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The impact of prenatal exposure to cocaine and tobacco on diffusion tensor imaging and sensation seeking in adolescents

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Abstract

Objective—To study white matter integrity using diffusion tensor imaging (DTI) in adolescents with prenatal cocaine and/or tobacco exposure.

Study design—Subjects included 20 adolescents with prenatal cocaine exposure (15 with tobacco exposure) and 20 non-cocaine-exposed subjects (8 with tobacco exposure). DTI measures were assessed in 5 subregions of the corpus callosum. The Sensation Seeking Scale for Children was administered to evaluate behavioral inhibition.

Results—No significant differences were found between cocaine-exposed and non-cocaine-exposed group in each subregion of the corpus callosum on measures of fractional anisotropy (FA) and mean diffusivity (MD), although the cocaine-exposed showed a trend ($P = 0.06$) toward higher FA in projections to the supplementary motor area (SMA) and premotor cortex (PMC). Prenatal tobacco exposure was associated with decreased FA in SMA-PMC projections after adjustment for relevant covariates ($P = 0.03$). Decreased FA was related to more sensation seeking in the adolescents who were prenatally exposed to tobacco.

Conclusion—Prenatal tobacco exposure could affect white matter integrity which is related to sensation seeking in adolescents. Developmental neurotoxins might have differential influences on white matter maturation in adolescence.

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Keywords

neuroimaging; impulsivity; prenatal drug exposure; response inhibition

Prenatal cocaine exposure has been associated with behavioral problems in children,¹ although limited data regarding the neurobiology of these effects exist. Structural MRI studies have found cocaine exposure related to smaller volumes in cortical grey matter and subcortical structures.^{2, 3} Children exposed to cocaine show an increment of relative blood flow to anterior brain structures as compared with decreased whole cerebral blood flow using perfusion fMRI.⁴ Of two task related fMRI studies, one found cocaine exposure related to stronger activation of fronto-striatal circuits in a behavioral inhibition paradigm,⁵ and the other found no differences in activation related exposure on a working memory task.⁶

Conclusions regarding the effects of prenatal cocaine exposure on behavior are often confounded in by the use of other drugs, most notably nicotine.⁷ Accordingly, co-occurrence of prenatal cocaine and tobacco exposure needs to be factored into neuroimaging studies. Brain morphometry studies have demonstrated volume and/or density loss in smokers of anterior cingulate cortex, orbitofrontal cortex, dorsolateral and ventrolateral prefrontal cortex.^{8, 9} Although grey matter alterations were the most reported findings, connectivity of fronto-striatal circuit was found to be involved in behavioral regulation as well.¹⁰ Nevertheless, little was known regarding the effect of prenatal cocaine and tobacco exposure on white matter integrity. Diffusion tensor imaging (DTI) offers a powerful tool to investigate the coherence/organization in white matters by measuring direction-dependent movement of water molecules. Increased diffusivity in the left frontal callosal fibers and right frontal projections fibers was found by DTI in 10 year old children exposed to cocaine.¹¹ Diffusion in the left frontal callosal fibers was also related to alcohol/marijuana exposure. The only DTI evidence of prenatal tobacco exposure demonstrated altered anisotropy in frontal regions and corpus callosum.¹² In the present study we used subject selection criteria to parse prenatal cocaine effects and, to separate prenatal cocaine effects from that of young adolescents prenatally exposed to tobacco. We hypothesized that both prenatal exposure to cocaine or tobacco would have similar disruptive effects on the microstructure of white matter maturation, resulting in higher diffusivity and/or lower anisotropy, especially in the anterior regions of corpus callosum. Despite the hypothetical role of executive function in impulsivity and sensation seeking behavior leading to later substance use, direct DTI- sensation seeking evidence from exposed individuals was scarce.¹³ Thus, we also hypothesized that white matter abnormalities associated with prenatal exposure to cocaine and tobacco would be associated with impulsivity in these children.

