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## **A Review of the Effects of Prenatal Cocaine Exposure Among School-Aged Children**

John P. Ackerman, Tracy Riggins and Maureen M. Black

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# A Review of the Effects of Prenatal Cocaine Exposure Among School-Aged Children

## abstract

**CONTEXT:** Studies through 6 years have shown no long-term direct effects of prenatal cocaine exposure (PCE) on children's physical growth, developmental test scores, or language outcomes. Little is known about the effects of PCE among school-aged children aged 6 years and older.

**OBJECTIVE:** We reviewed articles from studies that examined the effects of PCE on growth, cognitive ability, academic functioning, and brain structure and function among school-aged children.

**METHODS:** Articles were obtained by searching PubMed, Medline, TOXNET, and PsycInfo databases from January 1980 to December 2008 with the terms "prenatal cocaine exposure," "cocaine," "drug exposure," "substance exposure," "maternal drug use," "polysubstance," "children," "adolescent," "in utero," "pregnancy," "development," and "behavior." Criteria for inclusion were (1) empirical research on children aged 6 years and older prenatally exposed to cocaine, (2) peer-reviewed English-language journal, (3) comparison group, (4) longitudinal follow-up or historical prospective design, (5) masked assessment, (6) exclusion of subjects with serious medical disabilities, and (7) studies that reported nonredundant findings for samples used in multiple investigations. Thirty-two unique studies met the criteria. Each article was independently abstracted by 2 authors to obtain sample composition, methods of PCE assessment, study design, comparison groups, dependent variables, covariates, and results.

**RESULTS:** Associations between PCE and growth, cognitive ability, academic achievement, and language functioning were small and attenuated by environmental variables. PCE had significant negative associations with sustained attention and behavioral self-regulation, even with covariate control. Although emerging evidence suggests PCE-related alterations in brain structure and function, interpretation is limited by methodologic inconsistencies.

**CONCLUSIONS:** Consistent with findings among preschool-aged children, environmental variables play a key role in moderating and explaining the effects of PCE on school-aged children's functioning. After controlling for these effects, PCE-related impairments are reliably reported in sustained attention and behavioral self-regulation among school-aged children. *Pediatrics* 2010;125:554–565

**AUTHORS:** John P. Ackerman, PhD, Tracy Riggins, PhD, and Maureen M. Black, PhD

*Department of Pediatrics, University of Maryland School of Medicine, Baltimore, Maryland*

### KEY WORDS

cocaine, maternal exposure, prenatal exposure delayed effects, attention, behavior, growth, language, adolescent development

### ABBREVIATIONS

PCE—prenatal cocaine exposure

SES—socioeconomic status

GDS—Gordon Diagnostic System

fMRI—functional MRI

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Address correspondence to Maureen M. Black, PhD, University of Maryland School of Medicine, Department of Pediatrics, 737 W Lombard St, Room 161, Baltimore, MD 21201. E-mail: [mblack@peds.umaryland.edu](mailto:mblack@peds.umaryland.edu)

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The effects of prenatal cocaine exposure (PCE) have been examined in infants and young children across multiple developmental domains (eg, growth, intelligence, language, motor, attention, neurophysiology). A 2001 review of 36 peer-reviewed articles revealed that in most domains, the neurobiological effects of PCE play a subtle role, with effects no greater than other known teratogens or environmental factors.<sup>1</sup> Associations between PCE and negative developmental outcomes were typically attenuated when models included conditions that commonly co-occur with PCE (eg, tobacco or alcohol exposure, malnutrition, poor quality of care).

Little is known about the long-term effects of PCE. One possibility is that PCE has direct effects on brain structure or function, which may heighten children's vulnerability to negative developmental outcomes.<sup>2</sup> Another possibility is that PCE is a marker for environmental risk factors and, therefore, must be considered in the context of other developmental threats, including poverty, insensitive parenting, maternal stress and depression, caregiver drug dependence, limited educational resources, unstable home environments, and high rates of domestic violence.<sup>3-5</sup> Both perspectives highlight the need to consider the long-term effects of PCE within an environmental and developmental context that includes brain and behavioral development.

Over time, children face increasingly complex cognitive and social demands, requiring advances in aspects of executive control including sustained attention, working memory, planning, inhibitory control, and emotion regulation. Such higher-order processes are thought to underlie children's ability to engage in behavioral self-regulation, and preclinical models have suggested that PCE may target

brain regions and pathways associated with the development of these capabilities. Regions with strong dopaminergic innervation (eg, anterior cingulate cortex, prefrontal cortex, striatum) may be particularly susceptible to PCE.<sup>6</sup> Because these regions continue to develop throughout childhood and adolescence, the effects of PCE may not be evident until many years after the initial prenatal exposure.

The effects of PCE are manifest in distinct ways at different ages. Investigations using longitudinal models with covariate controls can examine the differential effects of drug exposure over time. Studies that include parenting and environmental influences (eg, school, neighborhood, peers) are necessary to determine the amount of variance attributed to each level of influence. We reviewed studies of PCE conducted with children aged 6 years and older, focusing on outcomes associated with physical, behavioral, cognitive, and neural development.

