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*Pediatrics* 2006;118;2014-2024

DOI: 10.1542/peds.2006-0003

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American Academy of Pediatrics

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# Diffusion Tensor Imaging of Frontal White Matter and Executive Functioning in Cocaine-Exposed Children

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The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

**BACKGROUND.** Although animal studies have demonstrated frontal white matter and behavioral changes resulting from prenatal cocaine exposure, no human studies have associated neuropsychological deficits in attention and inhibition with brain structure. We used diffusion tensor imaging to investigate frontal white matter integrity and executive functioning in cocaine-exposed children.

**METHODS.** Six direction diffusion tensor images were acquired using a Siemens 3T scanner with a spin-echo echo-planar imaging pulse sequence on right-handed cocaine-exposed ( $n = 28$ ) and sociodemographically similar non-exposed children ( $n = 25$ ; mean age: 10.6 years) drawn from a prospective, longitudinal study. Average diffusion and fractional anisotropy were measured in the left and right frontal callosal and frontal projection fibers. Executive functioning was assessed using two well-validated neuropsychological tests (Stroop color-word test and Trail Making Test).

**RESULTS.** Cocaine-exposed children showed significantly higher average diffusion in the left frontal callosal and right frontal projection fibers. Cocaine-exposed children were also significantly slower on a visual-motor set-shifting task with a trend toward lower scores on a verbal inhibition task. Controlling for gender and intelligence, average diffusion in the left frontal callosal fibers was related to prenatal exposure to alcohol and marijuana and an interaction between cocaine and marijuana exposure. Performance on the visual-motor set-shifting task was related to prenatal cocaine exposure and an interaction between cocaine and tobacco exposure. Significant correlations were found between test performance and fractional anisotropy in areas of the frontal white matter.

**CONCLUSIONS.** Prenatal cocaine exposure, alone and in combination with exposure to other drugs, is associated with slightly poorer executive functioning and subtle microstructural changes suggesting less mature development of frontal white matter pathways. The relative contribution of postnatal environmental factors, including characteristics of the caregiving environment and stressors associated with poverty and out-of-home placement, on brain development and behavioral functioning in polydrug-exposed children awaits further research.

[www.pediatrics.org/cgi/doi/10.1542/peds.2006-0003](http://www.pediatrics.org/cgi/doi/10.1542/peds.2006-0003)

doi:10.1542/peds.2006-0003

### Key Words

prenatal exposure, cocaine infants, neuroimaging, cognitive function, neuropsychology

### Abbreviations

PCE—prenatal cocaine exposure  
IQ—intelligence quotient  
ROI—regions of interest  
DTI—diffusion tensor neuroimaging  
 $D_{av}$ —average diffusion  
FA—fractional anisotropy  
SES—socioeconomic status  
TMT—Trail Making Test  
 $df$ —degrees of freedom

Accepted for publication Jul 5, 2006

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**A**S COCAINE-EXPOSED CHILDREN reach school age and approach puberty, many questions remain about the effects of prenatal cocaine exposure (PCE) on brain development and cognition. In well-controlled prospective studies, subtle deficits among cocaine-exposed children during the neonatal period and infancy and during early childhood have been reported: deficits that could have implications for behavioral and academic functioning. In the first weeks and months of life, slight difficulties with attention, arousal, and state regulation were found in cohorts of children with prenatal exposure to cocaine and other drugs.<sup>1</sup> In early childhood, cocaine-exposed children have demonstrated problems with visual attention and impulsivity using several different testing paradigms including computer-administered continuous performance tasks.<sup>2-7</sup> However, with a few exceptions, most studies examining broad cognitive skills as measured by standardized intelligence quotient (IQ) tests have revealed no significant negative effects of PCE.<sup>8-12</sup>

Problems related to cognition and daily functioning could emerge as cocaine-exposed children grow older and have more demands placed on them in school and other settings. A likely domain for later-emerging problems is executive functioning, a diverse set of skills needed to engage in independent, purposeful, goal-directed behavior.<sup>13</sup> Executive functioning includes supervisory and self-regulatory skills that organize, direct, and manage more basic cognitive, emotional, and behavioral functions, especially during active, novel problem solving.<sup>14</sup> Specific executive functioning skills include attention control, initiation, inhibition, and shifting between cognitive tasks. Pathologic and neuroimaging studies suggest that the underlying neural substrate for executive functions is the prefrontal cortex and its subcortical connections.<sup>15,16</sup>

Animal studies indicate that PCE can result in abnormal white matter development. Altered glial morphology, inappropriate positioning of neurons in white matter areas, and a 100% increase in white matter neurons in granule and pyramidal cells at postnatal year 3 have been demonstrated in nonhuman primate studies of PCE.<sup>17</sup> Investigations using rodents have shown decreased astroglial proliferation and increased density of less mature radial glial cells.<sup>18</sup>

The possibility of white matter abnormalities in cocaine-exposed children has been suggested by 2 well-controlled physiologic studies of brain development in prospectively enrolled samples. One study using quantitative electroencephalographic sleep recordings found that PCE was associated with lower spectral correlations between homologous brain regions at birth and lower spectral power values at birth and 1 year, suggesting fewer interhemispheric neuronal connections or delayed development of these connections.<sup>19</sup> Another study using auditory brainstem response measures revealed that

heavy PCE was associated with prolonged interpeak latencies, indicating slower neural transmission and delayed brain maturation.<sup>20</sup>

To date, very little neuroimaging has been conducted with cocaine-exposed children. One study<sup>21</sup> using proton magnetic resonance spectroscopy ( $N = 26$ ) found no gross structural abnormalities, no volumetric differences for the whole brain and 7 regions of interest (ROIs), and no differences for 4 of 5 metabolite concentrations measured in the frontal lobe and striatum. Cocaine-exposed children did, however, show a 13% increase in frontal white matter creatine levels with trends for decreased midbrain volume bilaterally and a decreased ratio of choline-containing compounds to creatine in frontal white matter.<sup>21</sup>

Diffusion tensor neuroimaging (DTI), a noninvasive procedure that uses MRI to investigate white matter microstructure, has ushered in a new era for the study of brain development. In simple terms, DTI involves measuring the movement (diffusion) of water molecules in tissues and determining the extent to which the diffusion is directionally independent (isotropic) and directionally dependent (anisotropic). Diffusion is more anisotropic in white matter than gray matter because the movement of water molecules is restricted by cell membranes and the myelin sheaths surrounding axons. In addition, water molecules are thought to move faster and longer distances along the white matter fibers rather than perpendicular to them. Water diffusion is represented quantitatively by the average diffusion ( $D_{av}$ ) coefficient, which provides a measure of isotropic diffusion, as well as by a number of measures of anisotropic diffusion, such as fractional anisotropy (FA). The FA index provides a scale- and orientation-independent measure of diffusion with values ranging from 0 (isotropic) to 1 (completely anisotropic).<sup>22</sup> More detailed reviews of the technical aspects of DTI can be found elsewhere.<sup>23-26</sup>

