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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 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.

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).

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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 sub-regions 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 and 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 et al., 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 ($\lambda_{||}$) 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. Par-