## METHODS

### Selection Criteria

We used the following criteria: (1) empirical research on children aged 6 years and older with PCE; (2) publication in peer-reviewed English-language journal between January 1980 and December 2008; (3) comparison group; (4) longitudinal follow-up or historical prospective design; (5) masked assessment; (6) not exclusive focus on pathology (eg, very low birth weight, HIV, brain injury, mental retardation, or other serious medical complications); and (7) production of findings that were distinct from previous reports from the same sample.

### Data Sources

Articles were obtained from PubMed, Medline, TOXNET, and PsycInfo by entering key words "prenatal cocaine ex-

posure," "cocaine," "drug exposure," "substance exposure," "maternal drug use," "polysubstance," "children," "adolescent," "in utero," "pregnancy," "development," and "behavior" alone and in combinations. References of selected articles were searched to identify additional articles that met selection criteria. We identified 32 unique studies of children and adolescents with PCE; 28 (88%) were published after 2003, representing children in longitudinal cohorts who have reached school age.

### Procedures

Eligible articles were reviewed independently by 2 authors to determine (1) domain assessed, (2) sample composition, (3) determination of PCE, (4) design and retention, (5) outcome variables and covariates, (6) results, and (7) methodologic strengths and limitations.

## RESULTS

Fifteen cohorts were represented in the 32 articles reviewed. Sample sizes ranged from 26 to 1056, with a median of 188. Twenty-seven studies (84%) enrolled participants prospectively when infants were younger than 6 months. Most studies (94%) used urine toxicology and/or meconium assay in combination with maternal report to determine PCE. Six studies (19%) examined dose-response effects of PCE.

All samples comprised polysubstance-exposed children, typically with high rates of tobacco, alcohol, and marijuana exposure. Samples for which demographic data were reported were urban, most were low income (3 had no income data), and most (94%) enrolled primarily black participants. The caregiver-child relationship often differed between the PCE and comparison groups. Twenty-two studies (69%) provided nonmaternal care status,

and 6 (19%) provided data on kinship status.

### Physical Growth

Six studies examined children's growth (Table 1).<sup>7-12</sup> Despite significant differences in weight, height, and head circumference at birth, there were few significant growth differences at school age.<sup>8-11</sup> Catch-up growth generally occurs by 6 months.<sup>11</sup> Four studies

found no significant PCE-related differences in weight or weight for age. One study revealed that children with PCE who were assessed at 1, 3, 7, and 10 years grew at a slower rate than comparison children.<sup>12</sup> Another study found that PCE dose was associated with weight-for-height standard scores.<sup>10</sup> In both studies, children with PCE had weight for age within normal

limits, which suggests that even those who were lighter than comparison children remained within normal limits.

Evidence for PCE differences in linear growth (ie, height) was mixed. Three studies showed no differences in children's height for age. Three studies revealed that children with PCE were shorter than nonexposed children (<1

**TABLE 1** Physical Growth

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Exposures	Selection/Matching	Control	PCE Effect	Other Effects/Comments
Covington et al <sup>7</sup> (2002), cohort 1	231 POLY, 309 CON	Weight, height	7	C, A, T	Low income, urban, black, GA > 38 wk	Child: T, BW, BL, nonmaternal care, blood lead level; caregiver: age, height, weight, SES, substance use, marital status, psychopathology, social support	Weight: none; height: PCE shorter	Associations stronger for caregiver > 30 y old; alcohol exposure contributed to lower weight
Arendt et al <sup>8</sup> (2004), cohort 2	101 POLY, 130 CON	Weight, height, HC	7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, race, nonmaternal care; caregiver: age, IQ, SES, parity, psychopathology, home environment	None	Groups differed on numerous prenatal and environmental variables
Kilbride et al <sup>9</sup> (2006), cohort 3	39 POLY, 12 CON	Weight, height	7	C, A, T	Low income, urban, black	Child: A, T	None	RCT, early intervention; high attrition rate; limited power
Minnes et al <sup>10</sup> (2006), cohort 4	154 POLY, 131 CON	Weight, height, morphology, neuromotor functioning	6-7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, race, nonmaternal care; caregiver: age, IQ, SES, parity, psychopathology, home environment	Height: PCE dose associated with shorter stature; weight: PCE dose associated with lower weight-for-height scores	No morphology or neuromotor findings
Lumeng et al <sup>11</sup> (2007), cohort 5	112 POLY, 90 CON	Weight, height, HC	6-7	C, A, M, T	Low income, urban, black, GA > 36 wk	Child: A, M, T gender, race, GA, nonmaternal care, blood lead level, anemia; caregiver: age, height, weight	None	No PCE dose associations reported
Richardson et al <sup>12</sup> (2007), cohort 6	99 POLY, 125 CON	Weight, height, HC	7, 10	C, A, M, T	Low income, urban, 50% black, 50% white, GA > 34 wk	Child: A, M, T gender, race, age, nonmaternal care; caregiver: age, height, SES, education, marital status, depression, home environment	Height: children with PCE shorter at 7 and 10 y; weight: children with PCE lighter at 7 and 10 y; HC: children with PCE smaller HC at 7 and 10 y	Children with PCE were 0.75 in shorter, 10 lb lighter than CON children at age 10 y; age and gender moderated effects

POLY indicates exposure to multiple drugs; CON, nonexposed controls; C, cocaine exposure; A, alcohol exposure; T, tobacco exposure; GA, gestational age; BW, birth weight; BL, birth length; HC, head circumference; M, marijuana exposure; RCT, randomized control trial.

in) at school age after controlling for relevant covariates including prenatal tobacco and alcohol exposure, comorbid drug use, ethnicity, parent height, and maternal care status.<sup>7,10,12</sup> In addition, PCE dose was associated with a small decrease in height.<sup>10</sup> Overall, despite significant growth differences between PCE and nonexposed children at birth, height and weight differences were typically small or absent by school age.

