS

- AA/occasion at conception and AA/day across pregnancy were strongly related to MD and L1 in several WM association regions, particularly in the more posterior association fibers.
- In the CC, only the genu showed a significant relation between alcohol at time of conception and L1.
- Interestingly, FA was typically *higher* in the PAE group, and MD, L1 and RD all *lower*.

These relations in isolation might suggest faster development in the PAE brains; however, that group also tended to have higher PD values, denoting higher water content. In this age range, a *decrease* in PD can be associated with chemical maturation of myelin, suggesting that this process has been slowed down in PAE subjects. In the association fibers, the posterior regions generally showed the most statistical significance, and in the CC, the genu in the anterior.

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