Maturation of white matter tracts in children can be traced by examining changes in  $D_{av}$  and anisotropic diffusion over time or in different age groups. A number of investigators have demonstrated convincingly in longitudinal and cross-sectional designs that DTI can be a powerful tool for evaluating white matter development in normally developing children<sup>27-36</sup> and children with problems ranging from leukodystrophy<sup>37</sup> to prematurity<sup>38</sup> to developmental delay.<sup>39</sup> In the brain as a whole,  $D_{av}$  has been shown to decrease significantly during the first year of life, reaching adult levels by age 7 years, whereas measures of anisotropy increase significantly with development. Changes in white matter anisotropy take place in different regions of the brain at different rates with, for example, posterior areas (visual cortex and posterior limb of the internal capsule) maturing before anterior areas (anterior limb of the internal capsule).<sup>40</sup> Anisotropic diffusion changes reflect maturation

of white matter microstructure but cannot be interpreted solely as the result of increased myelination because changes in anisotropy have been found in the absence of myelin.<sup>23,40</sup>

Using DTI to explore relationships between cognitive abilities and white matter microstructure in children and adolescents is still in its nascent stages, particularly in comparison to volumetric studies.<sup>41</sup> A review by Moseley et al<sup>42</sup> revealed that the majority of DTI studies examining cognitive performance have used adults and focused on aging or disease-related cognitive decline (eg, multiple sclerosis). Two DTI studies have found that performance on reading and related measures is correlated with anisotropy measures in the left temporoparietal region in both children<sup>43</sup> and adults.<sup>44</sup> A study of 8- to 18-year-olds combining DTI and functional MRI found significant correlations between FA in frontoparietal white matter and brain activity in the superior frontal sulcus and inferior parietal lobe during a working memory task.<sup>45</sup> In terms of executive functioning, a number of functional MRI studies have found significant age-related differences among children, adolescents, and adults using a variety of tasks<sup>41</sup>; however, no DTI studies relating white matter development and executive functioning could be found in the extant literature.

The threefold purpose of the current study was: (1) to compare cocaine-exposed and nonexposed children on DTI measures of frontal white matter development and on measures of executive functioning; (2) to determine whether there are significant associations between frontal white matter development and executive functioning; and (3) to test for the effects of PCE, both alone and in combination with other prenatal drug exposures, on frontal white matter development and on executive functioning. We hypothesized that cocaine-exposed children would show significantly less mature frontal white development (indicated by higher  $D_{av}$  and lower FA values) and significantly poorer performance on executive functioning measures (as indicated by slower time to completion and fewer items completed) than nonexposed children. We also expected to find significant correlations between frontal white matter DTI measures and executive functioning test performance.

## METHODS

### Procedures

Study approval was granted by the University of Florida Institutional Review Board, and a federal Certificate of Confidentiality protects the confidentiality of the data. Participants ( $N = 53$ ) were drawn from a prospective, longitudinal study on the developmental effects of PCE that began in 1991. A separate informed consent from the child's primary caregiver and assent by the child were obtained before the current study. Detailed information about the enrollment of the participants in the

larger longitudinal study has been published previously.<sup>46</sup> Briefly, pregnant women with no chronic illness that might affect pregnancy outcome or fetal development were recruited for the longitudinal study when they first entered prenatal care or, in the case of no prenatal care, at delivery. Women who admitted use or tested urine-positive for illegal drugs other than cocaine or marijuana were excluded from the study. A total of 308 women (154 cocaine users and 154 nonusers) matched on race, parity, socioeconomic status (SES) (A.B. Hollingshead, PhD, *Four-Factor Index of Social Status*, unpublished manual, 1975), and location of prenatal care (which was related to prenatal risk factors) were enrolled in the parent study. Cocaine users were identified by private, structured interviews conducted by experienced female research staff and/or positive urine screens confirmed by gas chromatography/mass spectrometry. Executive functioning measures were collected during the 10-year follow-up evaluation by a school psychologist blinded to the children's drug exposure status.

### Participants

Of the surviving 296 children, 263 (89%) participated in the 10-year follow-up assessment and completed all of the outcome measures. Families who lived within 2 hours of the study site, which reflects the area from which the original sample was drawn, were recruited by a brochure describing the study followed by a telephone call, when possible. Left-handed children and menstruating girls were excluded from the study. Of the 78 families who were contacted by telephone and met criteria, 18 were not willing or able to participate. Of the 60 children enrolled, 53 had data that could be analyzed for the purposes of this study. The MRI studies of the remaining 7 children were incomplete or collected using different imaging parameters.

Descriptive data for the participants (cocaine-exposed:  $n = 28$ ; nonexposed:  $n = 25$ ) are shown in Table 1. The current sample closely resembles the full cohort originally enrolled in the longitudinal study. Maternal characteristics for the cocaine-exposed and comparison children in the current study did not differ on the 4 matching variables used to select the original cohort (race, parity, SES, and location of prenatal care). Variables that differed significantly in the originally enrolled cohort but did not in the current sample (although  $P$  values were  $\leq .10$ ) were mean maternal age at delivery, week that the mothers entered prenatal care, and Hobel Prenatal Risk scores. As in the original cohort, cocaine-exposed children were exposed to much greater amounts of tobacco, alcohol, and marijuana.

In terms of birth outcome measures, the children in the current study were, on average, term infants with birth weights and head circumferences within normal limits. None was small for gestational age at birth, had a

**TABLE 1 Sample Description**

Characteristic	Cocaine-exposed (n = 28)	Nonexposed (n = 25)	P <sup>a</sup>
<b>Mother</b>			
Race, % black	64	72	.55
Parity, % multiparous	86	96	.20
SES	4.6 ± 0.6 (3–5)	4.7 ± 0.6 (3–5)	.92
Age at delivery, y	27.6 ± 4.7 (20–36)	25.4 ± 7.2 (18–39)	.09
Week entered prenatal care <sup>b</sup>	13.7 ± 6.4 (5–30)	11.0 ± 6.4 (3–29)	.10
Hobel Prenatal Risk <sup>c</sup>	48.2 ± 15.4 (20–75)	40.6 ± 13.0 (20–80)	.07
Cigarettes during pregnancy, No. per d	7.03 ± 6.49 (0–20.83)	2.83 ± 6.01 (0–20.09)	.004
Alcohol during pregnancy, oz absolute per d	0.27 ± 0.46 (0–1.69)	0.02 ± 0.07 (0–.31)	.004
Marijuana during pregnancy, joints per d	0.06 ± 0.28 (0–1.49)	0.002 ± 0.007 (0–.036)	.006
<b>Child</b>			
Birth weight, g	3169 ± 479 (2307–4188)	3414 ± 571 (1802–4357)	.04
Gestational age, wk	38.7 ± 1.7 (35–42)	39.0 ± 1.7 (34–42)	.57
Birth head circumference, cm	34.0 ± 1.6 (30.0–37.0)	34.7 ± 1.7 (30.0–37.5)	.33
Gender, % female	43	60	.21
Age at testing, y	10.6 ± 0.2 (9.6–10.9)	10.6 ± 0.1 (10.5–11.1)	.49
Age at scanning, y	11.1 ± 0.5 (10.4–12.2)	11.0 ± 0.4 (10.3–11.9)	.68
Weight at scanning, kg	43.1 ± 8.9 (29.5–60.4)	41.8 ± 8.91 (27.2–63.4)	.41
Estimated WISC-IV full-scale IQ	88.8 ± 18.5 (55–121)	92.6 ± 19.0 (53–123)	.54
WIAT basic reading standard score	95.2 ± 16.7 (71–123)	97.8 ± 16.9 (62–119)	.36

Plus-minus values are mean ± SD with range in parentheses. WIAT indicates Wechsler Individual Achievement Test; ISC-IV, Wechsler Intelligence Scale for Children-Fourth Edition.