### Global Intellectual Functioning and Academic Achievement

Eight studies examined intellectual or academic functioning (Table 2).<sup>3,4,8,9,13–16</sup> Children ranged in age from 6 to 12 years. Only 1 study showed that children with PCE had significantly lower full-scale IQ scores on standardized assessments of intellectual functioning than comparison children,<sup>8</sup> and these differences were substantially attenuated with the inclusion of maternal and environmental covariates. One study did not reveal overall IQ differences, but it was reported that children with PCE performed worse on perceptual reasoning tasks than comparison children and that results were mediated by head circumference.<sup>16</sup> Of the 4 studies that assessed academic achievement,<sup>3,4,14,16</sup> it was reported for only 1 that comparison children scored higher than children with PCE.<sup>14</sup> Most studies included in this review had low-income, urban samples with mean IQ scores between 0.5 and 1.0 SDs below the mean.

### Language Functioning

Five studies examined language functioning, including expressive, receptive, and global language functioning, with mixed results (Table 3).<sup>9,13,17,18,19</sup> Three studies that examined language longitudinally<sup>17–19</sup> found small but persistent PCE differences after controlling for relevant environmental and prenatal covariates. Language-related

differences were documented early in development and persisted to the same relative degree at school age.<sup>17,19</sup> In the only study that assessed children through the age of 9 years,<sup>18</sup> PCE differences were not evident after controlling for environmental covariates. Evidence for dose-response effects was also inconsistent. Environmental factors such as caregiver sensitivity, vocabulary, and socioeconomic status (SES) contributed significantly to child language functioning, whereas PCE effect sizes were often small (0.07–0.20 SDs).

### Behavioral Functioning

Eight studies targeted behavioral functioning (Table 4).<sup>3,4,9,20–24</sup> Most of them used parent and/or teacher report of internalizing and externalizing behaviors. Six studies revealed significant differences in behavioral functioning, all favoring nonexposed children<sup>3,20–24</sup>; however, they varied regarding the covariates and moderators in the analyses. Effect sizes for externalizing behavior problems (eg, aggression and attention) were generally small (average: 0.20 SD) and nonsignificant for internalizing behavior problems (average: 0.10 SD). Most studies, however, relied on behavioral rating scales rather than clinical interviews or other more sensitive diagnostic instruments.

In a dose-response analysis, high PCE was associated with more externalizing and total behavior problems at the age of 7 years than low or no PCE, even after covariate adjustment, including alcohol, tobacco, caregiver depression, and nonmaternal care.<sup>20</sup> In 3 other studies,<sup>21,23,24</sup> gender moderated behavioral outcomes; boys were at greater risk than girls for delinquency and aggression among PCE children. Three of 4 studies showed that nonmaternal care predicted externalizing problems.<sup>4,20,22</sup>

### Attention

Four unique studies examined sustained attention or aspects of executive control by using performance-based neuropsychological measures (Table 5)<sup>25–28</sup> such as the Gordon Diagnostic System (GDS),<sup>29</sup> the Test of Variables of Attention,<sup>30</sup> and Connors' Performance Test.<sup>31</sup> Children with attention problems exhibited poor performance with frequent omissions, an impulsive response style, or variable reaction times.<sup>30</sup> Poor performance has been linked to deficient frontal lobe regulatory functioning.<sup>32</sup>

In one study the GDS was used to assess attention,<sup>27</sup> and it was reported that children with PCE were more likely to demonstrate commission errors than nonexposed comparison children, after covariate control. Two studies assessed children's sustained attention by using visual continuous performance tasks at the ages of 6 and 7 years.<sup>25,26</sup> Both studies revealed PCE differences in reaction time and omission errors but not commission errors.<sup>25</sup> Covariates such as task complexity, nonmaternal care, and quality of caregiving environment influenced children's attention. An additional study, in which a novel visuospatial maze learning task<sup>28</sup> was used, showed that children with PCE made more delayed recall errors than controls and displayed slower processing speed on visuospatial learning tasks.

The mechanisms that underlie sustained attention and other aspects of executive control may be disrupted by PCE. However, the specific effects of PCE may depend on moderators, including drug type and dose, alcohol and/or tobacco exposure, child age, gender, and environmental factors (eg, SES, nonmaternal care, and caregiving quality).