METHODS

Adolescents (aged 13 to 15 years) were recruited from the Providence site of Maternal Lifestyle Study, a longitudinal study of children with prenatal cocaine exposure. Details of enrollment and exclusion criteria are described elsewhere.¹⁴ Prenatal cocaine exposure was determined based on maternal self-report of cocaine use during pregnancy and/or a positive confirmatory meconium assay for cocaine metabolites. Two groups of 20 subjects each, those who were and were not prenatally exposed to cocaine, were selected and matched on the maternal, infant and child characteristics (Table I). Subjects with opiate or marijuana exposure were excluded. Adolescents with autism, moderate to severe mental retardation or low IQ (<70) and females with a positive pregnancy test were also excluded. Both the adolescent and parent signed the IRB-approved consent form for this imaging study. Of the

20 subjects in the prenatal cocaine exposure group, 15 also had prenatal tobacco exposure. Of the 20 subjects who were not prenatally exposed to cocaine, 8 had prenatal tobacco exposure ($\chi^2 = 5.01$, $p = 0.03$). Demographic characteristics were similar between the subjects who were and were not exposed (Table I).

DTI Imaging Data Acquisition and Analysis

MRI was acquired with a Siemens 3 Tesla scanner. Siemens MDDW dual-spin-echo-planar imaging sequence was employed to obtain a series of diffusion-weighted images. Three essentially identical but slightly modulated acquisition protocols were used due to Siemens technical upgrades during the two-year course of study. The whole brain was obtained in seventy transversal slices with TE = 103 ms, TR = 10060~10100 ms, thickness = 1.8~1.9 mm, voxel size = 1.8*1.8 mm, field of view = 226 * 226 mm². Diffusion weighting was obtained along sixty four directions ($b = 1000$ s/mm²) following a non-diffusion-weighted normalization image with $b = 0$ s/mm².

Images without diffusion gradients were initially coregistered and averaged; subsequently, prealignment of all other diffusion weighted images to the non-diffusion average image was achieved by using the FSL FLIRT tool of a 12-degree affine transformation with a mutual information cost function, to correct for eddy current distortion and head motion during scan sessions.¹⁵ Diffusion tensor estimation was performed using the AFNI 3DDWItoDT tool.¹⁶ The symmetric tensor matrix for each voxel was further diagonalized to obtain three pairs of eigenvectors (v_1 , v_2 , v_3) and eigenvalues (λ_1 , λ_2 , λ_3) from which two tensor-derived values, mean diffusivity (MD) and fractional anisotropy (FA), were computed.¹⁷

A standardized placement protocol was employed to place the region-of-interests (ROI) on corpus callosum.¹⁸ Image data was de-identified before ROI drawing on the diffusion normalization image to insure blinding to exposure status. The midsagittal slice was identified by presence of fornix and interthalamic mass, on which geometrical boundary of anterior and posterior corpus callosum was localized and corpus callosum was divided into five subregions anterior to posterior using a DTI-based version of Witelson's scheme developed by Hofer and Frahm.¹⁸ The division scheme is illustrated in Figure 1. Based on published tractography results, the topographical organizations of white matters in these five subregions included: region I (fibers to prefrontal lobe), region II (fibers to premotor and supplementary cortical areas), region III (fibers to primary motor cortex), region IV (fibers to primary sensory cortex) and region V (fibers to parietal, temporal and occipital areas).¹⁸ The boundaries of ROIs were manually defined using a combination of diffusion normalization image and FA image to provide guidance regarding tissue types. Similarly, ROI placement was conducted on two adjacent slices next to the midsagittal. Averaged FA and MD values for each ROI of corpus callosum were calculated.

Sensation Seeking Measures

The Sensation Seeking Scale for Children (SSSC) was administered during the 10 year visit. SSSC is a 28-item self-report scale measuring motivation for irregularity, novelty and adventure with good validity.¹⁹ For each question, the participant was faced with a real life situation and required to choose a response from two statements with one choice reflecting more sensation-seeking than the other. A single summary score is computed with higher score indicating more sensation seeking. There were two children with missing data, one with only prenatal cocaine exposure and one with only prenatal tobacco exposure.

