

# PEDIATRICS

## A Review of the Effects of Prenatal Cocaine Exposure among School-Age Children

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6 A Review of the Effects of Prenatal Cocaine Exposure among School-Age Children  
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30 Short title: School-Age Effects of Prenatal Cocaine Exposure  
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35 Abbreviations: PCE= prenatal cocaine exposure; fMRI = functional magnetic resonance  
36  
37 imaging; IQ=intelligence quotient; SES=socioeconomic status; GDS=Gordon Diagnostic  
38  
39 System; TOVA=Test of Variables of Attention; CPT=Connors' Performance Test  
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44 Keywords: Cocaine, Maternal Exposure, Prenatal Exposure Delayed Effects, Attention,  
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46 Behavior, Growth, Language, Adolescent Development  
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53

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55  
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3 ABSTRACT  
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6 Context: Studies through six years show no direct effects of prenatal cocaine exposure (PCE) on  
7  
8 children's physical growth, developmental test scores, or receptive or expressive language. Little  
9  
10 is known about the effects of PCE among school-age children.

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12  
13 Objective: To review articles examining the effects of PCE on growth, cognitive and academic  
14  
15 functioning, and brain structure and function among school-age children.

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18 Data Sources: Articles obtained by searching PubMed, Medline, TOXNET, and PsycInfo  
19  
20 databases from January 1980 - December 2008 using terms *prenatal cocaine exposure, cocaine,*  
21  
22 *drug exposure, substance exposure, maternal drug use, polysubstance, children, adolescent, in*  
23  
24 *utero, pregnancy, development, and behavior.*

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26  
27 Study Selection: Criteria: (1) empirical research on children age 6 and older, (2) peer-reviewed  
28  
29 English-language journal; (3) comparison group; (4) longitudinal follow-up or historical  
30  
31 prospective design; (5) masked assessment; (6) exclusion of subjects with serious medical  
32  
33 disabilities, and (7) studies that reported non-redundant findings for samples used in multiple  
34  
35 investigations. 34 unique studies met criteria.

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37  
38 Data Extraction: Each article independently abstracted by 2 authors to obtain sample  
39  
40 composition, methods of PCE assessment, study design, comparison groups, dependent  
41  
42 variables, covariates, and results.

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46 Results: Associations between PCE and growth, IQ, academic achievement, and language  
47  
48 functioning are small and attenuated by environmental variables. PCE has significant negative  
49  
50 associations with sustained attention, inhibitory control, and behavioral regulation, even with  
51  
52 covariate control. Although emerging evidence suggests PCE-related alterations in brain  
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54 structure and function, interpretation is limited by methodological inconsistencies.  
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Conclusions: Consistent with findings among preschoolers, environmental variables play a key role in moderating and explaining the effects of PCE on school-age children’s functioning. After controlling for these effects, PCE related impairments are reliably reported in attention and executive functioning.

Review Copy

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

11  
12 Little is known about the long-term effects of PCE. One possibility is that PCE has direct  
13 effects on brain structure or function, which may heighten children's vulnerability to negative  
14 developmental outcomes.<sup>2</sup> Another possibility is that PCE is a marker for environmental risk  
15 factors and therefore must be considered in the context of other developmental threats, including  
16 poverty, insensitive parenting, maternal stress and depression, caregiver drug dependence,  
17 limited educational resources, and unstable home environments.<sup>3,4</sup> Both perspectives highlight  
18 the need to consider the long-term effects of PCE within an environmental and developmental  
19 context that includes brain and behavioral development.

20  
21 Over time, children face increasingly complex cognitive and social demands, requiring  
22 advances in working memory, sustained attention, inhibitory control, planning, organization, and  
23 emotion regulation. Collectively, these skills represent executive functions and coordinate the  
24 basic cognitive processes required for goal-directed action.<sup>5</sup> Preclinical models suggest that PCE  
25 may target brain regions and pathways involved in executive functions. Regions with strong  
26 dopaminergic innervation (e.g., anterior cingulate cortex, prefrontal cortex, striatum) may be  
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3 particularly susceptible to PCE.<sup>6</sup> Because executive functions are relatively immature in young  
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5 children, the effects of PCE may not be evident until school-age.  
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8 The effects of PCE are not necessarily linear. Longitudinal models with covariate  
9  
10 controls can examine the differential effects of drug exposure over time. Studies that include  
11  
12 parenting and environmental influences (e.g., school, neighborhood, peers) are necessary to  
13  
14 determine the amount of variance attributed to each level of influence. We review studies of PCE  
15  
16 conducted with children age six and older, focusing on outcomes associated with physical,  
17  
18 behavioral, cognitive, and neural development.  
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## 21 22 **METHOD**

### 23 24 **Selection Criteria**

25  
26 We used the following criteria: (1) empirical research on children age six and older with  
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28 PCE; (2) published in peer-reviewed English-language journal between January 1980 and  
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30 December 2008; (3) comparison group; (4) longitudinal follow-up or historical prospective  
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32 design; (5) masked assessment; (6) not exclusive focus on pathology (e.g. very low birthweight,  
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34 HIV, brain injury, mental retardation, or other serious medical complications), and (7) produced  
35  
36 findings distinct from previous reports from the same sample.  
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### 41 42 **Data Sources**

43  
44 Articles were obtained from PubMed, Medline, TOXNET, and PsycInfo entering  
45  
46 keywords *prenatal cocaine exposure, cocaine, drug exposure, substance exposure, maternal*  
47  
48 *drug use, polysubstance, children, adolescent, in utero, pregnancy, development, and behavior*  
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50 alone and in combinations. References of selected articles were searched to identify additional  
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52 articles that met selection criteria. We identified 34 unique studies of children and adolescents  
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3 with PCE; 29 (82%) were published after 2003, representing children in longitudinal cohorts  
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5 who have reached school-age.  
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## 8 **Procedures**

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10 Eligible articles were reviewed independently by two authors to determine: (1) domain  
11 assessed, (2) sample composition, (3) determination of PCE, (4) design and retention, (5)  
12 outcome variables and covariates, (6) results, (7) and methodological strengths and limitations.  
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## 17 **RESULTS**

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19 Seventeen cohorts were represented in the 34 papers reviewed (see Table 1). Sample  
20 sizes ranged from 26 to 1056 with a median of 188. Twenty-eight studies (82%) enrolled  
21 participants prospectively when infants were under six-months-old. Most studies (94%) used  
22 urine toxicology (26%) and/or meconium assay (70%) in combination with maternal report to  
23 determine PCE. Five studies (15%) examined dose-response effects of PCE.  
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32 Most samples (85%) included polysubstance-exposed children with high rates of  
33 cigarette, alcohol, and marijuana exposure. All samples were urban, most were low-income  
34 (three had no income data), and most (94%) enrolled primarily African-American participants.  
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38 The caregiver-child relationship often differed between the PCE and comparison groups.  
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## 48 **Physical Growth**