**TABLE 2** Global Intellectual Functioning and Academic Achievement

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Exposures	Selection/Matching	Control	PCE Effect	Other Effects/Comments
Nair et al <sup>5</sup> (2008), cohort 7	111 POLY, 62 CON	Stanford-Binet IV	6–7	C, T, H	Low income, urban, black, GA > 32 wk	Child: T, gender, age, nonmaternal care; caregiver: SES, employment, depression, home environment	None	Girls had higher scores on overall IQ and 4 of 8 Stanford-Binet IV subtests
Hurt et al <sup>4</sup> (2005), cohort 8	62 POLY, 73 CON	WPPSI-R; Stanford-9 reading, math, and science achievement	9–12	C, A, M, T	Low income, urban, black, GA > 34 wk	Child: gender, age, nonmaternal care; caregiver: substance use, home environment	None	School outcomes were predicted by child IQ, home environment, history of foster care, and computerized attention scores
Arendt et al <sup>8</sup> (2004), cohort 2	101 POLY, 130 CON	WISC-III	7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, race, nonmaternal care; caregiver: age, IQ, SES, parity, psychopathology, home environment	None	Unadjusted PCE deficits in full-scale and verbal IQ were attenuated after controlling for prenatal and environmental covariates; maternal IQ and home environment predicted child IQ
Kilbride et al <sup>9</sup> (2006), cohort 3	39 POLY, 12 CON	Stanford-Binet-III	7	C, A, T	Low income, urban, black	Child: A, T	None	RCT, early intervention; high attrition rate; limited power
Delaney-Black et al <sup>13</sup> (2000), cohort 1	186 POLY, 272 CON	WPPSI-R	6	C, A, M, T	Low income, urban, black, GA > 38 wk	Child: BW, BL, HC, age, gender, race, blood lead level, nonmaternal care; caregiver: age, education, marital status, substance use, SES, hypertension, home environment	None	None
Morrow et al <sup>14</sup> (2006), cohort 9	212 POLY, 197 CON	WISC-III; WIAT math and reading subtests	7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, BW, BL, HC, age, gender, blood lead level, Head Start attendance, nonmaternal care; caregiver: age, education, marital status, substance use, employment, home environment	None	Children with PCE were 3 times more likely than CON children to meet criteria for learning disability; no PCE dose effect; both groups below age-level expectations
Wasserman et al <sup>15</sup> (1998), cohort 10	98 POLY, 108 CON	WISC-III; Raven's Matrices	6–9	C, A, M, T	Low income, urban, black	Child: BW, age, gender, height, HC, blood lead level, nonmaternal care; caregiver: age, IQ, education, SES, substance use, home environment	None	Social adversity factors were strongest predictors of child IQ; both groups below age-level expectations
Singer et al <sup>16</sup> (2008), cohort 11	192 POLY, 179 CON	WISC-IV; Woodcock Johnson-III Tests of Achievement	9	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: BW, BL, HC, age, gender, race, blood lead level, nonmaternal care; caregiver: age, IQ, parity, prenatal care, education, marital status, substance use, employment, home environment	Children with PCE had lower perceptual reasoning scores	Perceptual reasoning deficits among children with PCE mediated by HC; no PCE effects for academic achievement

POLY indicates exposure to multiple drugs; CON, nonexposed controls; C, cocaine exposure; A, alcohol exposure; T, tobacco exposure; H, heroin exposure; GA, gestational age; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised edition; M, marijuana exposure; WISC, Wechsler Intelligence Scale for Children; WIAT, Wechsler Individual Achievement Test; RCT, randomized, controlled trial; BW, birth weight; BL, birth length; HC, head circumference.

**TABLE 3** Language Functioning

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Selection/Matching Exposures	Control	PCE Effect	Other Effects/Comments	
Kilbride et al <sup>19</sup> (2006), cohort 3	39 POLY, 12 CON	CELF-3	7	C, A, T	Low income, urban, black	Child: A, T	None	RCT, early intervention; high attrition rate; limited power
Bandstra et al <sup>17</sup> (2004), cohort 9	200 POLY, 176 CON	CELF-P; NEPSY Language Core; WISC-III short form	3, 5, 7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, BW, BL, HC, age, gender, blood lead level, Head Start attendance, nonmaternal care; caregiver: age, education, marital status, substance use, employment, home environment	Children with PCE had lower language functioning at each time point (~0.2 SD)	PCE dose associated with subtle differences in children's language at ages 3, 5, and 7 y; No differences in developmental trajectories of PCE and CON groups
Delaney-Black et al <sup>13</sup> (2000), cohort 1	186 POLY, 272 CON	Arizona Articulation Proficiency Scale; language samples coded from a dyadic interaction with an examiner	6	C, A, M, T	Low income, urban, black, GA > 38 wk	Child: BW, BL, HC, age, gender, race, blood lead level, nonmaternal care; caregiver: age, education, marital status, substance use, SES, hypertension, home environment	None	No PCE differences in expressive language; children with poor language were 2.4 times more likely to have had PCE; quality of language samples did not differ between PCE and CON children
Beeghly et al <sup>18</sup> (2006), cohort 5	85 POLY, 75 CON	Test of Language Development-3; CELF-3	6, 9.5	C, A, M, T	Low income, urban, black, GA > 36 wk	Child: A, M, T, gender, race, IQ, nonmaternal care, blood lead level, early intervention status; caregiver: age, race, education, parity, verbal IQ, SES, household size, substance use	Children with PCE had lower receptive language scores at 6 y of age but not at 9 y of age; no total language differences after controlling for covariates; no PCE dose associations	Positive predictors of language were caregiver verbal IQ, Head Start, no violence exposure, placement in nonkin foster care; outcomes moderated by BW, age, and gender
Lewis et al <sup>19</sup> (2007), cohort 11	192 POLY, 179 CON	Preschool Language Scale-3rd Edition (age 1-2); CELF-P (age 4); CASL (age 6)	1, 2, 4, 6	C, A, M, T	Low income, urban, black	Child: A, M, T, BW, BL, HC, age, gender, race, blood lead level, nonmaternal care; caregiver: age, IQ, receptive vocabulary, education, marital status, substance use, prenatal care, parity, SES, home environment, psychopathology	Children with PCE had lower language scores at each age assessed	Children with PCE demonstrated language deficits across all time points of ~0.20 SD; male and AA children scored ~0.33 SD below sample mean; no PCE dose association; home environment and caregiver language functioning were correlated to child language outcomes