Statistical Analyses

Statistical analysis was conducted using Stata 10.0 (StataCorp., College Station, TX, USA). Analysis of variance was performed on FA and MD metrics in each subdivision of the

corpus callosum controlling for scan protocols and particular covariates for each analysis. Specifically, DTI measures were first explored between groups with and without prenatal cocaine exposure with adjustment for scan protocol and prenatal tobacco exposure. Second, similar analysis was conducted to determine prenatal tobacco exposure effect. Third, DTI differences were assessed between subjects with prenatal exposure to both cocaine and tobacco ($n=15$) and subjects with no prenatal exposure to either cocaine or tobacco ($n=12$). To study DTI-SSSC relationships, correlation (Pearson r) was used of FA/MD and SSSC to determine the strength of linear relationships.

RESULTS

There were no statistically significant differences in mean FA/ MD values between the groups with and without prenatal cocaine exposure for any of the subregions of the corpus callosum. There was a trend in adjusted analysis for a higher FA value in the prenatal cocaine exposure group in region II ($F(1,35) = 3.90$, $p = 0.06$) (Table II). For prenatal tobacco exposure, FA in region II was significantly lower in adolescents with prenatal tobacco exposure after controlling for confounding variables ($F(1,35) = 5.32$, $p = 0.03$) (Table II). No significant FA/MD changes were found in the adolescents with prenatal exposure to both cocaine and tobacco (Table II). In terms of brain-behavior relationship, lower FA values in region II were significantly correlated with more sensation seeking specifically in the adolescents with prenatal tobacco exposure ($r = -0.51$, $p = 0.02$) and those without ($r = -0.11$, $p = 0.69$) (Figure 2).

DISCUSSION

In contrast to our findings, in the previous DTI study, children with prenatal cocaine exposure showed higher MD in the left frontal callosal and right frontal projection fibers.¹¹ The disparity could be due to different ROI placement techniques or an accelerated catch-up of brain maturation in adolescence.²⁰ Alternatively, we did observe a trend of elevated FA in SMA-PMC fibers related to prenatal cocaine exposure. The present trend might suggest a brain endophenotype of abnormality to be defined by future studies with stronger statistical power. In light of the evidence that higher FA in the white matter was also reported in prenatal exposure to methamphetamine exposure, another neurostimulant widely abused, future studies are warranted to clarify whether the elevated FA value might represent a phenotype of white matter maturation somehow modulated by prenatal exposure to neurostimulants.²¹

In terms of white matter development, prenatal tobacco exposure was related to decreased FA in SMA-PMC projections, an indicator of myelin dysfunction or degradation.²² Our results were consistent with a previous DTI study in that both findings suggested disruptive effect of prenatal tobacco exposure.¹² By binding to the nicotinic acetylcholine receptors (nAChRs), tobacco was able to deviate the neurotrophic functions of nAChRs at early age.²³ Animal immunohistochemical evidence has identified expression of nAChRs on glial precursor cells in brain tissue from corpus callosum.²⁴ Several neurobiological mechanisms were speculated to mediate the detrimental effect of tobacco exposure on white matter integrity. Tobacco was found to downregulate $\alpha 7$ receptors on astrocytes, which might adversely affect the stimulus-evoked myelination.²⁵ Altered expression of brain-derived neurotrophic factor due to tobacco could further cause myelin damage.²⁶ Tobacco-induced apoptosis could directly affect alignment of fiber tracts.²⁷ Some, if not all, of the three mechanisms could possibly be involved in the prenatal tobacco exposure-related impairment of white matter FA.

