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White-matter crossing-fiber microstructure in adolescents prenatally exposed to cocaine

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Abstract

Background—Prenatal cocaine exposure (PCE) is associated with risk-taking behaviors, including increased initiation of substance use in adolescence. The neurobiological underpinnings of these behaviors in adolescents with PCE are not well understood. The goal of this study was to compare diffusion-weighted imaging data between adolescents with and without PCE using crossing-fiber models, which may provide more comprehensive estimates of white-matter microstructure within regions of multiple (e.g., primary and secondary) fiber orientations.

Methods—Thirty-nine PCE individuals and 17 comparably aged prenatally non-drug-exposed (NDE) youths were recruited from a longitudinal cohort followed since birth. White matter was examined using tensor-derived and crossing-fiber models. Whole-brain investigations were performed, as were analyses on seven white-matter regions, which included the splenium, body

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Contributors

Drs. Potenza, Sinha and Mayes designed the study, generated the protocol and oversaw data acquisition. Dr. Morie and Dr. Zhai undertook the statistical analysis. Dr. Morie and Dr. Yip performed the imaging analyses. Dr. Morie wrote the first draft of the paper and worked with co-authors on subsequent drafts. All authors contributed to the editorial process and have approved the final submitted version of the manuscript.

Conflicts of Interest and Disclosures

The authors report no conflict of interest with respect to the content of this manuscript.

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and genu of the corpus callosum, bilateral cingulum, and the right and left superior longitudinal fasciculus (SLF).

Results—Whole-brain analyses revealed no group differences. However, ROI analyses for anisotropy estimates derived from the crossing-fiber model revealed significant group differences for secondary fibers, with reduced anisotropy among PCE adolescents compared to prenatally non-exposed youth in the right cingulum and the left SLF, and increased anisotropy in the genu.

Conclusions—Our findings suggest that white-matter differences in PCE adolescents are subtle and localized primarily within secondary fiber orientations, perhaps arising from altered white-matter development.

Keywords

Substance abuse; cocaine; pre-natal exposure; white matter; DTI

1. Introduction

Multiple behavioral and cognitive differences have been reported in children with prenatal cocaine exposure (PCE). Compared with non-exposed peers, youth with PCE exhibit more risk behaviors, including substance use, violence, and aggression (Bennett et al., 2007) and mild cognitive deficits (Ackerman et al., 2010). PCE status has been associated with increased likelihood of substance use in early adolescence (Delaney-Black et al., 2011; Minnes et al., 2014), even when controlling for environmental factors (Richardson et al., 2013).

The neurobiological underpinnings of these PCE-related differences are not yet well understood. Reward responsiveness and executive control undergo significant changes during adolescence (Galvan, 2010). Poorer development of white matter in PCE adolescents between executive areas and areas responsible for reward motivation may contribute to the behavioral and cognitive correlates of PCE, as suggested by (Lebel et al., 2013). For example, the superior longitudinal fasciculus (SLF), which can be divided into multiple sub-tracts, connects frontal areas to temporal and parietal areas (Kamali et al., 2014), and the cingulum connects areas of the cingulate with limbic regions (Catani et al., 2002). These and other white-matter tracts have been measured in PCE populations using diffusion-weighted magnetic resonance imaging (dMRI) (Lebel et al., 2013; Li et al., 2013).

Diffusion tensor imaging (DTI) (Basser and Pierpaoli, 1996) allows for the examination of the spread of water molecules in white-matter structures of the brain, using measurements of diffusivity (Ozarslan et al., 2005) (diffusion constants, such as directionally averaged mean diffusivity (MD)) and fractional anisotropy (FA), which is a measure of the directional dependence. This methodology has been used to examine white matter in PCE children. A study in children (mean age 10 years) with PCE demonstrated increased diffusion (according to MD values) in the frontal callosal and projection fibers (Warner et al., 2006). In addition, in this study FA values correlated with performance on a motor set-shifting task, although there were no group differences found for FA. Prenatal exposure to other types of drugs, including methamphetamine, has been associated with lower diffusivity in the genu and

splenium of the corpus callosum in children 3–4 years of age (Cloak et al., 2009). Increases in FA were found in the genu of older children with polydrug exposure (Colby et al., 2012). Another study of older children (9–11 years) with fetal polysubstance exposure demonstrated reduced FA in multiple white-matter tracts, including the splenium, and FA correlated with cognitive function (Walhovd et al., 2010).