POLY indicates exposure to multiple drugs; CON, nonexposed controls; CELF, Children's Evaluation of Language Fundamentals; C, cocaine exposure; A, alcohol exposure; T, tobacco exposure; RCT, randomized, controlled trial; NEPSY, Developmental Neuropsychological Assessment; WISC, Wechsler Intelligence Scale for Children; GA, gestational age; M, marijuana exposure; BW, birth weight; BL, birth length; HC, head circumference; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence-Revised edition; CASL, Comprehensive Assessment of Spoken Language.

**TABLE 4 Behavioral Functioning**

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Exposures	Selection/Matching	Control	PCE Effect	Other Effects/Comments
Nair et al <sup>1</sup> (2008), cohort 7	111 POLY, 62 CON	CBCL	6–7	C, T, H	Low income, urban, black, GA > 32 wk	Child: T, gender, age, nonmaternal care; caregiver: SES, employment, depression, home environment	None	Behavior differences attenuated after controlling for environmental covariates; boys displayed higher levels of attention problems and aggression than girls
Hurt et al <sup>4</sup> (2005), cohort 8	62 POLY, 73 CON	CBCL; TRF	9–12	C, A, M, T	Low income, urban, black, GA > 34 wk	Child: gender, age, nonmaternal care; caregiver: substance use, home environment	None	Despite numerous prenatal and environmental differences, no PCE effects were reported; high attrition may have contributed to limited power
Kilbride et al <sup>8</sup> (2006), cohort 3	39 POLY, 12 CON	CBCL, coded parent-child play interactions	7	C, A, T	Low income, urban, black	Child: A, T	None	RCT, early intervention; high attrition rate; limited power; Case-managed PCE group showed more positive interactions than PCE routine care group in play paradigm
Bada et al <sup>10</sup> (2007), cohort 2	658 POLY, 730 CON	CBCL	3, 5, 7	C, A, H, M, T	Low income, urban, black, GA > 32 wk	Child: A, H, M, T, HC, gender, race, violence exposure, nonmaternal care; caregiver: age, substance use, home environment, psychopathology	Children with PCE had more negative behavioral functioning; increased PCE dose was associated with negative trajectories of internalizing, externalizing, and total behavior problems	Additional negative effects on behavior outcomes are observed when PCE co-occurred with prenatal and postnatal tobacco and alcohol exposure; violence exposure and caregiver depression have a negative influence on all behavioral outcomes
Bennett et al <sup>21</sup> (2007), cohort 12	60 POLY, 94 CON	Self-reported substance use, aggression, and disregard for safety on Youth Risk Behavior Survey	10	C, A, M, T	Low income, urban, black, GA > 32 wk	Child: A, M, T, age, gender, race, blood lead level, neonatal medical problems, nonmaternal care; caregiver: SES, substance use, environmental risk	No direct PCE effects	Gender moderated PCE effects such that boys with PCE reported more high risk behavior than girls with PCE as measured by a composite health risk behavior score and more current tobacco use
Linares et al <sup>22</sup> (2006), cohort 11	169 POLY, 153 CON	CBCL; Dominic interactive (child self-report)	9	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, BW, BL, HC, age, gender, race, blood lead level, nonmaternal care; caregiver: age, IQ, prenatal care, education, marital status, substance use, home environment, psychopathology	Children with PCE self-reported higher average number of oppositional-defiant and ADHD symptoms than CON children; no CBCL differences	Only child self-reported PCE differences; Nonmaternal caregivers of children with PCE reported a higher number of externalizing behavior problems
Nordstrom Bailey et al <sup>23</sup> (2005), cohort 1	214 POLY, 285 CON	TRF	6–7	C, A, M, T	Low income, urban, black, GA > 38 wk	Child: A, T, BW, age, IQ, gender, race, blood lead level, violence exposure, nonmaternal care; caregiver: age, IQ, education, marital status, substance use, SES, social support, home environment	No PCE direct effects	Despite an absence of direct PCE effects, boys with PCE and alcohol exposure and girls with PCE and no alcohol exposure had elevated externalizing behavior scores
Sood et al <sup>24</sup> (2005), cohort 1	214 POLY, 285 CON	CBCL	6–7	C, A, M, T	Low income, urban, black, GA > 38 wk	Child: A, T, BW, age, IQ, gender, race, blood lead level, violence exposure, nonmaternal care; caregiver: age, IQ, education, marital status, substance use, SES, social support, home environment, psychopathology	No PCE direct effects	Findings extend teacher-report data from Nordstrom Bailey et al <sup>23</sup> and suggest that gender and alcohol exposure moderate associations between PCE and caregiver report of child aggression and delinquency

POLY indicates exposure to multiple drugs; CON, nonexposed controls; CBCL, Child Behavior Checklist (parent form); C, cocaine exposure; H, heroin exposure; AA, African American/black; GA, gestational age; TRF, Achenbach Teacher Report Form; A, alcohol exposure; M, marijuana exposure; ADHD, attention-deficit/hyperactivity disorder; RCT, randomized, controlled trial; HC, head circumference; BW, birth weight; BL, birth length.