<sup>a</sup> P values were calculated using Wilcoxon rank-sum test for continuous variables and  $\chi^2$  test for categorical variables.

<sup>b</sup> Two missing values for cocaine-exposed.

<sup>c</sup> One missing value for nonexposed.

head circumference below the 10th percentile for gestational age or birth weight, or was reported by their primary caregiver as having failure to thrive during multiple interviews between birth and middle childhood. As in the original cohort, the mean birth weight was significantly lower in the cocaine-exposed group, but only 5 children (3 cocaine-exposed and 2 nonexposed) had birth weights <2500 g. No group differences were found for mean gestational age or birth head circumference. Five children in the current sample were born before 37 weeks (1 nonexposed, born at 34 weeks; 2 cocaine-exposed, born at 35 weeks; and 2 cocaine-exposed, born at 36 weeks).

Follow-up assessments including a comprehensive neuropsychological test battery were conducted on the entire cohort when the children were ~10.5 years old. For the 53 children in the imaging study, the cocaine-exposed and nonexposed groups did not differ by male/female ratio, mean age at the time of testing, or mean weight. All but 1 child (a cocaine-exposed boy) fell below the 95th percentile for weight-for-age using gender- and race-specific growth charts derived from the Third National Health and Nutrition Examination Survey.<sup>47</sup> The groups attained similar mean estimated Wechsler Full Scale IQ<sup>48</sup> scores (low average range) and similar mean Wechsler Basic Reading<sup>49</sup> standard scores (average range). We deliberately chose children with a wide range of IQs (based on administration of a full Wechsler battery at age 7) because of the possibility that PCE and/or polydrug exposure might exert an adverse effect on IQ.

### Executive Functioning Measures

Two executive functioning measures were used to assess visual attention, inhibition, and the ability to shift between cognitive sets: the Stroop color and word test (Stroop)<sup>50</sup> and the Trail Making Test (TMT) parts A and B.<sup>51</sup> The Stroop is a well-studied measure of frontal lobe function.<sup>52</sup> Pediatric functional neuroimaging studies using Stroop tasks have demonstrated that improved performance is associated with increased activation in left lateral prefrontal cortex.<sup>53,54</sup> The TMT part B has been shown to be a sensitive screening instrument for possible neuropsychological impairment in children ages 9 to 14 years with academic difficulties.<sup>55</sup> A recent meta-analysis of adult studies reported that the Stroop and the TMT part A were sensitive to frontal lobe damage.<sup>56</sup>

The Stroop color-word task is a timed task in which the examinee is asked to name the color of the ink of the words “red,” “green,” and “blue” printed in capital letters in a competing color ink (eg, the word “red” printed in blue ink). The task requires inhibition of a prepotent word-reading response in favor of a competing color-naming response. Scoring for the Stroop is based on the number of correct responses given in 45 seconds. The TMT is a timed pencil-and-paper test consisting of 2 parts. Part A involves sequencing the numbers 1 to 15 scattered randomly on a page, and part B involves alternating between sequencing the numbers 1 to 8 and sequencing the letters A to G (eg, 1 to A to 2 to B). Part B is more demanding because it requires shifting between 2 cognitive sets. Scoring for the TMT is based on time to completion. As a check to determine whether

the Stroop and TMT were tapping similar aspects of executive functioning, we examined correlations between the 2 measures. As expected, a significant linear relationship was found between the TMT part B and the Stroop color-word score ( $r = -.30$ ;  $P = .03$ ).

### Imaging Data Collection

Imaging data were collected when the children were between 10 and 12 years old (mean:  $11.0 \pm .4$  years; range: 10.3–12.2 years). There was no significant difference in age at the time of scanning between the 2 groups (Table 1). Imaging was performed using a Siemens 3T Allegra MRI scanner (Siemens, Iselin, NJ). Conventional MRI sequences (axial fluid-attenuated inversion recovery and volumetric T1-weighted images) were obtained to detect possible confounding pathology. DTI acquisition used a spin-echo diffusion-weighted echo planar imaging pulse sequence with  $\beta$  values of 0, 250, and 1000 seconds/mm<sup>2</sup>, 3.5-mm slice thickness,  $210 \times 210$  cm field of view,  $128 \times 128$  matrix, 4200-ms repetition time, 90-ms echo time, and 4 excitations. Total acquisition time was 4 minutes.

### Image Processing

Conventional images were assessed for the presence of abnormal anatomy and signal intensities by a board-certified radiologist who holds an additional certificate of qualification in neuroradiology (I.M.S.).  $D_{av}$  and FA maps were generated using in-house software.<sup>57</sup> ROIs were measured using a semiautomated segmentation method, which involves hand drawing an ROI around the target anatomic structure, then applying a pixel-based threshold to shrink the boundaries of the region. This method has been described in detail elsewhere and has been shown to have high interrater and intrarater reliability.<sup>58</sup>

Two separate fiber pathways, medial and lateral fibers extending anteriorly into the frontal lobe white matter, could be discerned on the axial DTI sections. We termed the medial fibers the “frontal callosal fibers” and the lateral fibers the “frontal projection fibers.” The frontal callosal fibers project to the opposite hemisphere through the corpus callosum. The frontal projection fibers contain afferent and efferent fibers that project between a number of frontal and subcortical areas, including the dorsolateral prefrontal cortex (which is associated with executive functioning), caudate, dorsomedial nucleus of the thalamus, and reticular formation. The longer frontal projection fibers course through the internal capsule and the cerebral peduncles. Measurements were made on the axial section that showed both pathways. Figure 1 shows a sample image with an outline of the white matter ROIs.