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50 Six studies examined children's growth.<sup>7-12</sup> Despite significant differences in weight,  
51 height, and head circumference at birth, there were few significant growth differences at school-  
52 age.<sup>7-11</sup> Catch-up growth generally occurs by six months.<sup>11</sup> Five studies (83%) found no  
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3 significant PCE-related differences in weight or weight-for-age. One study found that PCE  
4  
5 children assessed at 1, 3, 7, and 10 years grew at a slower rate than comparison children.<sup>12</sup>  
6  
7 However, PCE was not confirmed by biological assays. PCE children had weight-for-age within  
8  
9 normal limits.  
10

11  
12 Evidence for PCE differences in linear growth (i.e., height) was mixed in the five studies  
13  
14 that examined height. Three studies found no differences in children's height-for-age. Two found  
15  
16 that PCE children were shorter than non-exposed children (2.5 cm) at school-age, after  
17  
18 controlling for prenatal tobacco and alcohol exposure, comorbid drug use, ethnicity, parent  
19  
20 height, and maternal.<sup>7, 10</sup> In nearly all studies there were significant anthropometric differences  
21  
22 between PCE and non-exposed children at birth that were typically not evident at school-age.  
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### 26 27 **Global Intellectual Functioning and Academic Achievement**

28  
29 Nine studies examined intellectual or academic functioning.<sup>3, 4, 8, 9, 13-17</sup> Children ranged  
30  
31 from six to 12 years. Two studies found that PCE children had significantly lower scores on  
32  
33 standardized measures of intellectual functioning than comparison children;<sup>8, 17</sup> however, group  
34  
35 differences were substantially attenuated with the inclusion of maternal and environmental  
36  
37 covariates. Of the four studies that assessed academic achievement,<sup>3, 4, 15, 17</sup> only one reported  
38  
39 significant differences; comparison children scored higher than PCE children.<sup>15</sup> It should be  
40  
41 noted that most studies utilized low-income, urban samples with mean IQ scores between .5 and  
42  
43 1.0 standard deviations below the mean.  
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### 47 48 **Language Functioning**

49  
50 Five studies examined language functioning, including expressive, receptive and global  
51  
52 language functioning.<sup>9, 13, 14, 18, 19</sup> They produced mixed results. Three studies examining  
53  
54 language longitudinally<sup>13, 18, 19</sup> found small but persistent PCE differences after controlling for  
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3 relevant environmental and prenatal covariates. Language-related differences were documented  
4  
5 early in development and persisted to the same relative degree at school-age.<sup>13, 19</sup> In the only  
6  
7 study that assessed children through age nine,<sup>18</sup> PCE differences were not evident after  
8  
9 controlling for environmental covariates. Evidence for dose-response effects was also  
10  
11 inconsistent. Environmental factors such as caregiver sensitivity, vocabulary, and  
12  
13 socioeconomic status (SES) often contributed significantly to child language functioning,  
14  
15 whereas PCE effect sizes were often small (.07-.20 standard deviations).  
16  
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### 20 Behavioral Functioning

21  
22 Eight studies targeted behavioral functioning.<sup>3, 4, 9, 20-24</sup> Most used parent and/or teacher  
23  
24 report of internalizing and externalizing behaviors. Six studies found significant differences in  
25  
26 behavioral functioning, all favoring non-exposed children;<sup>3, 20-24</sup> however, they varied regarding  
27  
28 the covariates and moderators in the analyses. The largest effect sizes were found with  
29  
30 externalizing problems (e.g. aggression and attention).  
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34 In a dose-response analysis, high PCE was associated with more externalizing and total  
35  
36 behavior problems at age seven than low or no PCE, even after covariate adjustment, including  
37  
38 alcohol, tobacco, caregiver depression, and non-maternal care.<sup>20</sup> In three other studies,<sup>21, 23, 24</sup>  
39  
40 gender moderated behavioral outcomes; males were at greater risk than females for delinquency  
41  
42 and aggression. Three of four studies found that non-maternal care predicted externalizing  
43  
44 problems.<sup>4, 20, 22</sup>  
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### 48 Attention and Executive Function

49  
50 Five studies examined attention or executive functioning using performance-based  
51  
52 neuropsychological measures,<sup>4, 25-28</sup> including the Gordon Diagnostic System (GDS),<sup>29</sup> the Test  
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54 of Variables of Attention (TOVA),<sup>30</sup> and the Connors' Performance Test (CPT).<sup>31</sup> Children with  
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3 attention problems exhibit poor performance with frequent omissions, an impulsive response  
4  
5 style, or variable reaction times.<sup>30</sup> Poor performance has been linked to deficient frontal lobe  
6  
7 regulatory functioning.<sup>32</sup>  
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9

10 Two studies used the GDS to assess attention<sup>4,27</sup> and reported that 7-12 year-old PCE  
11  
12 children were more likely to demonstrate commission errors than non-exposed comparison  
13  
14 children, after covariate control. Two studies assessed children's sustained attention using visual  
15  
16 continuous performance tasks at ages six and seven.<sup>25,26</sup> Both studies found PCE differences in  
17  
18 reaction time and omission errors, but not commission errors.<sup>25</sup> Covariates such as task  
19  
20 complexity, non-maternal care and quality of caregiving environment influenced children's  
21  
22 attention. An additional study using a novel visuospatial maze learning task<sup>28</sup> found that PCE  
23  
24 children made more delayed recall errors than controls and displayed slower processing speed on  
25  
26 visuospatial learning tasks.  
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31 The mechanisms underlying sustained attention and executive functioning may be  
32  
33 disrupted by PCE. However, the specific effects of PCE may depend on moderators, including  
34  
35 drug type and dose, alcohol and/or tobacco exposure, child age, gender, and environmental  
36  
37 factors (e.g., socioeconomic status, non-maternal care, and caregiving quality).  
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### 41 **Brain Structure and Function**