Studies have also examined white matter in PCE individuals as they move into adolescence. Studies have focused upon different brain regions and substances. In a study designed to examine white-matter integrity in subregions of the corpus callosum in individuals with PCE and prenatal tobacco exposure, researchers examined group differences in FA and MD in a cohort of 13–15 year-olds with and without such exposure (Liu et al., 2011). The authors found no differences between those with and without PCE in areas of the corpus callosum, although the PCE individuals showed a trend toward higher FA in areas of the supplementary motor area and premotor cortex. In addition, sensation-seeking was associated with decreased FA in PCE adolescents. Other DTI work investigating white matter in PCE adolescents between the ages of 12–18 years using probabilistic fiber-tracking methods to determine the integrity of the connectivity between pre-frontal areas and the amygdala revealed reduced FA values in these tracts (Li et al., 2013). Another study in adolescents between 14–16 years that employed tractography in regions of interest including the corpus callosum, cortico-spinal tract, anterior thalamic radiations, as well as the anterior, inferior-longitudinal and fronto-occipital and uncinate fasciculi revealed in PCE adolescents reduced FA in the right arcuate fasciculus and the right cingulum, along with higher MD in the right splenium of the corpus callosum (Lebel et al., 2013). These parameters of diffusion were correlated with poor performance on the Stroop, Wisconsin Card Sorting, and trail-making tests, all of which are standard laboratory measures of executive control. However, as in (Liu et al., 2011), whole-brain FA was not different between groups in this study.

Taken together, the previous work in this population has suggested that there are subtle alterations in white matter in PCE adolescents. In the current study, we sought to expand upon this literature. Our goal was to investigate white-matter differences between individuals with PCE and other prenatal substance exposure and those with no *in utero* cocaine exposure (NCE) using a crossing-fiber model (Behrens et al., 2007; Jbabdi et al., 2010). The crossing-fiber approach employed (Behrens et al., 2007) allows for the examination of white matter at multiple fiber orientations, increasing specificity within regions of complex white-matter architecture. This technique provides estimates of anisotropy for different fiber orientations (e.g., primary (F1) and secondary (F2) orientations) that may be interpreted within regions of complex architecture (regions containing more than one fiber orientation per voxel; estimated to include up to 90% of white-matter-containing voxels (Jeurissen et al., 2013)) with less ambiguity than traditional measures such as FA and other tensor-based indices (Baumgartner et al., 2015; Reveley et al., 2015). This crossing-fiber approach has recently been used to study adults with addictions (Savjani et al., 2014; Yip, 2016b) and is proposed to be a more comprehensive examination of white matter. This model will provide a comprehensive examination of white matter that is suitable for a population in which differences in white matter from prenatally non-exposed youth may be subtle.

The strengths of crossing-fiber models include the ability of the technique to characterize fiber bundles (for example, F2 fibers) that do not lie in the dominant direction (F1 fibers) and may correspond to different fiber populations. As an example, the SLF contains fibers that innervate the parietal lobe, which are easily traceable with traditional tensor-based diffusion technique. The SLF also contains connections to the motor cortex and cortical eye fields. (Rushworth et al., 2006). These non-dominant tracts are not discernible with traditional voxel-based techniques, but crossing-fiber methodologies are able to estimate them, as crossing-fiber techniques allow for the analysis of multiple fiber orientations within one voxel (Behrens et al., 2007). Thus, crossing-fiber analyses may be used to characterize difficult-to-discern fiber populations and may be useful for characterizing subtle white-matter differences in PCE individuals.

In this study, we aimed to characterize white-matter differences in PCE and prenatally non-drug-exposed (NDE) individuals using crossing-fiber analyses. We employed multiple indices of diffusion (MD and FA, including radial ($\lambda_{\perp}$) and axial ($\lambda_{\parallel}$) diffusivity), and specific estimates for primary and secondary fiber anisotropy. We focused our crossing-fiber approach upon seven regions of interest (ROIs) selected based on prior studies of PCE in children and adolescents; these regions included the splenium, body and genu of the corpus callosum, the right and left cingulum, and the right and left SLF (Cloak et al., 2009; Colby et al., 2012; Lebel et al., 2013; Walhovd et al., 2010; Warner et al., 2006). Given that previous work has demonstrated subtle differences upon examination of these regions in PCE and NDE populations, which may be attributable to white-matter differences in multiple fiber populations, we hypothesized that PCE adolescents would show reductions in anisotropy measures in both primary and secondary fibers in the corpus callosum, cingulum, and SLF.