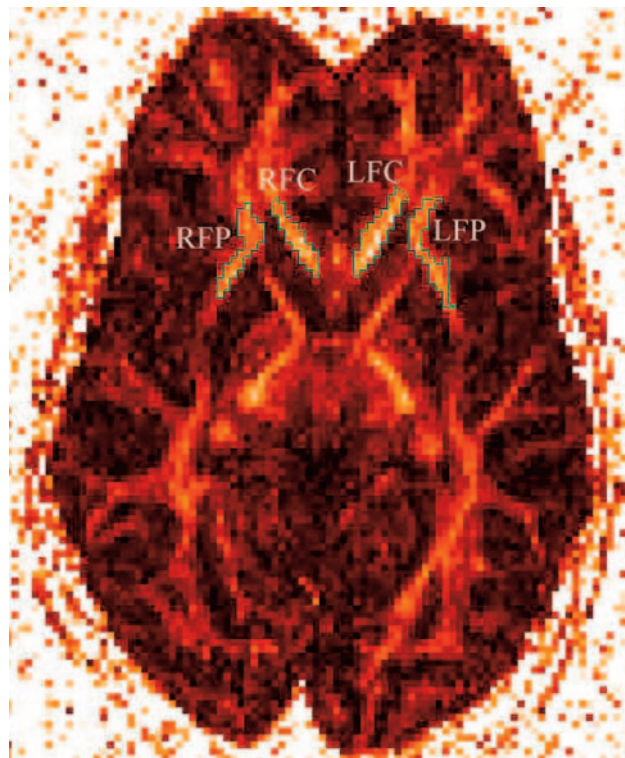


FIGURE 1

Axial image showing white matter ROIs. RFP indicates right frontal projection fibers; RFC, right frontal callosal fibers; LFC, left frontal callosal fibers; LFP, left frontal projection fibers.

### Statistical Analyses

SAS 8.2 (SAS Inc, Cary, NC) was used to conduct data screening and all of the statistical analyses. Group comparisons were made using the Wilcoxon rank-sum test for continuous data and the  $\chi^2$  statistic for categorical data. Correlation coefficients were computed using Spearman's  $r$ . Multiple regression analyses were conducted to assess the unique contribution of PCE alone and in combination with other variables. The criterion for significance tests was set at  $\alpha \leq .05$ , 2-tailed. Because neuroimaging in cocaine-exposed children represents a new area of inquiry, trends toward significance ( $\alpha \leq .10$ ) are reported, as well as results that meet the conventional criterion.

### RESULTS

To evaluate the hypothesis that cocaine-exposed children would demonstrate diffusion measures associated with less optimal white matter integrity, the mean  $D_{av}$  and FA of the groups were compared. As shown in Table 2, the cocaine-exposed children had significantly higher  $D_{av}$  in the left frontal callosal fibers ( $P = .02$ ) and right frontal projection fibers ( $P = .03$ ). The cocaine-exposed children also had higher  $D_{av}$  in the right frontal callosal fibers, but the difference from the comparison group ( $P = .09$ ) did not meet the conventional criterion for significance.

**TABLE 2** Average Diffusion, Fractional Anisotropy, and Executive Functioning Measures According to Exposure Status

Measure	Cocaine-exposed (n = 28)	Nonexposed (n = 25)	P
White matter ROIs			
Left frontal callosal $D_{av}$ <sup>a</sup>	0.80 ± 0.05 (0.71–0.93)	0.77 ± 0.04 (0.68–0.82)	.02
Left frontal projection $D_{av}$	0.78 ± 0.03 (0.73–0.85)	0.78 ± 0.03 (0.72–0.84)	.50
Right frontal callosal $D_{av}$	0.80 ± 0.05 (0.69–0.93)	0.78 ± 0.04 (0.71–0.88)	.09
Right frontal projection $D_{av}$	0.82 ± 0.03 (0.77–0.90)	0.80 ± 0.02 (0.75–0.85)	.03
Left frontal callosal FA <sup>b</sup>	0.68 ± 0.04 (0.63–0.75)	0.70 ± 0.04 (0.63–0.82)	.12
Left frontal projection FA	0.65 ± 0.02 (0.60–0.68)	0.64 ± 0.02 (0.58–0.70)	.11
Right frontal callosal FA	0.68 ± 0.04 (0.61–0.74)	0.68 ± 0.04 (0.58–0.77)	.51
Right frontal projection FA	0.63 ± 0.04 (0.56–0.72)	0.63 ± 0.03 (0.59–0.69)	.74
Executive functioning			
Stroop word raw score <sup>c</sup>	67 ± 11 (45–91)	68 ± 14 (35–88)	.50
Stroop color raw score	49 ± 7 (37–63)	48 ± 10 (26–69)	.71
Stroop color-word raw score	24 ± 5 (16–35)	27 ± 6 (14–41)	.09
TMT part A time, s <sup>d</sup>	22 ± 9 (12–41)	21 ± 10 (11–52)	.59
TMT part B time, s	53 ± 24 (23–99)	42 ± 19 (23–94)	.05

Plus-minus values are mean ± SD with range in parentheses.

<sup>a</sup>  $D_{av}$  indicates average diffusion ( $10^{-3} \mu\text{m}^2/\text{ms}$ ) with lower values associated with greater microstructural integrity.

<sup>b</sup> FA indicates fractional anisotropy (micrometers squared per millisecond) with higher values associated with greater microstructural integrity.

<sup>c</sup> Higher Stroop scores indicate better performance.

<sup>d</sup> Less time to completion on TMT indicates better performance.

To evaluate the hypothesis that cocaine-exposed children would perform more poorly than nonexposed children on executive functioning measures, we compared the mean Stroop and TMT scores of the groups. As shown in Table 2, cocaine-exposed children took significantly longer to complete the TMT part B than nonexposed children. A trend toward significance ( $P = .09$ ) was also found for lower Stroop color-word raw scores in the cocaine-exposed group.

Multiple regression analyses were used to assess the potential effects of PCE on the DTI and executive functioning measures while controlling a number of potentially confounding factors, namely, IQ, gender, and prenatal exposure to tobacco, alcohol, and marijuana. Interactions between PCE and gender and PCE and each of the other drugs were also included in the regression. In terms of the DTI measures, the model was significant for  $D_{av}$  in the left frontal callosal fibers ( $F = 2.81$ ; degrees of freedom [ $df$ ] = 10;  $P = .009$ ) and approached significance for FA in the left frontal callosal fibers ( $F = 1.96$ ;  $df = 10$ ;  $P = .06$ ). For  $D_{av}$  in the left frontal callosal fibers, significant main effects were found for prenatal exposure to alcohol ( $t = 2.05$ ;  $P = .05$ ) and marijuana ( $t = -2.27$ ;  $P = .03$ ), as well as a significant interaction between PCE and marijuana ( $t = 2.25$ ;  $P = .03$ ). The model accounted for 40% of the variance in  $D_{av}$  in the left frontal callosal fibers.

Figure 2 shows the mean  $D_{av}$  values in the left frontal callosal fibers by prenatal cocaine and marijuana exposure status. There is a clear separation between the lines for the 2 groups, with cocaine-exposed children showing higher  $D_{av}$  values than nonexposed children regardless of marijuana exposure. The highest (worst)  $D_{av}$  values were found among children with prenatal exposure to

both cocaine and marijuana followed by children with only PCE. Noncocaine-exposed children with no prenatal marijuana exposure had slightly higher (worse)  $D_{av}$  values than those with prenatal marijuana exposure; however, this finding should be interpreted with caution because there were only 2 children with solely prenatal marijuana exposure.