42  
43 Eight studies used neuroimaging methodologies to examine brain structure and  
44  
45 function.<sup>33-40</sup> Differences in both gray and white matter were reported. The PCE groups had  
46  
47 global decreases in cortical gray matter,<sup>34</sup> and selective volumetric decreases in the left occipital  
48  
49 lobe, right parietal cortex<sup>38</sup> and caudate.<sup>33,40</sup> Volumetric increases were reported in the  
50  
51 amygdala.<sup>40</sup> PCE-related differences in white matter include decreased volume of the corpus  
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53 callosum,<sup>38</sup> increased diffusion in bilateral frontal projection fibers,<sup>36</sup> and increased levels of  
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3 creatine in frontal white matter<sup>36</sup> suggesting abnormalities in energy metabolism and less mature  
4 development of frontal white matter pathways. Differences in gray and white matter varied as a  
5 function of the amount of substance exposure,<sup>36,38</sup> and number of substances to which the fetus  
6 was exposed.<sup>34</sup>  
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12  
13 Two investigations reported correlations between gray and white matter differences and  
14 behavioral task performance.<sup>36,38</sup> Two studies<sup>36,38</sup> provide evidence that PCE disrupts frontally  
15 mediated tasks. However, small sample sizes, lack of covariate control, and sample selection  
16 limit generalizability. Across studies and methodologies, alterations in gray and white matter  
17 vary by PCE<sup>36,38</sup> and other prenatal substances.<sup>34</sup>  
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24 Three studies examining brain function related to PCE revealed mixed results.<sup>35, 39, 40</sup>  
25 One reported reductions in global cerebral blood flow, with increases in anterior and superior  
26 regions during rest using perfusion functional magnetic resonance imaging (fMRI).<sup>40</sup> Another  
27 examined electrical brain responses (i.e., event-related potentials) during an inhibitory control  
28 task and found that the PCE group had slower, more prolonged event-related potential responses  
29 and a more diffuse pattern of activation than the comparison group.<sup>39</sup> The third study found PCE  
30 differences in regional oxygenated blood flow using Blood Oxygen Level Dependent contrast  
31 during a non-spatial working memory fMRI task.<sup>35</sup>  
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43 The limited data suggest subtle differences between PCE and non-exposed children on  
44 measures of brain structure and function. However, these findings await replication as distinct  
45 methods and data analysis techniques have been used with small samples of poly-substance  
46 exposed children with minimal control for potentially confounding environmental factors.  
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## 52 **DISCUSSION**

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3 There are four major findings regarding outcomes following PCE in school-age children.

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5 First, associations between PCE and indices of growth, intellectual functioning, academic  
6  
7 achievement, and language functioning are modest and often explained by social risk factors  
8  
9 such as poverty, caregiver education, placement stability, and quality of child-caregiver  
10  
11 relationships. PCE children encounter more environmental risk, making it difficult to disentangle  
12  
13 the two conditions. For example, it is unclear whether PCE contributes to disruptive behaviors,  
14  
15 which increases the possibility of out-of-home placement or whether caregiver instability leads  
16  
17 to negative effects on children's behavioral self-regulation.  
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20  
21 Most studies find that PCE children perform below normative age-level expectations on  
22  
23 global developmental measures. PCE children often have similar performance patterns to non-  
24  
25 exposed children living in similar low-income, urban settings. Across groups, children's general  
26  
27 intellectual outcomes and language functioning tended to decline over time. It is possible that  
28  
29 low SES, common to both the PCE and comparison groups, served to depress the children's  
30  
31 scores on tests of intellectual functioning and academic achievement, potentially obscuring group  
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33 differences. PCE does not appear to confer significant risk to school-age children's performance  
34  
35 on global measures of intellectual functioning which is consistent with findings from younger  
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37 children.<sup>1</sup>  
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43 The second finding is that executive functioning tasks, specifically sustained attention,  
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45 inhibitory control, and behavioral regulation are compromised by PCE, even after covariate  
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47 control. PCE is likely to disrupt neuronal pathways associated with arousal regulation and areas  
48  
49 of the brain responsible for executive functions.<sup>2</sup> Specifically, dopaminergic pathways  
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51 associated with attentional networks, such the striatal-prefrontal pathway, or other  
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53 monoaminergically regulated arousal systems, such as the mesolimbic pathway, are disrupted by  
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3 PCE. Impairments associated with PCE may not become evident until school-age or adolescence  
4  
5 as the prefrontal cortex undergoes substantial developmental changes.  
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8 The third finding relates to inconsistencies across research groups. Studies varied in  
9  
10 sample composition, sample size, attrition rates, determination of exposure status, covariate  
11  
12 control, and examination of potential moderators. Most studies (with the notable exception of  
13  
14 neuroimaging studies) have incorporated demographic, prenatal, and postnatal environmental  
15  
16 covariates into statistical analyses, but the specific covariates and the consistency of their use  
17  
18 vary widely. Gender, race, birth weight, prenatal alcohol and/or tobacco exposure, non-maternal  
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20 care, continued maternal drug use, caregiver mental health, and poverty often moderate  
21  
22 associations between PCE and developmental outcomes. Most investigators test for moderators  
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24 and confounders before attributing observed differences to PCE.  
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29 Most studies involved children who were exposed to multiple substances (both legal and  
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31 illegal drugs), reflecting that polysubstance use is common. Although studies of dose and timing  
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33 have yielded promising findings, measurement of specific substances, dose, and timing of  
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35 substance use is inconsistent because illicit substance use is unregulated, self-report varies in  
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37 reliability, and biological assays are not used consistently. Based on a teratogenic model,  
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39 increasing doses would lead to worsening outcomes. However, without evidence, negative  
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41 effects may be misattributed to PCE, rather than to other substances or environmental confounds.  
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43 Innovative methods are needed to study specific substances, dose-effect models, and the timing  
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45 and duration of exposure.  
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50 The fourth finding is that recent studies using neuroimaging techniques report subtle PCE  
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52 effects in both brain structure and function. Though preliminary, data suggest that structural  
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54 differences in brain development following PCE may be associated with specific neurocognitive  
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3 deficits. However, most studies lack covariate control, raising concerns about potential  
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5 confounds. A future aim will be to link neural differences and with meaningful behavioral  
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7 outcomes.  
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### 10 **Future Directions**

11  
12 Future studies should strive to include both traditional cognitive-behavioral measures and  
13  
14 ecologically valid assessments of executive function, decision-making, and emotion regulation,  
15  
16 in combination with measures of underlying brain structure and function. As participants in  
17  
18 longitudinal PCE investigations approach adolescence, their health risk behaviors may increase,  
19  
20 including adolescent drug use.<sup>21</sup> Measures that simulate risky decision-making in a laboratory  
21  
22 setting (e.g., Balloon Analogue Risk Task<sup>41</sup>) or that require emotion regulation skills would add  
23  
24 to the understanding of PCE effects, beyond the potential bias and unreliability of self-report  
25  
26 measures. Findings from laboratory based measures associated with adolescent health risk  
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28 behaviors not only enhance the ecological validity of the research, but also increase the relevance  
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30 to public health and policy by identifying adolescents in need of intervention.  
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37 Neuroimaging technology such as fMRI represents an opportunity to link PCE to  
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39 neurocognitive task performance and to the identifiable neural substrates associated with specific  
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41 outcomes. A shortcoming of traditional neuropsychological tests is an inability to attribute  
42  
43 performance to specific brain regions or pathways. Neuroimaging provides added explanatory  
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45 power by demonstrating that performance is linked to specific brain activities.  
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### 48 **Conclusion**