2. Methods

2.1 Participants

All participants were recruited from a cohort of adolescents who have been followed longitudinally since birth (Bridgett and Mayes, 2011; Chaplin et al., 2010; Yip et al., 2014), with assessments taken bi-annually. In the ongoing study, mothers were enrolled over a 5-year time frame from the Women's Center at a large urban hospital setting. Maternal cocaine use was determined based on maternal self-report and urine toxicology during pregnancy or following delivery. Children with PCE and children with NDE were enrolled. Of the present study participants, 100% of mothers of children in the PCE category reported cocaine use in the 30 days prior to delivery. None of the mothers of children with NDE reported cocaine use in the 30 days preceding delivery, with one reporting a single use of tobacco and four reporting a single use of alcohol. Of the cocaine-using mothers, 46% reported using alcohol in the 30 days prior to delivery, 65% reported using tobacco, and 20% reported marijuana use.

In the current study, all adolescent participants were eligible if they were part of the initial study and did not meet criteria for any DSM-IV Axis-I disorders. They were also excluded if they did not meet criteria for MRI safety, which included the presence of any metallic objects in the body, pregnancy, or claustrophobia. Participants were assessed at three visits—two intake visits to assess substance-use behaviors and one neuroimaging session involving

dMRI. Participants were assessed using self-reports on the Youth Risk Behavior Survey and via urinalysis, which was obtained at the first and/or second study visit. Reports of use, or positive urinalysis results, indicating use of amphetamines, cocaine, tobacco, alcohol, opiates, phenycyclidine, and cannabis were coded for each adolescent as a dichotomous variable as initiation of substance use. No participants met criteria for any Axis-I disorder, including substance-use disorders. There were no between-group differences in age, sex, race/ethnicity or substance use (Table 1).

2.2 DTI Acquisition information

Subjects were scanned on two Siemens 3T (Erlangen, Germany) scanners. Fourteen participants (5 HCE, 8 PCE) were scanned on one system, and the remainder were scanned on the other. Scanner was treated as a variable of no interest for all reported analyses in order to account for this. Within the multivariate analysis, there was no main effect of magnet ($F = 2.4$, $p = .061$). Forty contiguous slices parallel to the AC-PC line were acquired with the following parameters: TR=7400 ms; TE=115; B values=0, 1000s/mm²; bandwidth=1396 Hz/px; directions=32 [+0]; slice thickness=3.0mm; averages=2. Affine registration was used to correct for head movements and gradient coil eddy currents (Douaud et al., 2011; Smith et al., 2006b). Diffusion MR data were collected at a resolution of 2×2 mm in-plane with a 3mm slice thickness.

2.3 Pre-processing and diffusion estimates

As in our prior work, (Yip, 2016b), FSL software was used to analyze the dMRI data. Tract-based spatial statistics (TBSS) procedures were used, which incorporate both diffusion-tensor and crossing-fiber models (Jbabdi et al., 2010; Reveley et al., 2015; Smith et al., 2006b). Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, (Smith et al., 2006a), part of FSL (Smith et al., 2004), as was done in our previous work (Yip, 2016b). First, FA images were created by fitting a tensor model to the raw diffusion data using FSL's Diffusion Toolbox (FDT) (Behrens et al., 2007; Behrens et al., 2003). Then all subjects' FA data were aligned into a common space using the nonlinear registration tool FNIRT (Andersson, 2007a; Andersson, 2007b), which uses a b-spline representation of the registration warp field (D. Rueckert, 1999). Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data were then projected onto this skeleton and a threshold of .2 was used for the FA skeleton. The resulting data were fed into voxel-wise cross-subject statistics.

Crossing fiber analyses were performed as follows. Using the FSL algorithm "Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques for Crossing Fibers" (BEDPOSTX)(Behrens et al., 2007; Jbabdi et al., 2010), two diffusion estimates were conducted for each fiber orientation (primary and secondary) per voxel. This method provides one partial volume estimate (PVE) per fiber orientation (Behrens et al., 2007; Douaud et al., 2011; Jbabdi et al., 2010). TBSS_X is then used to analyze the PVE corresponding to either primary (F1) or secondary (F2) fiber orientations for each voxel (Jbabdi et al., 2010). Additional DTI measures of MD for each voxel were also incorporated in TBSS analysis using tbss_non_FA (Smith et al., 2006a). Individual participant aligned

data for FA, MD, F1 and F2 were projected onto the mean skeleton for voxel-wise statistical analyses.