The multiple regression model was also significant for the TMT part B time ( $F = 4.61$ ;  $df = 10$ ;  $P = .0002$ ). There was a significant main effect for PCE ( $t = 2.38$ ;  $P = .02$ ) and a significant interaction between PCE and tobacco ( $t = -2.32$ ;  $P = .03$ ). The model explained 52% of the variance in performance on the TMT part B. Figure 3 shows the mean TMT part B time-to-completion by prenatal cocaine and tobacco exposure status. Because of the wide range of tobacco exposure in both groups (from 0 to 20 cigarettes per day), tobacco exposure was divided into low and high groups based on the median value (10 cigarettes per day) for all of the tobacco users. Again, there is a clear separation between the lines for the groups, such that children with PCE had a higher mean time-to-completion regardless of tobacco exposure status. There was a paradoxical effect, however, where children with PCE and high levels of prenatal tobacco exposure performed better than children with PCE and low levels of prenatal tobacco exposure.

Finally, correlational analyses were used to investigate relationships between the executive functioning and frontal white matter DTI measures. As seen in Table 3, 3 significant relationships were found between the executive functioning measures and FA (more directionality in the selected structures). Better performance on the Stroop color-word task was associated with increased FA in the left frontal callosal fibers ( $r = 0.29$ ;  $P$

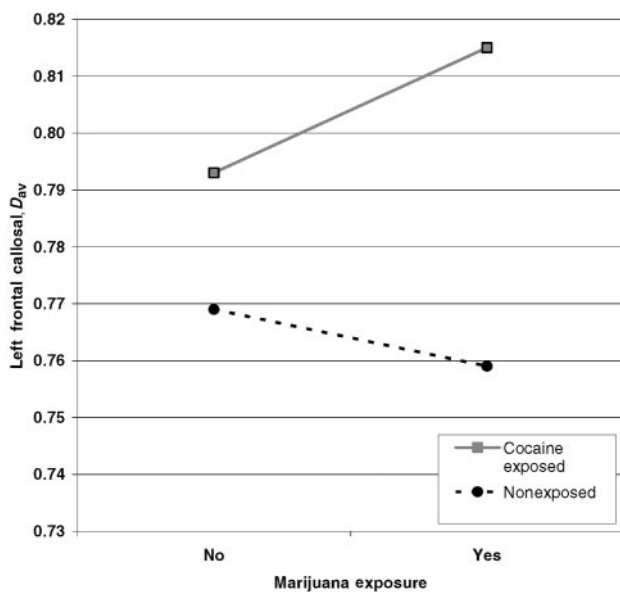


FIGURE 2 Relationship between prenatal cocaine and marijuana exposure and  $D_{av}$  in the left frontal callosal fibers.

= .03). Faster performance on the TMT part B was also associated with increased FA in the left frontal callosal fibers ( $r = -0.39$ ;  $P = .004$ ), as well as increased FA in the right frontal projection fibers ( $r = -0.27$ ;  $P = .05$ ). There was a trend for an association between faster performance on the TMT part A and increased FA in the left frontal callosal fibers ( $r = -0.24$ ;  $P = .08$ ). Figure 4 shows a scatterplot of the linear association of FA in the left frontal callosal fibers and TMT part B time. No significant correlations were found between the executive functioning measures and  $D_{av}$  in any of the ROIs.

## DISCUSSION

This study is the first to use DTI to investigate frontal white matter development in children with PCE. We found that children with PCE had significantly higher values of  $D_{av}$  (all directions) in 2 frontal white matter regions, the left frontal callosal and right frontal projection fibers, compared with controls. There was also a trend for higher  $D_{av}$  values in the right frontal callosal fibers in the group with PCE. Because  $D_{av}$  values in children are known to decrease with age and development, these differences could suggest less integrity and/or slower maturation of these areas in cocaine-exposed children.

No significant between-group differences were found for FA (more directionality) in the 4 frontal white matter ROIs examined. That group differences were found for  $D_{av}$  but not FA could be because of a number of factors, including the age of our sample, the areas studied, and the fact that, theoretically,  $D_{av}$  and FA are independent measurements<sup>40</sup> and may reflect different physiologic processes.<sup>33</sup> Our sample consisted of children between 10

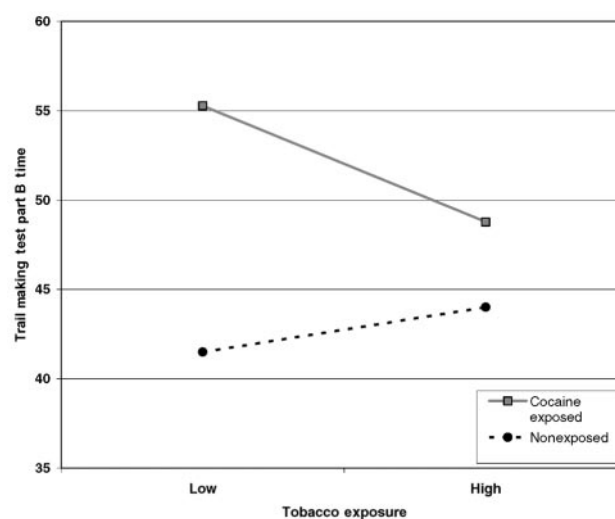


FIGURE 3 Relationship between prenatal cocaine and tobacco exposure and an executive functioning measure (TMT part B).

and 12 years old, and volumetric studies indicate that myelination of frontal white matter tracts continues well into adolescence and beyond.<sup>41,59-61</sup> In addition, FA is sensitive to the direction of greatest diffusion and is, therefore, limited in characterizing tracts with crossing fibers or fibers that are incoherently oriented. For example, relatively low FA values are typically found in the centrum semiovale and U-shaped fibers, although they are highly myelinated.<sup>62</sup> The white matter tracts that we chose may contain fibers that lack sufficient directional coherence for FA to provide a sensitive measure of their relative development. This is particularly likely for the frontal projection fibers, which include afferent and efferent fibers between cortical and subcortical areas, including the dorsolateral prefrontal cortex, caudate, dorsomedial nucleus of the thalamus, and reticular formation. Also, as shown in Fig 1, the frontal projection fiber tract that we chose for analyses is somewhat curved. Finally, it may be that  $D_{av}$  is more sensitive than FA to the changes associated with PCE. A study of patients with multiple sclerosis found that  $D_{av}$  was more sensitive than FA in detecting disease-related white matter changes.<sup>63</sup>

Multiple regression revealed that the variability of  $D_{av}$  in the left frontal callosal fibers in our sample was because of prenatal exposure to alcohol and marijuana in addition to an interaction between PCE and marijuana. The negative effects of alcohol, marijuana, and tobacco on brain development and executive functioning are well known.<sup>64</sup> The interaction between PCE and marijuana as seen in Fig 2 suggests that prenatal exposure to both cocaine and marijuana is worse than exposure to cocaine alone as measured by  $D_{av}$ . Although it seems from the figure that children with prenatal marijuana exposure but not cocaine exposure have better (lower)