49  
50 Until recently, there have been few well-controlled longitudinal studies of PCE that  
51  
52 assessed the physical, behavioral, cognitive, and neural development of school-age children.  
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54 Current studies provide evidence that PCE is associated with deficits in sustained attention and  
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3 behavioral regulation, perhaps by altering brain activity in areas susceptible to the effects of  
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5 toxins in utero. For global indices of development, such as growth and general intelligence, PCE  
6  
7 does not provide much additional risk beyond the multiple co-occurring environmental risk  
8  
9 factors. However, a drug-using lifestyle increases the likelihood that children will experience  
10  
11 multiple environmental risks, making it difficult to isolate the teratogenic effects of PCE.  
12  
13 Progress continues to be made by including moderators and explanatory variables in statistical  
14  
15 models to improve the interpretation of short- and long-term effects of PCE.  
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19  
20 From a public health perspective, prevention efforts should be aimed not only at reducing  
21  
22 the incidence of drug use during pregnancy, but also providing educational and therapeutic  
23  
24 resources to caregivers in low-income, urban environments who face multiple environmental  
25  
26 stressors. Developing services that promote caregiver self-care, supportiveness, and behavior  
27  
28 management may help caregivers and their children reduce the negative impact of PCE and  
29  
30 environmental risk factors on children's development and behavior.  
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Review Copy

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Table 1. Studies Examining the Effects of Prenatal Cocaine Exposure at School Age and Early Adolescence

Domain(s)	Author/ Year/ Cohort (1-17)	Sample Composition (n, type of exposure, age, income, ethnicity, relatedness, drug exposure assessment method)	Design Type (longitudinal, prospective, comparison group)	Dependent Variables Assessed	Covariates considered in analyses (other substances; Child characteristics; Caregiver characteristics)	Primary Results	Conclusions/ Comments (Advantages, Limitations)
Physical Growth	Covington et al., 2002 Cohort 1	n=540 child age 7 low-income, urban, AA; GA > 38 weeks; PCE group 29% non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	Prospective design of COC, ALC, CIG exposed children enrolled at age 6; PCE=231, NE=309 from initial sample of 665 (81%)	Child BW & height Age 7 weight and height converted to age-based percentiles	CIG and ALC exposure, child BW and length, blood lead level, caregiver age, height, weight, SES, current substance use, psychopathology, marital status, social support, non-maternal care status	<u>Birth</u> : PCE, ALC, and CIG exposure negatively associated with BW and length. <u>Age 7</u> : PCE was not sig associated with child weight but was sig associated w/ decreased height. Findings moderated by maternal age such that associations were stronger for mothers over 30.	PCE children up to 1-inch shorter at age 7; growth restriction most severe for drug-using mothers over 30—not accounted for by nutritional intake alone; ALC was related to age 7 weight differences
Physical Growth	Minnes et al., 2006 Cohort 2	n=285 child age 6-7 low-income, urban, AA; GA> 37 weeks; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	PLF PCE=154, NE=131 from initial sample of 415 (69%)	Anthropometric measurements; dysmorphic measurements, neuromotor outcomes	CIG, ALC, and MAR exposure; race; maternal age; parity; maternal IQ; HOME score; maternal psychopathology; non-maternal care status	<u>Birth</u> : PCE had lower BW, HC; older mothers, less prenatal care, co-occurring substance use; <u>Age 6-7</u> : Dose of PCE associated with lower height and height for weight z-scores; no sig morphological or neuromotor differences	PCE differences observed in standardized height and weight for height; good use of covariates; additional dose/metabolite data provided
Physical Growth	Lumeng et al., 2007 Cohort 3	n=202 child age 6-7 low-income, urban, AA; GA> 36 weeks; maternal care status not reported PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	PLF PCE=112, NE=90 from initial sample of 252 (80%)	Anthropometric measurements including weight-for-age, height-for-age, weight-for-length, HC-for-age z-scores; overweight status	CIG, ALC, and MAR exposure; birth mother anthropometrics; Child's gestational age, gender, race, age at assessment, non-maternal care status	PCE had lower BW, length, and HC at birth; COC effects on growth did not persist beyond infancy with catch-up growth occurring by 6 months of age, no dose-response effect on child growth parameters	No persistent anthropometric differences over time among PCE children at age 8 controlling for numerous confounds
Physical Growth	Richardson et al., 2007 Cohort 4	n=222 child age 1, 3, 7, 10 low-income, urban, 50% AA; GA> 34 weeks; 13% non-maternal care at	PLF PCE=99, NE=125 from initial sample of 295 (76%)	Anthropometric measurements including weight-for-age, height-for-age, HC	CIG, ALC, and MAR exposure, Child age, gender, race, maternal height, caregiver	First semester PCE was negatively associated with weight-for-age, height-for-age, and HC at age 7 and 10 (not age 1 and 3). Adjusted analyses indicated that PCE children were on average .75 inches shorter and 10 pounds lighter than	PCE children displayed weight-for-age, height-for-age, and HC decreases at age 7 and 10. Age and gender moderated growth differences among PCE children. Effect sizes were relatively small.

		age 10; PCE Assessment: Structured interview at 4-5 month prenatal visit determined COC/crack exposure during first trimester			depression, home environment, education, income, marital status, non-maternal care status	comparison children at age 10. There was a sig PCE x age interaction for weight and HC. PCE children grew slower over time despite no differences at age 1 and 3. A gender x age interaction indicated that boys began longer and heavier than girls, but there were no differences at age 10.	
<b>Physical Growth, Intelligence, Language, and Behavior</b>	Kilbride et al., 2006 Cohort 5	n=51 child age 7 low-income, urban, AA; GA not reported; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine or meconium) and maternal report	Randomized Follow- up Intervention PCE=39, NE=12 from initial sample of 159 (32%); 24 of PCE group received case management, 15 received routine care	Anthropometric measurements; Stanford-Binet-III; CELF-3; CBCL; Parent-child play interactions	CIG and ALC exposure	No PCE differences on growth, IQ, language, or behavior outcomes; No intervention group differences on growth, IQ, language, or behavioral indices; Case-managed PCE group showed more positive interactions than PCE routine care group in play paradigm	Follow-up of a randomized early case- management intervention of PCE children; high attrition rate across all subgroups; limited power to detect group differences; minimal inclusion of key environmental covariates
<b>Intelligence, Academic Achievement, and Behavior</b>	Nair et al., 2008 Cohort 6	n=173 child age 6-7 low SES, urban, AA, GA > 32 weeks; maternal care status: 100% NE in maternal care, 54.9% PCE in non- maternal care (primarily kinship), PCE assessment: TOX measures (maternal & infant urine, meconium), maternal report	PLF of a one-year Randomized Control Trial of a developmental intervention for drug- using mothers; PCE=111, NE=62 from initial sample of 265 (65%)	Stanford-Binet Intelligence Scales, Fourth Edition, Wide Range Achievement Test 3, CBCL	TOB exposure, gender, number of caregiver changes, public assistance status, employment status, caregiver depressive symptoms	After adjusting for environmental covariates, there were no significant PCE differences in IQ, academic performance, or behavior problems. Females had higher scores on overall IQ and 4 of 8 SB-IV subtests, fewer caregiver-reported attention and aggression problems, and higher reading achievement scores.	Associations between PDE and cognitive-behavioral functioning at age 7 were attenuated after controlling for postnatal environmental factors. PCE and non-exposed comparison children were from low-SES families and obtained scores substantially below normative expectations.
<b>Intelligence and Academic Achievement</b>	Wasserman et al., 1998 Cohort 7	n=206 child age 6-9 low-income, urban, AA; GA not reported; PCE group 45% non- maternal care; PCE Assessment: TOX measures (mother & infant urine or meconium)	HPD PCE=98, NE=108 from initial sample of 560 (37%)	WISC-III IQ score; Raven's Matrices	Child BW, sex, age, biological relatedness, history of foster care, housing stability; age 6-9 child height, HC, blood lead level; Caretaker age, IQ, education, housing, public assistance, recent drug use, employment, home environment	Caregivers in PCE group were older, more likely to be non-maternal caregivers; unemployed; use COC; have a lower IQ; PCE children were shorter, more likely to be in foster care; no PCE group differences in IQ; HOME, caregiver IQ, and homelessness were strongest predictors of child IQ	Low IQs in both PCE and NE comparison group but no group differences; Social adversity factors were strongest predictors of child intellectual functioning; Low retrieval rate could have affected representativeness; limited variability (all low) in maternal and child IQ may reduce ability to detect effects