This decrease in FA in SMA-PMC fibers related to prenatal tobacco exposure was coupled with the trend for increased FA in the same region related to prenatal cocaine exposure. It would be interesting to determine if prenatal cocaine and tobacco exposure exert distinctive effects on white matter microstructural integrity. If this mechanism was true, it could help to explain mixed findings from published data. Failure to find recognizable brain damages in a population with multiple drug exposure might reflect joint effects from different toxins which could “offset” each other in a single-dimensional measure. This is supported by our finding of nonsignificant combined prenatal cocaine and tobacco exposure effects. The value of one measure might reflect combined influence; however, the “blind spot” of this method was that individual influence could not be cancelled out biologically due to the distinctive temporal and regional pattern from each toxin.

Our findings that FA was related to sensation seeking suggest a brain behavior relationship specific to prenatal tobacco exposure. As a composite component of the personality trait of Impulsive-Sensation Seeking, sensation seeking we measured was a valid predictor for risk-taking behavior.²⁸ Stronger sensation seeking has been consistently documented to be associated with a variety of risk behaviors due to compromised top-down modulation system.^{28, 29} Our results illustrated that in the subjects prenatally exposed to tobacco, the lower FA in anterior region of corpus callosum, the more sensation seeking behaviors the individual endorsed. The weakened sensation seeking suppression could be related to the unique anatomical and functional connections of SMA-PMC. Recent evidence has illustrated that SMA-PMC (Brodmann's area 6) has extensive connections with the parietal lobe, limbic system, basal ganglia, hypothalamus, amygdale, and prefrontal cortex and as a result of the widespread communication with different tiers of structures in executing a planned motor response, the SMA-PMC is one key neural node in regulating delayed response function.³⁰ Impaired white matter structure in this region could impede transmission and integration of information flow in executing top-down inhibition and therefore lead to increased sensation seeking.³¹ This could help explain brain mechanisms involved in adolescent-onset drug use in children with prenatal drug exposure. For example, sensation seeking in our study was measured at age 10, 3-4 years before DTI was measured. Thus, our findings relating sensation seeking to changes in DTI could suggest that one of the consequences of prenatal tobacco exposure was to accelerate the normal development of risk taking behavior characteristic during adolescence.²⁰

There are several limitations to this study. First, participant matching was solely based on the dichotomous variables of cocaine, tobacco and alcohol exposure. It would be ideal to take into account actual dose of drugs of abuse. Second, the measures of sensation seeking and DTI were not obtained simultaneously. However, the stable nature of personality trait might lend support to the purposed brain-behavior association in adolescence. Third, we did not control for multiple comparisons. However, white matter integrity of anterior subregions (region I and region II) was our priori hypothesis. To completely characterize structural integrity of corpus callosum, posterior subregions were examined as post-hoc analysis. In regions I and II there were 6 comparisons, one of which was statistically significant. Thus, we feel that our findings are meaningful but should be interpreted with caution. Fourth, environmental factors can also affect brain development. Although we matched participants on SES and poverty, other environmental factors could have been involved. In summary, our study presented new evidence of long-term effect of prenatal tobacco exposure and possible concurrent prenatal cocaine exposure effect in a differential pattern. Furthermore, the impaired white matter myelination was found to be related to higher level of sensation seeking behaviors in subjects prenatally exposed to tobacco. Future studies with larger sample size are warranted to identify the potential unique influence of prenatal cocaine exposure.

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List of Abbreviations

DTI	diffusion tensor imaging
FA	fractional anisotropy
MD	mean diffusivity
nAChR	nicotinic acetylcholine receptor
PMC	premotor cortex
ROI	region of interest
SMA	supplementary motor area
SSSC	Sensation Seeking Scale for Children

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Figure 1.

Example of corpus callosum parcellation, which illustrates the placement protocol to select regions of interest on corpus callosum. There were five vertical subregions from anterior to posterior axis of corpus callosum.

Figure 2.

The relationship between FA in region II and *SSSC* score. Subjects prenatally exposed to tobacco are labeled in solid triangles and subjects who were not prenatally exposed to tobacco in open circles. The brain –behavior association in subjects prenatally exposed to tobacco is shown in solid line, and the association in subjects who were not prenatally exposed to tobacco is shown by dotted line. Inverse correlation between FA and *SSSC* score was only significant with adolescents prenatally exposed to tobacco ($r = -0.51$, $p = 0.02$), but not for those who were not prenatally exposed ($r = -0.11$, $p = 0.69$).