2.4 Region-of-interest (ROI) Analysis

Based upon previous findings from tensor-based investigations of adolescents (Lebel et al., 2013; Li et al., 2013; Walhovd et al., 2010), we focused on the following ROIs for all analyses: right and left cingulum, the body, genu and splenium of the corpus callosum, and the right and left SLF. The average anisotropy measure for each participant along these tracts was extracted using FSL, and analyses were performed in SPSS. ROIs were defined using the FSL JHU-ICBM-DTI-81 White Matter Label Atlas (Mori and van Zijl, 2007; Oishi et al., 2008), and the atlas values were applied to each participant's diffusivity maps (the overlap between the participant's FA skeleton and the FSL JHU-ICBM-DTI-81 Atlas map) in order to generate mean ROI values for each participant in each region. Separate multivariate ANOVAs comparing between group (PCE or NDE) for FA, F1 and F2 MD, and radial ($\lambda_{\perp}$) and axial ($\lambda_{\parallel}$) fibers, were conducted. All analyses controlled for demographic variables of age, sex, and MRI scanner as factors of non-interest. Follow-up t-tests were performed only after significant main and/or interactive effects were observed to elucidate the precise nature of the findings. Since t-tests were only performed after a significant ANOVA finding, they are justified in order to determine the nature of the significant findings.

2.5 Whole-brain analysis

As an exploratory analysis, a two-way analysis of variance (ANOVA) was conducted, with factor of group (PCE, NCE), to compare individuals on tensor-based anisotropy measures (FA, F1 and F2) and measures of diffusion (MD, radial ($\lambda_{\perp}$) and axial ($\lambda_{\parallel}$)). The models included age and scanner as variables of no interest and were conducted using FSL's 'randomise' (Winkler et al., 2014) with 5000 permutations. Resultant statistical maps were family-wise-error-corrected (FWE-corrected) for multiple comparisons using FSL's threshold-free cluster-enhancement (TFCE) (Smith and Nichols, 2009) and considered significant at $\alpha=.05$.

3. Results

3.1 ROI analysis

3.1.1 Tensor-based approach—Multivariate analyses for FA revealed no main effect of group ($F_{1,55} = 1.3, p>.25$). Multivariate analyses of MD revealed a main effect of group ($F_{1,55} = 2.3, p < .04$), but no individual region reached significance at the group level (all p 's $>.1$). Multivariate analyses on axial fibers revealed a main effect of group ($F = 3.2, p < .01$). Follow-up analyses on individual regions revealed only marginal effects in the left cingulum ($F = 3.1, p < .08$) and the body of the corpus callosum ($F = 2.9, p < .09$). Multivariate analyses on radial fibers revealed no group differences.

3.1.2 Crossing fibers approach—Figures 1 and 2 display the mean values for F1 and F2 averaged across participants for each ROI. The 2X7 multivariate ANOVA for F1 fibers revealed no main effect of group ($F_{1,55}=1.6, p=.3$). The multivariate ANOVA for F2 fibers

revealed a main effect of group ($F_{1,55}=2.49$, $p < .01$). Secondary t-tests on each region revealed reduced F2 in the right cingulum ($F_{1,55}=5.6$, $p < .03$) and left SLF ($F_{1,55}=6.4$, $p < .02$), and increased F2 in the genu of the corpus callosum ($F_{1,55}=8.5$, $p < .01$). Comparisons between groups in each of the ROIs for anisotropy in F1 and F2 fiber orientations are shown in figure 1.

3.1.3 Examination of drug use—It is possible that drug use by the participant may impact white matter. To explore this possibility, we performed the same multivariate ANOVAs using participant substance use as a covariate. As before, the multivariate ANOVA for F2 fibers revealed a main effect of group ($F_{1,55}=2.49$, $p < .01$), and the same follow-up t-tests on each region revealed reduced F2 in the right cingulum ($F_{1,55}=6.7$, $p < .02$) and left SLF ($F_{1,55}=4.1$, $p < .05$), and increased F2 in the genu of the corpus callosum ($F_{1,55}=6.4$, $p < .02$). Once again, there were no differences found for F1 fibers.

