Diffusion Changes in Frontal White Matter in Prenatally Cocaine Exposed Children

K. R. Padgett[1], M. Behnke[2], F. D. Eyler[2], C. M. Leonard[3], K. M. Crandall[3], I. M. Schmalfuss[4], C. S. Garvan[5], T. D. Warner[2], S. J. Blackband[3,6]

[1]Medical Physics, University of Florida, Gainesville, Florida, United States, [2]Pediatrics, University of Florida, Gainesville, Florida, United States, [3]Neuroscience, University of Florida, Gainesville, Florida, United States, [4]Radiology, Univeristy of Florida, Gainesville, Florida, United States, [5]Biostatistics, University of Florida, Gainesville, Florida, United States, [6]NHMFL, Tallahassee, Florida, United States

Introduction: Cocaine easily crosses the fetal blood-brain barrier and accumulates in the CNS (1, 2). Various mechanisms such as hypoxia or disruption of the monoaminergic system as potential causes of brain injury in children exposed to cocaine prenatally have been therefore suggested. Hypoxia places the hippocampus and frontal white matter at risk, and may also affect white matter development. The neurotransmitters of the monoaminergic system greatly influence the developmental trajectory of their targets. These possible mechanisms of injury may alter tissue microstructure. Therefore, the purpose of our study was to examine the brains of the cocaine exposed children versus their control group for microstructural abnormalities that may relate to emerging developmental issues. DTI was employed for its ability to detect such changes.

Subject Population: A prospective longitudinal study was designed to evaluate the neurodevelopmental outcome of children whose mothers used (mostly crack) cocaine during pregnancy compared to matched controls. Exclusion criteria included major illness diagnosed *prior* to pregnancy; chronic use/abuse of medications; illicit drug use except cocaine and marijuana; and heavy alcohol use. Subjects were matched on: high vs. low perinatal risk; level of Socioeconomic Status (SES); first vs. subsequent births; African-American vs. other reported race. Based on statistical power analyses, a sample size of 154 users and 154 matched controls were enrolled during pregnancy; their children have been followed since birth and are now 11-12 years of age. From this group of child subjects, 53, all with right hand dominance, have been scanned, and their images processed and analyzed. The exposed (n=28) and non-exposed (n=25) groups of children in this subset were generally balanced for gender and intelligence test scores. During MR scanning and data processing, researchers were blinded to the drug exposure status of each child.

Methods: The MRI datasets were collected on a Siemens 3T Allegra equipped with gradients capable of 40mT/m, interfaced to a Syngo console. The MRI scanning protocol consisted of radiological scans for detection of confounding pathology, a high resolution 3D gradient echo scan for volumetric analysis and a 6 direction DTI acquisition. For the DTI sequence, a spin-echo diffusion weighted EPI pulse sequence was utilized with b values= 0, 250, and 1000 s/mm^2, FOV = (210 mm)^2, matrix = 128^2, slice thickness = 3.5 mm, TR = 4200 ms, TE = 90 ms, and NEX = 4 yielding an acquisition time of 4 min. In house developed software was used for the tensor processing. FA and <D> maps were created with this software and these images were used for analysis. Frontal white matter structures studied included right and left callosal fibers, right and left projection fibers as seen in the anterior posterior commissure plane. A semi-automated region shrink segmentation technique was implemented relying on intensity thresholding where ROIs were segmented off the FA images. The mean and standard deviations of FA and <D> were tabulated. Two tailed student t tests were conducted probing for differences between the cocaine exposed and control group for each structure. Linear relationships between two variables were assessed using the Pearson correlation coefficient. Alpha was set at $\leq$0.05 for all statistical tests.

Results & Discussion: Table 1 shows an increase in <D> in 2 of 4 frontal white matter areas in the cocaine exposed population displayed in figure 1. The exposed population has also shown a trend of decreased FA in these same areas, but no significance. None of the exploratory white matter areas studied showed significant group differences. Earlier work completed on a subset of this population discovered that several frontal white matter areas exhibited a trend of increased <D> values combined with significantly decreased FA values in the exposed population(3). The smaller study group used in the first analysis and/or the different segmentation techniques employed may explain this discrepancy in significance.

Table 2 shows significant negative correlations of <D> and one significant positive correlation of FA with brain volume in the unexposed population. Controversially, no significant correlations were found in either FA or <D> with brain volume in the exposed population.

Adult cocaine exposure has been reported to cause damage to the frontal white matter(4). Our results are concordant with the published results as we found significant increase in frontal white matter <D> and trend of FA reduction. Possible microstructural changes from prenatal cocaine exposure include alterations to cytoskeletal structure, axonal thickness, myelin thickness, and neuronal density. Changes in these areas may explain an increase in <D> or a decrease in FA and may also lead to degradation in brain function and development. Therefore, our data suggest a link between prenatal cocaine exposure and microstructural alteration in frontal white matter in children, potentially causing a developmental disruption at the microstructural level.

References & Acknowledgements: NIH support from DA05854 & the National High Magnetic Field Laboratory, also thanks to Ann Welch (project director), Ty Black (computer science), Wei Hou, and Vijay Komaragiri (biostatisticians). [1] Dow DL, et al., Mothers babies and Cocaine, 5-17, 1995. [2] Mayes LC, et al., Mothers babies and Cocaine, 251-272, 1995. [3] Padgett KR, et al., ISMRM conference proceeding, 2004. [4] Lim KO, et al., Biol Psychiatry, 51, 890-895, 2002.

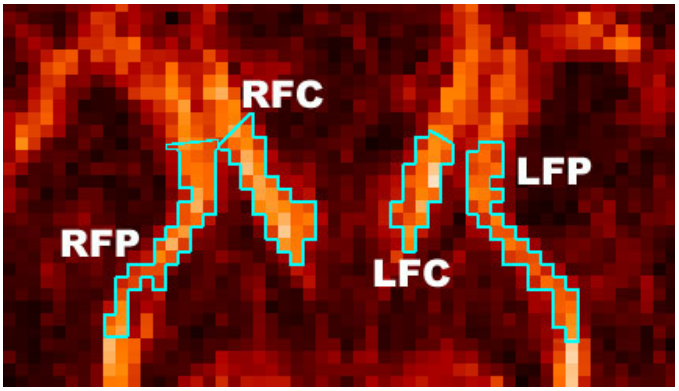

Figure 1: Areas of frontal white matter studied. Located on the ACPC plane these areas are RFP: right frontal projection fibers, RFC: right frontal callosal fibers. LFC: left frontal callosal fibers, and LFP: left frontal projection fibers.

Structure	<D>Control μm^2/ms	<D>Exposed μm^2/ms	p-value
RFP	0.799±0.024	0.820±0.034	0.012
LFC	0.768±0.036	0.802±0.049	0.005

Table 1: This two frontal white matter structures, defined in figure 1, exhibited a significantly increased <D> coefficient in the exposed population.

Structure	Control L_Vol	Control R_Vol	Exposed L_Vol	Exposed R_Vol
LFC FA	0.06	-0.04	0.01	0.11
RFC FA	0.38	0.19	0.02	0.18
LFP FA	0.27	0.16	-0.01	0.07
RFP FA	0.50	0.51	-0.19	-0.19
LFC <D>	0.08	-0.06	-0.16	-0.20
RFC <D>	-0.49	-0.46	0.02	0.06
LFP <D>	-0.39	-0.34	0.03	0.04
RFP <D>	-0.59	-0.59	0.17	0.12

Table 2: Pearson correlations among diffusion measures with right and left hemispheric brain volumes. Examples of these segmented structures may be seen in figure 1.