Table 1

Subject Characteristics

	Cocaine		p	Tobacco		p
	No exposure (n=20)	Exposed (n=20)		No exposure (n=17)	Exposed (n=23)	
Maternal characteristics						
Age (years[MHI])	26.73 (5.40)	28.23 (5.79)	0.40	25.69(5.02)	28.80(5.62)	0.07
Alcohol use (%)	65	65	1.00	53	74	0.17
Poverty (%)	55	45	0.42	47	55	0.64
Race (% minority)	50	70	0.20	71	52	0.24
Marital status (% married)	20	21	1.00	29	14	0.26
Lowest SES level	20	15	1.00	18	17	0.99
Infant characteristics						
Male (%)	60	55	0.75	65	57	0.43
Gestational age (wk)	38.9 (2.05)	38.25 (1.97)	0.31	38.82(1.74)	38.39(2.21)	0.49
Head circumference (cm)	34.08 (2.03)	34.00 (1.81)	0.90	34.36 (1.87)	33.79 (1.93)	0.35
Length (cm)	50.42 (3.40)	49.10 (2.71)	0.18	50.21(3.60)	49.43(2.72)	0.46
Child characteristics						
Age	13.35 (0.75)	13.65 (0.75)	0.21	13.35 (0.70)	13.61 (0.78)	0.29
IQ score at 10-year	96.70(10.69)	96.25(11.08)	0.90	96.41(11.58)	96.52(10.36)	0.97

Table 2
Mean and Standard Deviation of DTI Parameters in Different Subregions of Corpus Callosum

DTI	ROI	Non-PCE (n=20)	PCE (n=20)	Adjusted <i>p</i>	Non-PTE (n=17)	PTE (n=23)	Adjusted <i>p</i>	Non-PCE-PTE (n=12)	PCE&PTE (n=15)	Adjusted <i>p</i>
FA	Region I	0.74 (0.01)	0.76 (0.01)	0.36	0.76 (0.01)	0.73 (0.01)	0.17	0.77(0.06)	0.75 (0.06)	0.70
	Region II	0.65 (0.01)	0.70 (0.02)	0.06	0.70 (0.01)	0.64 (0.02)	0.03	0.71 (0.08)	0.68 (0.09)	0.73
	Region III	0.64 (0.03)	0.70 (0.02)	0.12	0.70 (0.02)	0.65 (0.02)	0.19	0.71 (0.13)	0.70 (0.11)	0.81
	Region IV	0.67 (0.02)	0.71 (0.02)	0.15	0.71 (0.02)	0.67 (0.02)	0.19	0.70 (0.10)	0.70 (0.07)	0.81
	Region V	0.78 (0.01)	0.79 (0.01)	0.38	0.80 (0.01)	0.77 (0.01)	0.08	0.80 (0.04)	0.78 (0.05)	0.46
MD	Region I	0.64 (0.01)	0.65 (0.01)	0.61	0.64 (0.01)	0.65 (0.01)	0.79	0.64 (0.06)	0.64 (0.06)	0.52
	Region II	0.67 (0.02)	0.66 (0.01)	0.60	0.66 (0.02)	0.67 (0.02)	0.76	0.67 (0.12)	0.64 (0.09)	0.92
	Region III	0.76 (0.03)	0.77 (0.02)	0.76	0.77 (0.02)	0.76 (0.03)	0.91	0.78 (0.16)	0.76 (0.14)	0.92
	Region IV	0.73 (0.02)	0.76 (0.02)	0.28	0.75 (0.02)	0.74 (0.02)	0.67	0.76 (0.15)	0.75 (0.11)	0.52
	Region V	0.65 (0.01)	0.67 (0.01)	0.39	0.65 (0.01)	0.66 (0.01)	0.53	0.65 (0.09)	0.66 (0.08)	0.16