**TABLE 5** Attention

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Exposures	Selection/ Matching	Control	PCE Effect	Other Effects/Comments
Accornero et al <sup>25</sup> (2007), cohort 9	219 POLY, 196 CON	TOVA; CPT; CBCL attention scale; NEPSY attention/executive function domain	5, 7	C, A, M, T	Low income, urban, black, GA > 37 wk	Child: A, M, T, BW, BL, HC, age, IQ, gender, blood lead level, special services, nonmaternal care; caregiver: age, education, marital status, substance use, employment, home environment	Children with PCE made more omission errors, had slower response time, and more response-time variability on computerized sustained attention tasks	Children with PCE performed 0.25–0.32 SD below CON children on sustained attention measures from 3–7 y of age; children with PCE displayed slower response time and greater variability at 7 y of age and more omission errors 5 and 7 y of age
Ackerman et al <sup>26</sup> (2008), cohort 7	88 POLY, 56 CON	CPT	7	C, A, T, H	Low income, urban, black, GA > 32 wk	Child: BW, age, IQ, gender, nonmaternal care; caregiver: age, IQ, education, marital status, substance use, SES, employment, early-intervention status, psychopathology	Children with PCE in maternal care displayed more omission errors on computerized sustained attention task	Findings indicated that children with PCE raised in a drug-using context may be vulnerable to attention problems
Savage et al <sup>27</sup> (2005), cohort 8	40 POLY, 40 CON	GDS; Trail Making Test; Seashore Rhythm Test	10	C, A, T, M	Low income, urban, black, GA > 32 wk	Child: IQ, gender, nonmaternal care; caregiver: substance use	Children with PCE made more commission errors on the most difficult distractibility task on the GDS	No differences between PCE and CON children on attention or impulsivity except when cognitive demands were high; limited power, high attrition reported
Schroder et al <sup>28</sup> (2004), cohort 13	40 POLY, 11 CON	Groton Maze Learning Test	8	Not reported	Low income, black, GA not reported	Child: IQ	Children with PCE displayed slower visual-motor speed and made more errors on a delayed procedural learning task	Children with PCE were less efficient at completing visual mazes, particularly after a delay; limited sample size and covariate control

POLY indicates exposure to multiple drugs; CON, nonexposed controls; TOVA, Test of Variables of Attention; CBCL, Child Behavior Checklist (parent form); CPT, Conners' Continuous Performance Test; NEPSY, Developmental Neuropsychological Assessment; C, cocaine exposure; A, alcohol exposure; M, marijuana exposure; T, tobacco exposure; GA, gestational age; BW, birth weight; BL, birth length; HC, head circumference; H, heroin exposure.

### Brain Structure and Function

Eight studies used neuroimaging methodologies to examine brain structure and function (Table 6).<sup>33–40</sup> Differences in both gray and white matter were reported. The PCE groups had global decreases in cortical gray matter,<sup>34</sup> and selective volumetric decreases in the left occipital lobe, right parietal cortex<sup>38</sup> and caudate.<sup>33,40</sup> Volumetric increases were reported in the

amygdala.<sup>40</sup> PCE-related differences in white matter include decreased volume of the corpus callosum,<sup>38</sup> increased diffusion in bilateral frontal projection fibers,<sup>36</sup> and increased levels of creatine in frontal white matter<sup>36</sup> suggesting abnormalities in energy metabolism and less mature development of frontal white matter pathways. Differences in gray and white matter varied as a function of the amount of

substance exposure<sup>36,38</sup> and number of substances to which the fetus was exposed.<sup>54</sup> Two investigations reported correlations between gray and white matter differences and behavioral task performance were reported.<sup>36,38</sup> These studies provide evidence that PCE disrupts frontally mediated tasks. However, small sample sizes, lack of covariate control, and sample selection limit generalizability.