We also performed the analyses for F2 fibers with maternal cigarette use as a covariate, as previous samples of tobacco-exposed adolescents were found to have increased FA in the genu (Jacobsen et al., 2007). In this model, the group differences remained for the left SLF ($F = 6.4$, $p < .02$) and the right cingulum ($F = 7.01$, $p < .02$). However, the group difference for the genu disappeared. Thus, maternal cigarette use during pregnancy may have been driving the difference in the genu ($F = 5.12$, $p < .03$), where those whose mothers reported tobacco use had higher F2 values ($M = .12$, $SD = .02$) than those whose mothers did not ($M = .10$, $SD = .03$).

3.2 Whole-brain analysis

There were no main effects of group on either primary or secondary fibers at the whole-brain level, as assessed using voxel-wise ANOVAs corrected for multiple comparisons across space ($pFWE > .05$.) Similarly, no effects of group were found for any other tensor-based measures of diffusivity (MD, FA, radial ($\lambda_{\perp}$) and axial ($\lambda_{\parallel}$)) ($pFWE > .05$.)

4. Discussion

White matter, as indexed using dMRI, was compared between adolescents with PCE and NCE. Unlike previous studies which have employed tensor-derived indices (Cloak et al., 2009; Lebel et al., 2013; Liu et al., 2011), we implemented a crossing-fiber diffusion model (Jbabdi et al., 2010). Whole-brain analyses did not reveal group differences in any of our diffusion measures for PCE status, which is consistent with previous literature that also revealed no whole-brain differences in prenatally-opiate exposed and PCE adolescents (Lebel et al., 2013; Liu et al., 2011). ROI analyses for measures of diffusion (FA, MD, radial ($\lambda_{\perp}$) and axial ($\lambda_{\parallel}$)) did not reveal any group differences at the level of specific regions, although the ANOVA revealed a main effect of group for MD and the ANOVA revealed a marginal main effect of group for axial fibers. It is possible the effect size for the multivariate model ($MD \eta^2 = .242$) was not large enough for individual regions to meet significance.

However, ROI analyses using crossing-fiber measures revealed between-group differences. These differences were observed for anisotropy of secondary fiber orientations (F2) and

were localized to the right cingulum, the genu, and the left SLF. Intriguingly, in areas of dense white-matter architecture with a large proportion of crossing fibers (e.g., right Cingulum, left SLF) (Schmahmann et al., 2007), PCE individuals demonstrated lower F2 values, but within the genu, PCE individuals demonstrated increased F2 values compared to NDE youth.

Our findings in the SLF are not surprising considering previous examinations of white matter in children prenatally exposed to multiple substances, where the SLF, along with the inferior longitudinal fasciculus, had the greatest proportion of voxels with lower FA values in exposed children when compared to non-exposed children (Walhovd et al., 2010). Our study advances previous findings by localizing the white-matter differences specifically to secondary fibers. Considering the large amount of secondary fibers in the SLF and the complex crossing-fiber architecture seen in subdivisions of the SLF (Descoteaux et al., 2009; Schmahmann et al., 2007), our findings suggest that previously observed FA differences in this fiber tract may be a result of alterations in development of these secondary fibers (Barnea-Goraly et al., 2005). However, longitudinal assessments would be valuable in testing this hypothesis directly. The SLF is a long white-matter tract with numerous connections between frontal areas and parietal and temporal areas, and has been implicated in processing emotions, memories and language (Schmahmann et al., 2008). This pathway develops throughout adolescence and is important for the healthy development of cognition (Lebel et al., 2008; Snook et al., 2005). Alterations in this pathway could indicate poorer connectivity between frontal and sensory cortices that could have ramifications for behavioral or cognitive outcomes (Cascio et al., 2007). However, further research is needed to examine this hypothesis.

PCE adolescents also demonstrated lower anisotropy for secondary fiber orientations in the cingulum. This is reminiscent of previous findings in PCE adolescents using FA (Lebel et al., 2013), and raises the possibility that alterations in the anisotropy of secondary fiber orientations may have contributed to prior findings of altered FA in this region. The cingulum contributes to a circuit connecting the frontal lobes and the limbic system and has been implicated in processing emotions, rewards and craving states (Heimer and Van Hoesen, 2006; Myrick et al., 2004). Abnormal development of this circuit may relate to emotional difficulties and risk behaviors in PCE adolescents (Minnes et al., 2014; Richardson et al., 2013; Yip, 2016a), and this possibility warrants direct examination.