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<p><b>Intelligence, Academic Achievement, Behavior, and Attention</b></p>	<p>Hurt et al., 2005 Cohort 8</p>	<p>n=135 child age 9-12 low-income, urban, AA; GA &gt; 34 weeks; PCE group 40% history of non-maternal care; PCE Assessment: TOX measures (mother &amp; infant urine) and maternal report</p>	<p>PLF PCE=62, NE=73 from initial sample of 224 (60%)</p>	<p>Grade progression; grade point average; WPPSI-R; Stanford-9 reading, math, and science achievement; Gordon Diagnostic System (GDS); Trails A &amp; B; Achenbach TRF and parent CBCL; child self-reported depression and self-esteem</p>	<p>ALC, CIG, and MAR exposure; HOME score, history of foster care; ongoing drug use assessed by urine screen and self-report; child IQ (when applicable) and gender</p>	<p><b>Birth:</b> PCE group had more ALC, CIG, MAR exposure; older mothers, less prenatal care, shorter gestation, more non-maternal care <u>Age 9-12:</u> No IQ, behavior, or achievement differences; marginal school progression differences; PCE children more distractible and impulsive on the GDS; HOME total sig different, non-maternal care; and current drug-use</p>	<p>No group differences on IQ or achievement scores despite numerous neonatal and environmental differences. There were sig differences on the GDS sustained attention task suggesting distractibility and impulsivity may result from PCE. School outcomes influenced by child IQ, HOME, history of foster care, and performance on GDS</p>
<p><b>Intelligence and Academic Achievement</b></p>	<p>Morrow et al., 2006 Cohort 10</p>	<p>n=409 child age 7 low-income, urban, AA; GA&gt; 37 weeks; PCE group 41% non-maternal care; PCE Assessment: TOX measures (mother &amp; infant urine, meconium) and maternal report of quantity and duration of drug use</p>	<p>PLF PCE=212, NE=197 from initial sample of 476 (86%)</p>	<p>Abbreviated WISC-III; WIAT reading and math achievement subtests</p>	<p>ALC, CIG, and MAR exposure; child age, gender, BW, length, HC; Age 7 child blood lead level, hearing status, Headstart attendance; Caregiver age, education, marital status, recent substance use, employment, home environment, non-maternal care status</p>	<p><b>Birth:</b> PCE shorter gestation, lower BW, length, and HC; older mothers, less prenatal care, more use of CIG and ALC in utero; <u>Age 7:</u> PCE caregivers had higher rate of unemployment; ongoing drug use; non-maternal care status; no child IQ differences; PCE exposure sig predicted learning disability (LD) status controlling for prenatal and environmental covariates; PCE dose not associated with LD status</p>	<p>At age 7, PCE children were 3x more likely than controls to meet criteria for an LD; no PCE-related dose effect; Well-controlled study with good retention (over 86%); low overall IQ scores in both groups limited variability and power to detect differences; quite low rates of LD (PCE 7.3% and CC 2.6%)</p>
<p><b>Intelligence and Academic Achievement</b></p>	<p>Singer et al., 2008 Cohort 11</p>	<p>n=371 child age 9 low-income, urban, AA; GA&gt; 37 weeks; PCE group 23% non-maternal care; PCE Assessment: TOX measures (mother &amp; infant urine, meconium) and maternal report of quantity and duration of drug use</p>	<p>PLF PCE=192, NE=179 from initial sample of 415 (89%)</p>	<p>WISC-IV; Woodcock Johnson-III Tests of Achievement; HOME</p>	<p>ALC, CIG, and MAR exposure; Child age, gender, race, BW, length, HC; Child blood lead level; Caregiver age, education, parity, prenatal care, SES, caregiver IQ, marital status, current substance use, HOME environment, non-maternal care status</p>	<p><b>Birth:</b> PCE lower BW, length, HC, more exposure to ALC, CIG, MAR, and PCP, more iron deficient, more likely to be in non-maternal care; caregivers older, less prenatal care, less education, less likely to be married; <u>Age 9:</u> Lower perceptual reasoning scores, mediated by smaller HC (possible marker of brain growth); academic achievement not associated with PCE; negative effects of lead, ALC, iron deficiency noted</p>	<p>PCE children demonstrated some decrements in intelligence-particularly perceptual reasoning but not in academic achievement at age 9 controlling for numerous confounds</p>