**TABLE 6** Brain Structure and Function

Study/Cohort	Subjects	Outcome Measures	Age, y	Substance Exposures	Selection/Matching	Control	PCE Effect	Other Effects/Comments
Avants et al <sup>13</sup> (2007), cohort 8	25 POLY, 24 CON	Bilateral caudate volume	14	C, A, T, M	Low income, black, GA > 34 wk	None reported	Children with PCE had smaller caudate	PCE is associated with reduced caudate volume; caudate is an area of dopaminergic innervation and implicated in attention; limited sample size and covariate control
Rivkin et al <sup>14</sup> (2008), cohort 5	14 POLY, 21 CON	Volumes of cortical gray and white matter; subcortical gray matter, cerebral spinal fluid, and total parenchyma, HC	12	C, A, T, M	Low income, black, GA > 36 wk	Child: A, M, T, age, gender, total intracranial volume	Children with PCE had reduced cortical gray, total parenchymal volumes, and HC	As number of prenatal substance exposures increased, cortical gray and total parenchymal volume decreased; smallest volumes found in children with PCE exposed to multiple substances; limited sample size and covariate control
Hurt et al <sup>15</sup> (2008), cohort 8	17 POLY, 17 CON	Behavioral accuracy to nonspatial working memory task and mean BOLD signal from fMRI	14	C, A, T, M	Low income, urban, black, GA > 34 wk	Discrimination scores from behavioral task, no covariates but matched by gender and IQ	None	No PCE effects detected in behavioral or imaging data; limited sample size and covariate control
Warner et al <sup>16</sup> (2006), cohort 14	28 POLY, 25 CON	Frontal white matter integrity using DTI during Stroop and Trail Making Test	10	C, A, T, M	Black, GA > 36 wk	Child: A, M, T, IQ, gender	DTI: children with PCE had higher average diffusion coefficients in frontal fibers; Behavior: children with PCE had longer completions times on part B of the Trail Making Test	PCE was related to higher diffusion values in frontal white matter, which suggests less integrity and/or slower maturation of frontal areas; differences were related to poorer performance on Trail Making Test by PCE group
Smith et al <sup>17</sup> (2001), cohort 15	14 POLY, 12 CON	Whole and regional brain volumes; metabolite concentrations using <sup>1</sup> H-MRS in right frontal white matter and right striatum	8–9	Not reported	Variable SES, urban, 40% black, 40% white, GA > 36 wk	Child: age, gender	Volume: none; Metabolites: children with PCE had a 13% increase in right frontal white matter levels of creatine	Increased creatine found in right frontal white matter suggests that biochemical changes caused by PCE may occur at cellular level; no evidence for PCE-related structural or volumetric damage; limited sample size and covariate control
Singer et al <sup>18</sup> (2006), cohort 11	21 POLY, 14 CON	Gray and white matter volumes; NEPSY subtests; CASL	8	C, A, T, M	Low income, urban, black, GA > 37 wk	Not reported	Volume: children with PCE had gray matter reductions in occipital and parietal lobes; White matter reductions in corpus callosum; PCE dose effects for gray and white matter volume	PCE associated with long-term changes in brain composition, which were related to performance on neuropsychological tests; limited sample size and covariate control
Mayes et al <sup>19</sup> (2005), cohort 13	15 POLY, 14 CON	Reaction time, accuracy, latency and amplitude of ERP signals during a Stroop paradigm	8	C, A, T, M	Urban, black, GA not reported	Experimental and control groups were matched on the basis of age, race, and SES; no covariate control	Children with PCE had slower and prolonged ERP signals across a wider range of electrode sites	Brain responses in PCE group were slower and more distributed suggesting PCE inhibits regional specialization; limited sample size and covariate control
Rao et al <sup>10</sup> (2007), cohort 8	25 POLY, 24 CON	Absolute and relative CBF using perfusion fMRI, overall and regional gray matter volume in frontal lobe, limbic structures, occipital lobe, and thalamus	14	C, A, T, M	Low income, urban, black, GA > 34 wk	Child: age, gender, global CBF and gray matter volume	CBF: children with PCE had reduced global CBF intensities in posterior and inferior brain regions and relative increases in adjusted-CBF in anterior and superior brain regions; Volume: children with PCE had regional decreases in gray matter in caudate and increased gray matter in amygdala	PCE was related to reductions in global CBF during adolescence and specific gray matter alterations, which suggests that compensatory mechanisms may develop during neural ontogeny; limited covariate control

POLY indicates exposure to multiple drugs; CON, nonexposed controls; C, cocaine exposure; A, alcohol exposure; T, tobacco exposure; M, marijuana exposure; GA, gestational age; HC, head circumference; BOLD, blood oxygen level dependent; DTI, diffusion tensor imaging; <sup>1</sup>H-MRS, proton magnetic resonance spectroscopy; NEPSY, Developmental Neuropsychological Assessment; CASL, Comprehensive Assessment of Spoken Language; ERP, event-related potential; CBF, cerebral blood flow.

Three studies that examined brain function related to PCE revealed mixed results.<sup>35,39,40</sup> One reported reductions in global cerebral blood flow, with increases in anterior and superior regions during rest with perfusion functional MRI (fMRI).<sup>40</sup> Another examined electrical brain responses (ie, event-related potentials) during an inhibitory control task and showed that the PCE group had slower, more prolonged event-related potential responses and a more diffuse pattern of activation than the comparison group.<sup>39</sup> The third study revealed PCE differences in regional oxygenated blood flow by using blood oxygen level dependent contrast during a nonspatial working memory fMRI task.<sup>35</sup>

The limited data suggest subtle differences between PCE and nonexposed children on measures of brain structure and function. However, these findings await replication, because distinct methods and data-analysis techniques have been used with small samples of polysubstance-exposed children with minimal control for potentially confounding environmental factors.

## DISCUSSION

There are 4 major findings regarding outcomes in school-aged children with PCE. First, associations between PCE and indices of growth, intellectual functioning, academic achievement, and language functioning are modest and often explained by social risk factors such as poverty, caregiver education, placement stability, and quality of child-caregiver relationships. Children with PCE encounter more environmental risk, making it difficult to disentangle the 2 effects. For example, it is unclear whether PCE contributes to disruptive behaviors, which increases the possibility of out-of-home placement, or whether caregiver instability leads to negative effects on children's behavioral self-regulation.