**TABLE 3** Correlations Between Frontal White Matter Diffusion and Executive Functioning Measures (N = 53)

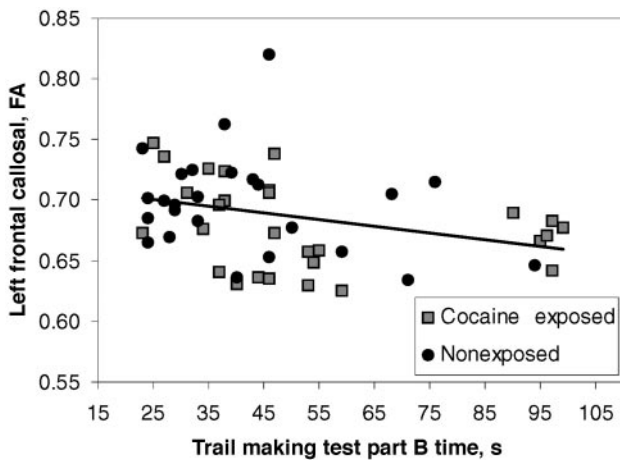
Variable	Stroop Color-Word Raw Score	TMT Part A Time, s	TMT Part B Time, s
Left frontal callosal $D_{av}$	-0.11	-0.16	-0.16
Left frontal projection $D_{av}$	-0.05	-0.14	0.05
Right frontal callosal $D_{av}$	-0.03	-0.13	-0.07
Right frontal projection $D_{av}$	0.06	0.10	0.10
Left frontal callosal FA	0.29 <sup>b</sup>	-0.24 <sup>c</sup>	-0.39 <sup>a</sup>
Left frontal projection FA	-0.09	0.11	-0.01
Right frontal callosal FA	0.10	-0.19	-0.20
Right frontal projection FA	0.14	-0.19	-0.27 <sup>b</sup>

$D_{av}$  indicates average diffusion (micrometers squared per millisecond); FA, fractional anisotropy (micrometers squared per millisecond).

<sup>a</sup>  $P \leq .01$ .

<sup>b</sup>  $P \leq .05$ .

<sup>c</sup>  $P \leq .10$ .



**FIGURE 4** Scatterplot and regression line showing the significant correlation between an executive functioning measure (TMT part B time) and FA in the left frontal callosal fibers.

$D_{av}$ , there were only 2 children in this group, casting doubt on the reliability of this finding.

This study also examined performance on 2 executive functioning measures in children with PCE. We found that the cocaine-exposed group was significantly slower on average than nonexposed children in completing a timed task that involves shifting between sequencing numbers and sequencing letters (TMT part B). Cocaine-exposed children also performed more poorly, although not significantly, on a timed task that requires inhibition of reading a color word in favor of naming the competing color ink in which the word is printed (Stroop color-word task). Poorer executive functioning in the cocaine-exposed children is consistent with other reports in the literature of visual attention and motor inhibition difficulties in this population.<sup>2-7</sup> A multiple regression analysis showed that performance on the TMT part B was significantly predicted by PCE and an interaction with PCE and prenatal tobacco exposure. Paradoxically, however, children with PCE and higher levels of prenatal tobacco exposure were faster rather than slower at com-

pleting the task than children with PCE and lower levels of tobacco exposure.

Finally, this study demonstrates a brain-behavior relationship between frontal white matter anisotropy and executive functioning performance. In the sample as a whole, better performance on both executive functioning measures was associated with greater anisotropic diffusion (FA) in the left frontal callosal fibers. Faster performance on the set-shifting task (TMT part B) was also associated with greater anisotropic diffusion (FA) in the right frontal projection fibers.

The association between Stroop color-word scores and FA in left frontal callosal fibers may be related to the verbal nature of the test and the fact that children may require bilateral hemispheric coordination to complete the task. Adleman et al<sup>53</sup> showed that developmentally specific Stroop-related activation of the left prefrontal cortex begins in adolescence and increases through early adulthood. The immature left hemisphere specialization in children could also explain why no association was found between Stroop performance and FA in the left frontal projection fibers that emanate from the prefrontal cortex. The association between the TMT part B performance and left frontal callosal FA may also be related to the language demands of the task (interpreting letters and numbers), whereas the association between TMT part B performance and right frontal projection FA may be because of the visual-spatial nature of the task (drawing lines to sequence symbols scattered randomly on a page). Functional MRI studies that evaluate activation patterns associated with the various task components of the TMT could further elucidate these brain-behavior relationships.

The significant correlations between one of the executive functioning measures and FA but not  $D_{av}$  is not unexpected. The few studies that have correlated cognitive performance with DTI measures have only used anisotropy measures.<sup>42</sup> Use of anisotropy measures is logical as a marker of myelination and axonal thickness, particularly in adults for whom brain maturation is considered complete. Notably, the single DTI study of cog-

nitive performance in children ages 7 to 13 years found significant correlations with FA in a temporoparietal area but not in a frontal area. We chose to examine possible correlations with  $D_{av}$  in part because there are so few data on the association between DTI and cognition in children and none in children with PCE. In addition, we thought that  $D_{av}$  may provide as useful an index of frontal lobe white matter development as FA in our sample of 10.5-year-olds, whose frontal lobes are expected to be less myelinated relative posterior cortical areas.

The study findings are presented as the first pieces of a puzzle designed to elucidate the effects of PCE on the developing brain. Many questions remain unanswered. For example, it is curious to us that the between-group differences were found for  $D_{av}$  in the left frontal callosal and right projection fibers but the significant correlations between one of the executive functioning measures was with FA for these same 2 structures. Also, the state of the science does not allow us to speculate as to laterality of the group differences in  $D_{av}$  (ie, higher  $D_{av}$  in callosal fibers on the left and the projection fibers on the right in the cocaine-exposed group). In addition, the paradoxical finding that PCE in combination with higher levels of prenatal tobacco exposure was associated with better executive functioning warrants further investigation and replication.

In future studies, we would like to evaluate the relative contribution of postnatal environmental factors on brain development and cognitive functioning in cocaine-exposed children. Environmental factors have been found to influence the development of executive functioning in typically developing children<sup>65</sup> and the development of dopaminergic innervation of the prefrontal cortex in laboratory animals.<sup>66,67</sup> The deleterious effects of trauma, maltreatment, and abuse on brain development have been shown in terms of total cerebral volume and changes in evoked related potentials and electroencephalogram studies.<sup>68</sup> For children with PCE, a number of studies have indicated that postnatal environmental factors, such as maternal psychological functioning, the caregiving environment, and early intervention, may have effects that are equal to, if not more important than, prenatal drug exposure on child functioning.<sup>9,10,69–71</sup> The possible effects on brain development of stressors associated with poverty and out-of-home placement early in life for the children with PCE in our cohort<sup>72</sup> merit close consideration as well.