Intelligence, Growth, and Motor Functioning	Arendt et al., 2004 Cohort 12	n=231 child age 7 low-income, urban, AA; GA > 37 weeks; PCE group 56% non-maternal care; 13% controls non-maternal care; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE=101, NE=130 from initial sample of 267 (87%)	WISC-III; Berry-Buktenica Developmental Test of Visual-Motor Integration (VMI); Bruininks-Oseretsky Fine Motor Composite; weight, height, HC	ALC, CIG, and MAR exposure; race; caregiver age; parity; caregiver IQ; HOME score; caregiver psychopathology; non-maternal care status	<u>Birth</u> : PCE lower BW, length, and HC; older mothers, less prenatal care, more prenatal CIG and ALC use; lower SES; higher parity; <u>Age 7</u> : PCE group more caregiver drug use; lower caregiver IQ; more placement in non-maternal care; lower HOME; no child IQ differences; no height, weight or HC differences; PCE sig predicted VMI Motor scores and WISC-III verbal IQ and full-scale IQ scores but associations were attenuated after controlling for caregiver IQ and HOME scores; in a subset PCE dose was associated with VMI.	PCE group performed more poorly than the NE group on VMI Motor performance and WISC-III verbal and full-scale scores. Groups differed on numerous prenatal and environmental variables and when these were included in regression analyses group differences were largely attenuated. Maternal IQ and HOME scores remained sig predictors of child IQ and visual motor and fine motor performance.
Intelligence and Expressive Language	Delaney-Black et al., 2000 Cohort 1	n=458 child age 6 low-income, urban, AA; GA > 38 weeks; PCE group 29% non-maternal care; PCE Assessment: maternal report, medical records including TOX measures (mother & infant urine)	HPD COC, ALC, CIG exposed children enrolled at age 6 PCE=186, NE=272 from initial sample of 665 (69%)	Arizona Articulation Proficiency Scale; Coded language samples from a dyadic interaction with an examiner; WPPSI-R	ALC, CIG, and MAR exposure; Child age, gender, BW, length, HC; Age 6 blood lead level; Caregiver age, SES, marital status, education, hypertension, current substance use, home environment, non-maternal care status	<u>Birth</u> : PCE shorter gestation, lower BW, length, HC; older mothers, more CIG and ALC exposure; <u>Age 6</u> : more caregiver substance use; lower caregiver IQ; more placement in non-maternal care; Quality of language samples did not differ between PCE and NE groups; children with poor language skills were more likely to have been PCE and CIG exposed	No PCE group differences in IQ or expressive language. Children with poor language were 2.4x more likely to have been PCE controlling for confounds. Study provides limited evidence that PCE is associated with aspects of expressive language.
Intelligence and Language	Bandstra et al., 2004 (Bandstra et al., 2002*) Cohort 10	n=476 child age 3, 5, 7 low-income, urban, AA; GA > 37 weeks; PCE group 28-41% in non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report of quantity and duration of drug use	PLF PCE=200, NE=176 from initial sample of 476 (79%)	CELF-P; NEPSY Language Core Domain; McCarthy Scales of Children's Abilities; WPPSI-R/ WISC-III	ALC, CIG, and MAR exposure; Child age, gender, BW, length, HC; Age 7 blood lead level, hearing status, Headstart enrollment; Caregiver age, education, marital status, current substance use, employment, HOME, non-maternal care status	<u>Birth</u> : PCE shorter gestation, lower BW, length, HC; older mothers, less prenatal care, more CIG, ALC, and MAR exposure; <u>Age 3-7</u> : PCE children placed in non-maternal care more often; less Headstart, more daycare, lower HOME language score; Latent Growth Curve Analysis revealed small but sig PCE-related language differences but not in language trajectories age 3-7.	PCE dose was associated with subtle differences in children's language at age 3, 5, and 7. There were no differences in the developmental trajectories of the PCE and NE groups. Study included numerous environmental covariates. Efficient use of available data through latent growth curve modeling.
Language	Beeghly et al., 2006 Cohort 3	n=160 child age 6 and 9.5 low-income, urban, AA;	PLF PCE=85, NE=75 from initial sample of	Test of Language Development-3, CELF-3, WPPSI-R (age 4)	Child age, gender, IQ, non-maternal care status, hearing, blood	<u>Birth</u> : PCE children had lower BW z-scores, caregivers were older, more CIG, ALC, and MAR exposure; more ongoing substance use, less employment; more	Effects of PCE on language functioning were small and found only in specific subgroups of children; all low SES children were at risk for below

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		GA > 36 weeks; PCE group 36-50% in non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report of quantity and duration of drug use	252 (63%)		lead level, early intervention; Caregiver age, verbal IQ, education, parity, race, public assistance, household size, current substance use, employment, homelessness, social support, psychological functioning, exposure to violence, father involvement	non-maternal care; Age 6-9: all children performed in low-average range on language measures; marginal bivariate associations between PCE and total language scores, no PCE dose effects, PCE children scored lower on receptive language at age 6 but not at 9.5; outcomes moderated by BW, age, and gender.	average language functioning; exposure to violence and a lack of preschool or Headstart was also related to poor language outcomes; caregiver verbal abilities were positively associated with child outcomes; placement in nonkin foster care was positively related to language outcomes
Language	Lewis et al., 2007 Cohort 11	n=371 child age 1, 2, 4, 6 low-income, urban, AA; GA not restricted (93 participants <37 weeks GA); PCE group 23% non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report of quantity and duration of drug use	PLF PCE=192, NE=179 from initial sample of 415 (89%) at age 6	Age 1 & 2: Preschool Language Scale-3 <sup>rd</sup> Edition  Age 4: CELF-P  Age 6: Comprehensive Assessment of Spoken Language	ALC, CIG, and MAR exposure; Child age, gender, race, BW, length, HC; maternal age, education, parity, prenatal care, SES, caregiver receptive vocabulary, IQ, psychopathology, marital status, concurrent substance use, HOME environment, non-maternal care status	PCE children demonstrated language deficits across all time points of about 1/5 of a SD; male and AA children also scored about 1/3 of a SD below sample mean; Limited dose-response PCE effects beyond the first two years of life; HOME scores and caregiver vocabulary influenced later language outcomes	Found that PCE children demonstrated early language deficits which persisted through age 6; effect sizes were often quite small; use of different language measures at different ages made longitudinal comparisons hard to interpret; environmental factors play a role in language development
Behavior	Nordstrom Bailey et al., 2005 (Delaney-Black et al., 2000*) (Delaney-Black et al., 1998*) Cohort 1	n=499 child age 6-7 low-income, urban, AA; GA > 37 weeks; PCE group 29% non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	HPD COC, ALC, CIG exposed children enrolled at age 6 PCE=214, NE=285 from initial sample of 665 (75%)	TRF	ALC and CIG exposure; Child age, gender, BW; child IQ, blood lead level, child report of violence exposure; Caregiver age, family SES, marital status, IQ, education, substance use, home environment, social support, non-maternal care	No main effect for PCE in predicting TRF behavior problems; however, there was a sig ALC x PCE interaction such that boys with PCE and ALC exposure and girls with PCE and no ALC exposure had elevated externalizing behavior scores.	Gender and ALC moderated associations between PCE and child externalizing behavior problems reported by teachers. Unusual finding that PCE girls with no prenatal ALC exposure had more ext problems than PCE girls with ALC exposure.

