Reduction of Fractional Anisotropy in Frontal White Matter in Prenatally Cocaine Exposed Children

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INTRODUCTION: We have tested the hypothesis that Diffusion Tensor Imaging (DTI) shows a decrease in fractional anisotropy (FA) in frontal white matter areas of children who were prenatally exposed to cocaine. The subject population consists of a group of prenatally cocaine exposed children and a control group; children in both groups are now 10 to 11 years of age. There have been no drug-group differences in perinatal or subsequent deaths(1) nor were there signs at birth of withdrawal(2) or congenital abnormalities(3,4). Only a few drug-group differences have been found in overall growth and development since birth, from 6 months to 7 years (5,6). Because of these findings, we wanted to examine the brains of the population for abnormalities that may relate to emerging developmental issues. Cocaine easily crosses the fetal blood-brain barrier and accumulates in the CNS(7,8). Possible methods of injury are hypoxia and disruption of the monoaminergic system. Hypoxia puts 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. DTI was employed for its ability to detect such changes. This study suggests prenatal cocaine exposure induces microstructural changes in frontal white matter because of significant reduction of FA in these regions in the exposed population.

SUBJECT POPULATION: This prospective longitudinal study was designed to evaluate women and their children from a mostly rural, understudied population. Most women received prenatal care, but had minimal access to drug treatment. However, they represented a wide range of amount of (mostly "crack") cocaine use. 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. To equate the user and control groups on commonly occurring potential confounders, 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, 154 users were enrolled during pregnancy, and 154 were matched as controls; the child subjects have been followed since birth and are now 10-11 years of age. From this group 13 cocaine exposed and 9 non-exposed children have been scanned, and their images processed and analyzed. During MR scanning and data processing researchers were blinded as to the assignment of each child to a particular group.

METHODS: Datasets were collected on a Siemens 3T Allegra head scanner equipped with gradients capable of 40mT/m, interfaced to a Syngo console. Several different MRI scans were collected for every subject, consisting of localizers and radiological scans for confounding pathological detection. A high resolution 3D gradient echo structural scan was acquired for a volumetric study and to co-register structural images with the DTI images. For the DTI acquisition, a spin-echo diffusion weighted EPI pulse sequence was utilized with b values of 0, 250, and 1000 s/mm^2 and 6 diffusion directions. The imaging parameters were: FOV = (210 mm)^2, matrix = 128^2, slice thickness = 3.5 mm, TR = 4200 ms, TE = 90 ms, avg = 4, and acquisition time = 4 min. In house software was used for the tensor processing. FA and <D> maps were created with this software and these images were used for analysis. ROIs were drawn over several anatomical structures from the FA and <D> images. The mean and standard deviations of the signal from these ROIs were tabulated. A separate unblinded researcher performed statistical data analysis. Two tailed student t tests were conducted looking for differences between the cocaine exposed and control group for every structure; test criteria was a p-value less than 0.05.

RESULTS AND DISCUSSION: White matter structures studied include right and left callousal fibers, right and left projection fibers at the ACPC plane. Structures studied at 8mm above the ACPC plane are the right and left genu, splenium, and internal capsule, also including a core ROI from the genu and splenium. From these ROIs both FA and <D> means and standard deviations were collected. This data were tested for a normal distribution and passed. Two of the four frontal white matter areas showed a statistically significant lower FA in the exposed population with the other two showing a trend of lower FA values (see figure 1 and figure 2). The other structures studied also showed a trend of lower FA in the exposed group with the left genu having a significantly lower FA. No structures studied showed a statistically significant change in <D>, but a strong trend of higher <D> in the exposed group was detected.

Disruption of the monoaminergic system and hypoxia to the fetus may alter white matter structure and development and may have a negative impact upon an individual during development. Frontal white matter is an area at risk from prenatal cocaine exposure, and has shown to be damaged in an adult cocaine exposure study(9). The significant decrease in frontal white matter FA in this study is consistent with the adult cocaine study(9). 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 a decrease in FA and may also lead to degradation in brain function and development. These data suggest a link between prenatal cocaine exposure and microstructural alteration in frontal white matter in children.

REFERENCES AND ACKNOWLEDGEMENTS: NIH support from DA05854 & the National High Magnetic Field Laboratory, also thanks to Ann Welch, Wei Hou, Tamara Warner, and Vijay Komaragiri. [1] Eyler FD, et al., Pediatrics, 101, 229-237, 1998. [2] Eyler FD, et al., Neurotoxicol Teratol, 23, 399-411, 2001. [3] Behnke M, et al., Pediatrics, 107, E74, 2001. [4] Eyler FD, et al., Pediatrics, 101, 237-241, 1998. [5] Eyler FD, et al., SRCD, lecture, 2003. [6] Behnke M, et al., Neurotoxicol Teratol, 24, 283-295, 2002. [7] Dow DL, et al., Mothers babies and Cocaine, 5-17, 1995. [8] Mayes LC, et al., Mothers babies and Cocaine, 251-272, 1995. [9] Lim KO, et al., Biol Psychiatry, 51, 890-895, 2002.

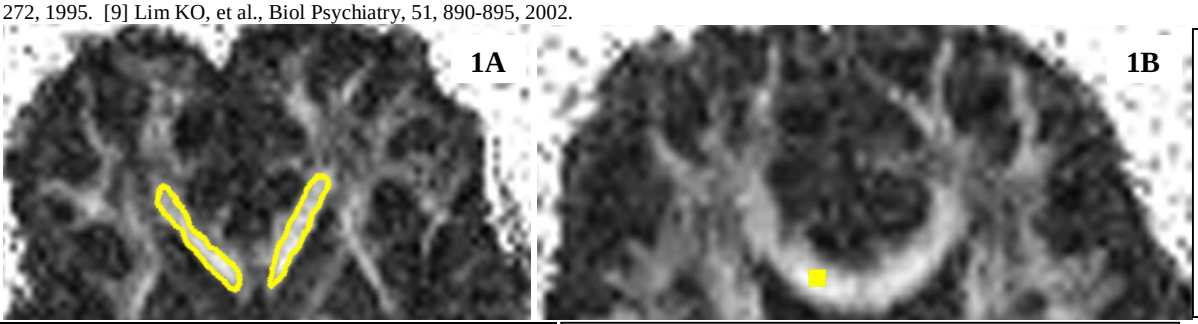

Figure 1: Image A; callousal white matter fibers with significantly reduced FA in the exposed population. Image B; a core sample of the left Genu with significantly lower FA in the exposed population.

Structure	FA Control	FA Exposed	p-value
Right Callousal Fibers	0.713	0.678	0.041
Left Callousal Fibers	0.685	0.639	0.049
Left Genu Core	0.914	0.874	0.039

Figure 2: A table displaying mean FA values and p-values from structures exhibiting a significant decrease in FA in the exposed population. A strong trend of lower FA values in the exposed population was shown in the other structures studied. Also a trend of higher <D> values in the exposed population was detected