## CONCLUSION

To better understand the outcomes of cocaine-exposed children, investigations will need to account for the teratogenic effects of multiple prenatal drug exposures and their possible interactions in the context of a variety of other environmental risk factors.

## ACKNOWLEDGMENTS

Financial support was provided by National Institutes of Health grants R01-DA05854 (to Drs Eyer and Behnke), R01-NF36992 (Dr Blackband), and the National High Magnetic Field Laboratory. MRI data were obtained at the Advanced Magnetic Resonance Imaging and Spectroscopy facility in the McKnight Brain Institute of the University of Florida.

We acknowledge the assistance of Ann Welch for coordination of the project, Vijay Komaragiri for data management, Kenneth Crandall for manual anatomical tracing, and Eric Corpus for article preparation.

## REFERENCES

1. Eyer FD, Behnke M. Early development of infants exposed to drugs prenatally. *Clin. Perinatol.* 1999;26:107–150
2. Bandstra ES, Morrow CE, Anthony JC, Accornero VH, Fried PA. Longitudinal investigation of task persistence and sustained attention in children with prenatal cocaine exposure. *Neurotoxicol Teratol.* 2001;23:545–559
3. Bendersky M, Gambini G, Lastella A, Bennett DS, Lewis M. Inhibitory motor control at five years as a function of prenatal cocaine exposure. *J Dev Behav Pediatr.* 2003;24:345–351
4. Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: effects on attention and impulsivity of 6-year olds. *Neurotoxicol Teratol.* 1999;21:109–118
5. Noland JS, Singer LT, Short EJ, et al. Prenatal drug exposure and selective attention in preschoolers. *Neurotoxicol Teratol.* 2005;27:429–438
6. Richardson GA, Conroy ML, Day NL. Prenatal cocaine exposure: Effects on the development of school-age children. *Neurotoxicol Teratol.* 1996;18:627–634
7. Savage J, Brodsky NL, Malmud E, Giannetta JM, Hurt H. Attentional functioning and impulse control in cocaine-exposed and control children at age ten years. *J Dev Behav Pediatr.* 2005;26:42–47
8. Frank DA, Augustyn M, Knight WG, Pell T, Zuckerman B. Growth, development, and behavior in early childhood following prenatal cocaine exposure: A systematic review. *JAMA.* 2001;285:1613–1625
9. Bennett DS, Bendersky M, Lewis M. Children's intellectual and emotional-behavioral adjustment at 4 years as a function of cocaine exposure, maternal characteristics, and environmental risk. *Dev Psychol.* 2002;38:648–658
10. Arendt RE, Short EJ, Singer LT, et al. Children prenatally exposed to cocaine: Developmental outcomes and environmental risks at seven years of age. *J Dev Behav Pediatr.* 2004;25:83–90
11. Singer LT, Minnes S, Short E, et al. Cognitive outcomes of preschool children with prenatal cocaine exposure. *JAMA.* 2004;291:2448–2456
12. Frank DA, Rose-Jacobs R, Beeghly M, Wilbur M, Bellingier D, Cabral H. Level of prenatal cocaine exposure and 48-month IQ: Importance of preschool enrichment. *Neurotoxicol Teratol.* 2005;27:15–28
13. Lezak MD, Howieson DB, Loring DW. *Neuropsychological Assessment.* 4th ed. New York, NY: Oxford University Press; 2004
14. Gioia GA, Isquith PK, Kenworthy L, Barton RM. Profiles of everyday executive function in acquired and developmental disorders. *Child Neuropsychol.* 2002;8:121–137
15. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci.* 2000;12:1–47
16. Fuster JM. *The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe.* New York, NY: Raven; 1997