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Behavioral and Psychological Functioning	Linares et al., 2006 Cohort 11	n=322 child age 6 low-income, urban, AA; GA > 37 weeks; PCE group 32% non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	PLF PCE=169, NE=153 from initial sample of 415 (78%)	Dominic Interactive (child self-report), CBCL	ALC, CIG, and MAR exposure; Child age, gender, race, IQ, BW, length, HC; maternal age, education, prenatal care, SES, caregiver IQ, psychopathology, marital status, current substance use, HOME environment, non-maternal care status	PCE children self-reported a higher average number of oppositional-defiant and ADHD symptoms than non-drug-exposed children. There was no PCE-related difference in caregiver report of behavior problems on the CBCL. Non-maternal caregivers of PCE children reported a greater number of externalizing behavior problems.	Good inclusion of child report data, but difficult to disentangle rater variance from outcome data.
Behavior	Sood et al., 2005 Cohort 1	n=506 child age 6-7 low-income, urban, AA; GA > 37 weeks; PCE group 29% non-maternal care; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	HPD COC, ALC, CIG exposed children enrolled at age 6 PCE=214, NE=292 from initial sample of 665 (76%)	CBCL	ALC and CIG exposure; Child age, gender, BW; child IQ, blood lead level, violence exposure; Caregiver age, SES, marital status, IQ, education, current substance use, home environment, psychopathology, caregiver social support, non-maternal care status	Analyses stratified by gender and prenatal ALC exposure found that boys with PCE and ALC exposure and girls with PCE and no ALC exposure had sig more delinquent behavior problems. Girls with PCE and no ALC exposure were 17x more likely to have elevated Aggression scores.	Findings extend teacher report data from the Nordstrom Bailey et al. (2005) and suggest that gender and ALC exposure moderate associations between PCE and caregiver report of child externalizing behavior problems.
Behavior	Bada et al., 2007 Cohort 12	n=1056 child age 3, 5, and 7 low-income, urban, AA; GA > 32 weeks; PCE group 16-23% non-maternal care; PCE Assessment: TOX measures (infant meconium) and maternal report of quantity and duration of drug use	PLF 1056 from initial sample of 1388 (76%); Original sample of PCE=658 and NE=730	CBCL	ALC, CIG, MAR, and HER exposure; Study site, child gender, race, birth HC, Caregiver age, HOME score, caregiver depression, current substance use, family violence, and non-maternal	PCE dose was associated with trajectories of internalizing, externalizing, and total behavior problems. These effects were independent of and less than the sig combined effect of prenatal and postnatal CIG and ALC exposures. Caregiver depression and family violence had a negative influence on all behavioral outcomes. Non-maternal care status mediated the effect of PCE on behavioral outcomes.	PCE has a negative impact on child behavior outcomes. Additional negative effects on behavior outcomes are observed when PCE co-occurs with prenatal and postnatal CIG and ALC exposure.

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<b>Behavior and Illicit Substance Use</b>	Bennett et al., 2007 Cohort 13	n=154 child age 10 low-income, urban, AA; GA > 32 weeks; maternal care status not reported; PCE Assessment: TOX measures (infant meconium) and maternal report	PLF PCE=60, NE=94 from initial sample of 258 (60%)	Self-reported substance use, aggression, and disregard for safety on Youth Risk Behavior Survey	ALC, CIG, and MAR exposure; Child age, gender, neonatal medical problems, non-maternal care status, current drug use, environmental risk	Gender moderated effects of PCE. PCE boys reported engaging in more high risk behavior as measured by a composite health risk behavior score. PCE boys also reported more current tobacco use.	Findings show that PCE places boys at risk for problems with inhibitory control, emotion regulation, and antisocial behavior.
<b>Neurological Functioning</b>	Hurt et al., 2001 Cohort 8	n=115 child age 6 low-income, urban, AA; GA > 37 weeks; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE=52, NE=63 from initial sample of 224 (52%)	Standard neurological examination; WPPSI-R	None	No PCE-related differences in neurological or intellectual functioning; no weight or HC differences	No PCE group differences evident in standard neurological exam.
<b>Attention</b>	Accornero et al., 2007 Cohort 10	n=415 child age 5 and 7 low-income, urban, AA; GA > 37 weeks; PCE group 32-41% in non-maternal care at time of visit; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report of quantity and duration of drug use	PLF PCE=219, NE=196 from initial sample of 476 (87%)	TOVA; Conners' CPT; CBCL Attention scale; NEPSY Attention/EF domain; WPPSI-R; WIAT	ALC, CIG, and MAR exposure; Child age, gender, BW, length, HC, blood lead level, hearing status, IQ, special services; Caregiver age, education, marital status, employment, primigravida, prenatal visits, current substance use, non-maternal care status	<b>Birth:</b> PCE shorter gestation, lower BW, length, and HC; older mothers, less prenatal care, more CIG and ALC exposure; <b>Age 5-7:</b> PCE children placed in non-maternal care more often; higher caregiver unemployment, more ongoing drug use; GLM/GEE models showed small (.25-.32 SD) but reliable PCE differences in omission errors, response time, and response time variability on CPT tasks even after rigorous covariate control, no commission errors differences	Large, well-controlled study of sustained attention; findings suggest PCE children show a pattern of impaired sustained visual attention marked by slower response time and greater variability at age 7, and more omission errors at age 5 and 7; temporal differences could reflect method (age 5 TOVA vs. age 7 CPT) or maturational issues
<b>Attention</b>	Ackerman et al., 2008 Cohort 6	n=144 (88 exposed, 56 non), child age 7 low-income, urban, AA; GA >32weeks; PCE group 51% in non-maternal care at time of visit; PCE assessment: TOX	PLF of a one-year Randomized Control Trial of a developmental intervention for drug-using mothers; PCE=88, NE=56 from initial sample of 265 (54%)	Conners' CPT; CBCL, Wide Range Achievement Test-3; Stanford-Binet Intelligence Scales—Fourth Edition (SB-IV)	CIG, and ALC exposure, Child age, gender, BW, IQ; Caregiver age, home-intervention status; employment status, current	PCE children remaining in maternal care displayed more omission errors than comparison children. CPT errors of omission and commission were significantly correlated with parent-reported attention problems and academic achievement scores.	Prospective study of the interactions between polysubstance exposure and caregiving environment. PCE in the context of maternal care marked by ongoing drug use may contribute to children's attention problems. PCE children raised in a drug-using context may be vulnerable to problems with self-regulation.