Most studies have shown that children with PCE perform below normative age-level expectations on global developmental measures. Children with PCE often have similar performance patterns to nonexposed children living in similar low-income, urban settings. Across groups, children's general intellectual outcomes and language functioning tended to decline over time. It is possible that low SES, common to both the PCE and comparison groups, served to depress the children's scores on tests of intellectual functioning and academic achievement, potentially obscuring group differences.<sup>41</sup> PCE does not seem to confer significant risk to school-aged children's performance on global measures of intellectual functioning, which is consistent with findings reported for younger children.<sup>1</sup>

Second, performance on tasks that assess sustained attention and behavioral self-regulation seem to be compromised by PCE. Emerging evidence indicates that PCE is likely to disrupt neuronal pathways associated with arousal regulation and areas of the brain responsible for functions such as sustained attention and behavioral self-regulation.<sup>2</sup> Specifically, dopaminergic pathways associated with attentional networks, such as the striatal-prefrontal pathway, or other monoaminergically regulated arousal systems, such as the mesolimbic pathway, are disrupted by PCE. Impairments associated with PCE may not become evident until school age or adolescence as the prefrontal cortex and its associated networks undergo substantial developmental change.

The third finding relates to inconsistencies across research groups. Studies varied in sample composition, sample size, attrition rates, determination of exposure status, covariate control, and examination of potential moderators. Most studies (with the notable ex-

ception of neuroimaging studies) have incorporated demographic, prenatal, and postnatal environmental covariates into statistical analyses, but the specific covariates and the consistency of their use vary widely. Gender, race, birth weight, prenatal alcohol and/or tobacco exposure, nonmaternal care, continued maternal drug use, caregiver mental health, and poverty often moderate associations between PCE and developmental outcomes. Most investigators evaluate moderators and confounders before attributing observed differences to PCE, but often with low power to detect differences. Generalization is also a concern; most samples are limited to low-income, urban, black children.

Most studies involved children who were exposed to multiple substances (both legal and illegal drugs), reflecting that polysubstance use is the rule rather than an exception. Although studies of dose and timing have yielded promising findings, measurement of specific substances, dose, and timing of substance use is inconsistent because illicit substance use is unregulated, self-report varies in reliability, and biological assays are not used consistently. On the basis of a teratogenic model, increasing doses would lead to worsening outcomes. However, without evidence, negative effects may be misattributed to PCE rather than to other substances or environmental confounds. Innovative methods are needed to study specific substances, dose-effect models, and the timing and duration of exposure.

Finally, from recent studies that used neuroimaging techniques, subtle PCE effects in both brain structure and function have been reported. Although preliminary, data suggest that structural differences in brain development after PCE may be associated with specific neurocognitive deficits. However, most studies have lacked covariate

control, raising concerns about potential confounds. A future aim will be to link neural differences with meaningful behavioral outcomes.

### Future Directions

In future studies, researchers should strive to include both traditional cognitive-behavioral measures and assessments of executive function, decision-making, and emotion regulation in combination with measures of underlying brain structure and function. As participants in longitudinal PCE investigations approach adolescence, their health risk behaviors may increase, including adolescent drug use.<sup>21</sup> Measures that simulate risky decision-making in a laboratory setting (eg, Balloon Analog Risk Task<sup>42</sup>) or that require emotion-regulation skills would add to the understanding of PCE effects, beyond the potential bias and unreliability of self-report measures. Findings from laboratory-based measures associated with adolescent health risk behaviors not only enhance the ecological validity of the research but also increase the relevance to public health and policy by identifying adolescents in need of intervention.

Neuroimaging technology such as fMRI represents an opportunity to link PCE to neurocognitive task performance and to the identifiable neural substrates associated with specific outcomes. A shortcoming of traditional

neuropsychological tests is an inability to attribute performance to specific brain regions or pathways. Neuroimaging provides added explanatory power by demonstrating that performance is linked to specific brain activities.

Investigators should be encouraged to pool data when appropriate to enable the examination of statistical interactions. Potential moderating effects of age, gender, and caregiving stability on developmental outcomes have been noted in several studies. Others have examined severity and timing of PCE and found that PCE dose is associated with specific developmental outcomes. The evaluation of moderators will enhance our understanding of vulnerabilities associated with PCE in critical ways, but such analyses require large sample sizes to be powered adequately.

### CONCLUSIONS

Until recently, there have been few well-controlled longitudinal studies of PCE that assessed the physical, behavioral, cognitive, and neural development of school-aged children. Recent studies have provided evidence that PCE is associated with deficits in sustained attention and behavioral regulation, perhaps by altering brain activity in areas susceptible to the effects of toxins in utero. For global indices of development, such as physical growth

and cognitive ability, PCE does not provide much additional risk beyond the multiple co-occurring environmental risk factors. However, a drug-using lifestyle increases the likelihood that children will experience multiple environmental risks, making it difficult to isolate the teratogenic effects of PCE. Progress continues to be made by including moderators and explanatory variables in statistical models to improve the interpretation of the short- and long-term effects of PCE.

From a public health perspective, prevention efforts should be aimed at not only reducing the incidence of drug use during pregnancy but also providing educational and therapeutic resources to caregivers in low-income, urban environments who face multiple environmental stressors. Developing services that promote caregiver self-care, supportiveness, and behavior-management skills may reduce the negative impact of PCE and environmental risk factors on children's development and behavior.

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## A Review of the Effects of Prenatal Cocaine Exposure Among School-Aged Children

John P. Ackerman, Tracy Riggins and Maureen M. Black

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