17. Lidow MS. Consequences of prenatal cocaine exposure in non-human primates. *Dev Brain Res.* 2003;147:23–36
18. Whitaker-Azmitia PM. Role of the neurotrophic properties of serotonin in the delay of brain maturation induced by cocaine. *Ann N Y Acad Sci.* 1998;846:158–164
19. Scher MS, Richardson GA, Day NL. Effects of prenatal cocaine/crack and other drug exposure on electroencephalographic sleep studies at birth and one year. *Pediatrics.* 2000;105:39–48
20. Lester BM, Lagasse L, Seifer R, et al. The Maternal Lifestyle Study (MLS): effects of prenatal cocaine and/or opiate exposure on auditory brain response at one month. *J Pediatr.* 2003;142:279–285
21. Smith LM, Chang L, Yonekura ML, et al. Brain proton magnetic resonance spectroscopy and imaging in children exposed to cocaine in utero. *Pediatrics.* 2001;107:227–231
22. Ulug AM, Van Zijl PCM. Orientation-independent diffusion imaging without tensor diagonalization: Anisotropy definitions based on physical attributes of the diffusion ellipsoid. *J Magn Reson Imag.* 1999;9:804–813
23. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR Biomed.* 2002;15:435–455
24. Basser PJ, Jones DK. Diffusion-tensor MRI: Theory, experimental design and data analysis - A technical review. *NMR Biomed.* 2002;15:456–467
25. Le Bihan D, Mangin JF, Poupon C, et al. Diffusion tensor imaging: concepts and applications. *J Magn Reson Imag.* 2001;13:534–546
26. Watts R, Liston C, Niogi S, Ulug AM. Fiber tracking using magnetic resonance diffusion tensor imaging and its applications to human brain development. *Ment Retard Dev Disabil Res Rev.* 2003;9:168–177
27. Li TQ, Noseworthy MD. Mapping the development of white matter tracts with diffusion tensor imaging. *Dev Sci.* 2002;5:293–300
28. McGraw P, Liang L, Provenzale JM. Evaluation of normal age-related changes in anisotropy during infancy and childhood as shown by diffusion tensor imaging. *AJR Am J Roentgenol.* 2002;179:1515–1522
29. Morriss MC, Zimmerman RA, Bilaniuk LT, Hunter JV, Haselgrove JC. Changes in brain water diffusion during childhood. *Neuroradiology.* 1999;41:929–934
30. Mukherjee P, Miller JH, Shimony JS, et al. Normal brain maturation during childhood: developmental trends characterized with diffusion-tensor MR imaging. *Radiology.* 2001;221:349–358
31. Mukherjee P, Miller JH, Shimony JS, et al. Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. *Am J Neuroradiol.* 2002;23:1445–1456
32. Neil JJ, Shiran SI, McKinstry RC, et al. Normal brain in human newborns: apparent diffusion coefficient and diffusion anisotropy measured by using diffusion tensor MR imaging. *Radiology.* 1998;209:57–66
33. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study. *Radiology.* 2002;222:212–218
34. Schneider JF, Il'yasov KA, Hennig J, Martin E. Fast quantitative diffusion-tensor imaging of cerebral white matter from the neonatal period to adolescence. *Neuroradiology.* 2004;46:258–266
35. Ulug AM. Monitoring brain development with quantitative diffusion tensor imaging. *Dev Sci.* 2002;5:286–292
36. Zhang L, Thomas KM, Davidson MC, Casey BJ, Heier LA, Ulug AM. MR Quantitation of volume and diffusion changes in the developing brain. *Am J Neuroradiol.* 2005;26:45–49
37. Engelbrecht V, Scherer A, Rassek M, Witsack HJ, Modder U. Diffusion-weighted MR imaging in the brain in children: Findings in the normal brain and in the brain with white matter diseases. *Radiology.* 2002;222:410–418
38. Nagy Z, Westerberg H, Skare S, et al. Preterm children have disturbances of white matter at 11 years of age as shown by diffusion tensor imaging. *Pediatr Res.* 2003;54:672–679
39. Filippi CG, Lin DD, Tsiouris AJ, et al. Diffusion-tensor MR imaging in children with developmental delay: preliminary findings. *Radiology.* 2003;229:44–50
40. Neil J, Miller J, Mukherjee P, Huppi PS. Diffusion tensor imaging of normal and injured developing human brain - A technical review. *NMR Biomed.* 2002;15:543–552
41. Paus T. Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci.* 2005;9:60–68
42. Moseley M, Bammer R, Illes J. Diffusion-tensor imaging of cognitive performance. *Brain Cogn.* 2002;50:396–413
43. Deutsch GK, Dougherty RF, Bammer R, Siok WT, Gabrieli JD, Wandell B. Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex.* 2005;41:354–363
44. Klingberg T, Hedehus M, Temple E, et al. Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron.* 2000;25:493–500
45. Olesen PJ, Nagy Z, Westerberg H, Klingberg T. Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network. *Cogn Brain Res.* 2003;18:48–57
46. Eyster FD, Behnke M, Conlon M, Woods NS, Wobie K. Birth outcome from a prospective, matched study of prenatal crack/cocaine use: I. Interactive and dose effects on health and growth. *Pediatrics.* 1998;101:229–236
47. Halls SB, Hanson J Child growth charts for height, weight, and body mass index. Available at: [www.halls.md/chart/child-growth/pediatric.htm](http://www.halls.md/chart/child-growth/pediatric.htm). Accessed March 9, 2006
48. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children.* 3rd ed. San Antonio, TX: The Psychological Corporation; 1991
49. Wechsler D. *Manual for the Wechsler Individual Achievement Test.* San Antonio, TX: The Psychological Corporation; 1992
50. Golden CJ, Freshwater SM, Golden Z. *Stroop Color and Word Test Children's Version for Ages 5–14: A Manual for Clinical and Experimental Uses.* Wood Dale, IL: Stoelting Company; 2003
51. Reitan RM. Trail Making Test results for normal and brain-damaged children. *Percept Mot Skills.* 1971;33:575–581
52. MacLeod CM. Half a century of research on the Stroop effect: An integrative review. *Psychol Bull.* 1991;109:163–203
53. Adleman NE, Menon V, Blasey CM, et al. A developmental fMRI study of the Stroop color-word task. *NeuroImage.* 2002;16:61–75
54. Schroeter ML, Zysset S, Wahl M, von Cramon DY. Prefrontal activation due to Stroop interference increases during development—an event-related fNIRS study. *NeuroImage.* 2004;23:1317–1325
55. Reitan RM, Wolfson D. The Trail Making Test as an initial screening procedure for neuropsychological impairment in older children. *Arch Clin Neuropsychol.* 2004;19:281–288
56. Demakis GJ. Frontal lobe damage and tests of executive processing: A meta-analysis of the Category Test, Stroop Test, and Trail-Making Test. *J Clin Exp Neuropsychol.* 2004;26:441–450
57. Ozarslan E, Mareci TH. Generalized diffusion tensor imaging and analytical relationships between diffusion tensor imaging and high angular resolution diffusion imaging. *Magnet Reson Med.* 2003;50:955–965
58. Padgett KR. *Optimizing High Field T1 and Diffusion Tensor Structural Magnetic Resonance Imaging* [dissertation]. Gainesville, FL: University of Florida; 2005

59. Giedd JN, Blumenthal J, Jeffries NO, et al. Brain development during childhood and adolescence: A longitudinal MRI study. *Nat Neurosci*. 1999;2:861–863
60. Sowell ER, Thompson PM, Holmes CJ, Jernigan TL, Toga AW. In vivo evidence for post-adolescent brain maturation in frontal and striatal regions. *Nat Neurosci*. 1999;2:859–861
61. Spear LP. The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*. 2000;24:417–463
62. Pierpaoli C, Basser PJ. Toward a quantitative assessment of diffusion anisotropy. *Magnet Reson Med*. 1996;36:893–906
63. Castriota-Scanderbeg A, Fasano F, Hagberg G, Nocentini U, Filippi M, Caltagirone C. Coefficient Dav is more sensitive than fractional anisotropy in monitoring progression of irreversible tissue damage in focal nonactive multiple sclerosis lesions. *Am J Neuroradiol*. 2003;24:663–670
64. Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neurosci Biobehav Rev*. 2006;30:24–41
65. Klenberg L, Korkman M, Lahti-Nuutila P. Differential development of attention and executive functions in 3- to 12-year-old Finnish children. *Dev Neuropsychol*. 2001;20:407–428
66. Neddens J, Brandenburg K, Teuchert-Noodt G, Dawirs RR. Differential environment alters ontogeny of dopamine innervation of the orbital prefrontal cortex in gerbils. *J Neurosci Res*. 2001;63:209–213
67. Winterfeldt KT, Teuchert-Noodt G, Dawirs RR. Social environment alters both ontogeny of dopamine innervation of the medial prefrontal cortex and maturation of working memory in gerbils (*Meriones unguiculatus*). *J Neurosci Res*. 1998;52:201–209
68. Glaser D. Child abuse and neglect and the brain—a review. *J Child Psychol Psychiatry*. 2000;41:97–116
69. Accornero VH, Morrow CE, Bandstra ES, Johnson AL, Anthony JC. Behavioral outcome of preschoolers exposed prenatally to cocaine: role of maternal behavioral health. *J Pediatr Psychol*. 2002;27:259–269
70. Frank DA, Jacobs RR, Beeghly M, et al. Level of prenatal cocaine exposure and scores on the Bayley Scales of Infant Development: modifying effects of caregiver, early intervention, and birth weight. *Pediatrics*. 2002;110:1143–1152
71. Johnson HL, Nusbaum BJ, Bejarano A, Rosen TS. An ecological approach to development in children with prenatal drug exposure. *Am J Orthopsychiat*. 1999;69:448–456
72. Wobie K, Eyler FD, Garvan CW, Hou W, Behnke M. Prenatal cocaine exposure: an examination of out-of-home placement during the first year of life. *J Drug Issues*. 2004;34:77–94

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## Diffusion Tensor Imaging of Frontal White Matter and Executive Functioning in Cocaine-Exposed Children

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*Pediatrics* 2006;118;2014-2024

DOI: 10.1542/peds.2006-0003

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