The finding that PCE adolescents had higher F2 values in the genu of the corpus callosum runs counter to our original hypothesis. The finding that differences were localized only to secondary fibers is rather surprising, especially considering that previous work has identified group differences in PCE individuals in regions of the corpus callosum (Cloak et al., 2009; Liu et al., 2011), which has been thought to contain fibers that are largely primary-direction dominant. However, more recent research has suggested that the corpus callosum contains crossing fibers, and fibers with different dominant directions have termination points in lateral regions of the frontal lobes (De Benedictis et al., 2016). Increased FA in the genu has also been found in individuals exposed to methamphetamine (Colby et al., 2012), along with greater axial diffusivity and lower radial diffusivity in that region compared to control

subjects, suggesting different effects of stimulant exposure on different fiber orientations similar to findings we report here in PCE adolescents.

Also similar to the Colby et al. study, PCE individuals had increased, not decreased, F2 values in the genu. Increased FA in exposed populations is not unusual. In addition, previous work investigating white matter in individuals prenatally exposed to tobacco smoke indicated increased FA in anterior cortical areas (Jacobsen et al., 2007), and 65% of the cocaine-using mothers in the current study reported tobacco use in the 30 days pre-delivery. The authors of that study suggested that increased FA in the genu may reflect disrupted maturation of white-matter tracts that contribute to less efficient processing. We found similar results in our additional analysis. The notion that drug exposure, and particularly tobacco exposure, may disrupt normal maturation of white matter in the genu may explain the current findings. Specifically, the current finding of increased F2 in the genu and reduced F2 in the SLF and cingulum may indicate compensatory development in adolescence as a result of prenatal exposure to substances, including tobacco. In sum, our findings suggest that white-matter tracts are affected by exposure to substances *in utero*, and these differences may be subtle and involve predominantly non-dominant fiber tracts.

4.1 Strengths and limitations

A strength of this study includes the use of both tensor-based and crossing-fiber models, allowing for a more comprehensive comparison of white-matter tracts across NDE and PCE populations. This strength should be considered alongside some weaknesses, which include a wide range of substances used by the mothers beyond just cocaine (which is reflective of this clinical population) and the small number of NDE individuals to serve as comparison subjects. In addition, a larger sample of PCE adolescents would have allowed for investigation of the effects of different pre-natal substance exposures, including alcohol and nicotine, on white matter in exposed and non-exposed adolescents. In addition, it would be helpful in future studies to examine the potential impact of severity of prenatal exposure (e.g., by collecting quantity/frequency measures of maternal substance use). Unfortunately, we do not have these data.

Despite these weaknesses, this work adds to the literature on white-matter development in exposed adolescents and introduces more comprehensive examination of white-matter microstructures by employing a crossing-fiber model, not previously used to study adolescents with PCE. The findings suggest that white-matter differences in PCE adolescents may be subtle and present in secondary fiber tracts, raising the possibility that they may arise from altered development of white-matter tracts. Future work should focus upon how subtle white-matter differences are generated, which fiber populations may be particularly vulnerable to substances at specific developmental stages, and how the white-matter differences may relate to emotional processing, cognitive functioning, risky behaviors and addiction propensities.

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Figure 1.

Comparison of the anisotropy of F1 (primary) and F2 (secondary) fiber orientations between prenatally cocaine exposed (PCE) and non-cocaine-exposed (NCE) adolescents in each of the seven regions of interest. Significant differences in anisotropy were found in the right cingulum, the genu, and the left SLF in F2 fiber orientations, as indicated with asterisks.

Table 1

Participant demographics

	PCE (n=39)	NCE (n=17)	p value
Age (SD)	14.9 (.60)	14.6 (1.10)	0.34
Gender (%Male)	24(61.5)	11 (64.7)	0.86
Ever used (%)	17(56.6)	5(29.4)	0.13
Race/Ethnicity n (%)			
<i>African American</i>	<i>25(64.0)</i>	<i>9(52.9)</i>	<i>0.44</i>
<i>Hispanic/Biracial</i>	<i>5(12.0)</i>	<i>5(29.4)</i>	<i>0.14</i>
<i>Caucasian</i>	<i>1(2.5)</i>	<i>2(11.7)</i>	<i>0.17</i>
<i>Other/Unreported</i>	<i>8(20.0)</i>	<i>1(5.8)</i>	<i>0.24</i>