		measures (maternal & infant urine, meconium), maternal report			drug use, income, depression, IQ		
<b>Attention</b>	Bandstra et al., 2001 Cohort 10	n=442 child age 3, 5, and 7 low-income, urban, AA; GA > 37 weeks; PCE group 28-41% in non-maternal care at time of visit; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report of quantity and duration of drug use	PLF PCE=219, NE=196 from initial sample of 476 (87%)	Individualized Assessment of Mastery Motivation; TOVA; Conners' CPT; McCarthy Scales of Children's Abilities/ WPPSI-R/WISC-III	ALC, CIG, and MAR exposure; Child age, gender, BW, length, HC, blood lead level, hearing status, IQ, special services; Caregiver age, education, marital status, employment, primigravida, prenatal visits, current substance use, non-maternal care status	<u>Birth</u> : PCE shorter gestation, lower BW, length, and HC; older mothers, less prenatal care, more CIG and ALC exposure; <u>Age 3-7</u> : PCE children placed in non-maternal care more often; higher caregiver unemployment, more ongoing drug use; Across the three ages GLM/GEE models showed small (.20 SD) but reliable PCE differences when combining multiple indicators of attention, even after controlling for prenatal and postnatal covariates; Fetal growth did not mediate these associations; analyses revealed a modest dose-response association between PCE and omission errors	Longitudinal analyses indicated that PCE children performed approximately .2 SD worse than comparison children on measures of vigilance and sustained attention from age 3-7. A high level of covariate control was incorporated in graduated steps. Heavy ALC used in combination with PCE may lead to the worst outcomes. Fetal growth was not a sig mediator.
<b>Attention and Behavior</b>	Savage et al., 2005 Cohort 14	n=80 child age 10 low-income, urban, AA; GA >34 weeks; PCE group 40% history of non-maternal care; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE=40, NE=40 from initial sample of 219 (37%)	Gordon Diagnostic System (GDS); Trail making Test; Seashore Rhythm Test; TRF	ALC, CIG, and MAR exposure; child IQ, gender, history of foster care; caregiver current drug use assessed by urine screen and self-report	PCE and NE children performed similarly on IQ, GDS outcomes, Trail Making Test, and Seashore Rhythm Test with the exception that PCE children made more commission errors on the most difficult distractibility task on the GDS	Few differences between PCE and NE children on measures of attention or impulsivity except when cognitive demands were high; authors concluded that environmental risk and poverty may obscure PCE-related differences.
<b>Executive Functioning</b>	Mayes et al., 2005 Cohort 15	n=29 child age 8 income not reported, urban, AA; GA not reported; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	PLF PCE=15, NE=14 From initial sample of 396 (7%)	Reaction time and accuracy; latency and amplitude of event-related potentials (ERPs) during a Stroop paradigm	Experimental and control groups were matched based on age, race, and SES	There were group differences in behavioral measures. However, during the first 500 ms of stimulus processing on the Stroop the PCE group generated slower and prolonged ERP responses across a wider range of electrode sites. The NE group produced briefer responses from a more discrete set of sites.	Brain responses in the PCE group were slower and more distributed suggesting that PCE may inhibit "regional specialization" during neurodevelopment.
<b>Neuroimaging (DTI)</b>	Duckworth Warner et al., 2006 Cohort 16	n=53 child age 10 income not reported, urban/rural not reported, AA; GA >36 weeks; maternal care status not	PLF PCE=28, NE=25 From initial sample of 296 (15%)	Frontal white matter integrity (average diffusion and fractional anisotropy), Stroop and Trail Making Test	ALC, CIG, and MAR exposure; Child IQ and gender	PCE group had higher average diffusion coefficients in frontal fibers and longer completion times on part B of the Trail Making Test. Fractional anisotropy measures were negatively correlated with completion time for Trail Making Test and positively correlated with Stroop	PCE was related to higher diffusion values in frontal white matter which suggests less integrity and/or slower maturation of frontal areas. These differences were related to performance on Trail Making Test, which was worse in the PCE group.

		reported; PCE Assessment: TOX measures (mother urine) and maternal report				performance.	
Neuroimaging (Perfusion fMRI)	Rao et al., 2007 Cohort 8	n=49 child age 14 low income, urban, AA; GA >34 weeks; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine) and maternal report, medical record review	PLF PCE=25, NE=24 From initial sample of 224 (22%)	Absolute CBF (ml of blood per 100 g of tissue per minute), relative CBF, and overall and regional gray matter volume in frontal lobe, limbic structures, occipital lobe, and thalamus	Child age and gender; global CBF, and gray matter volume	Global CBF intensities were reduced (by 10%) in PCE group over posterior and inferior brain regions. Relative increases in adjusted-CBF were reported in PCE group in anterior and superior brain regions. There were no group differences in overall gray matter volume, but regional analyses revealed decreased gray matter in the caudate and increased gray matter in the amygdala. Group differences in CBF remained in all regions except amygdala after entering gray matter as a covariate.	PCE was related to reductions in global CBF during adolescence. After controlling for global reductions, the PCE group showed a relative increase in adjusted-CBF in anterior and superior brain regions suggesting compensatory mechanisms may develop during neural ontogeny.
Neuroimaging (Proton MRS)	Smith et al., 2001 Cohort 17	n=26 child age 8-9 variable SES, urban, 40% Caucasian, 40% AA, 20% Hispanic; GA >36 weeks; maternal care status not reported; PCE assessment: maternal report and referral from drug treatment program	Design type not specified PCE=14, NE=12	Whole and regional brain volumes; metabolite concentrations of sodium, creatine, choline-containing- compounds, myoinositol, glutamate + glutamine in right frontal white matter and right striatum	Child age and gender	PCE group had a 13% increase in right frontal white matter levels of creatine but no group difference was reported in other metabolites. There were no gross structural abnormalities, no volumetric differences for whole brain and 7 regions of interest between groups.	Similar to findings in abstinent adult COC users, increased creatine was found in right frontal white matter suggesting that biochemical alterations due to PCE may occur at the cellular level. However, measures of NA were normal in both groups, suggesting no sig neural loss or damage.
Neuroimaging	Singer et al., 2006 (as reported in Dow- Edwards et al., 2006) Cohort 11	n=35 child age 8 low-income, urban, AA; GA >37 weeks; 100% in maternal care; PCE assessment: maternal report, TOX measures (mother & child urine, meconium), or research staff report	Design type? PCE=21, NE=14 From initial sample of 415 (8%)	Gray and white matter volumes; NEPSY (automated segmentation; ANIMAL) and Comprehensive Assessment of Spoken Language (CASL); WPPSI	ALC, CIG, and MAR exposure	PCE was associated with reductions in corpus callosum, occipital and parietal lobes. Regional volumes were correlated with performance on measures of visual attention, visual motor precision and performance, sensorimotor abilities, and syntax construction.	Long-term alterations in brain structure associated with PCE and are related to performance on neuropsychological tests.
Visuo-spatial Working Memory	Schroeder et al., 2004 Cohort 15	n=51 child age 8 low-income, AA; urban/rural, GA not reported; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE=40, NE=11; Attrition data not reported	Visuomotor speed, immediate and short- term memory for visuospatial information from Groton Maze Learning Test (Computerized touchscreen version); Mental Processing Composite score	Mental Processing Composite (K- ABC)	PCE group had fewer correct moves per second than NE on simple visuomotor speed task and on the last 3 (of 5) trials on the maze test. When visuomotor speed was controlled, there was a group difference on first maze trial only. PCE group also took longer to complete and made more errors on the 8-min delay trial. When K-ABC was used as a covariate, only the group difference on the delay trial remained.	The major source of variance between groups was not accuracy but rather slowed visuomotor speed and efficiency accessing the internal spatial map, which suggests a deficit in procedural learning as a result of PCE.

				from K-ABC			
Neuroimaging	Avants et al., 2007 Cohort 8	n=49 child age 14 low income, AA, urban/rural not reported; GA > 34 weeks; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE=25, NE= 24 From initial sample of 224 (22%)	Relative bilateral caudate volumes (automatic diffeomorphic registration, "SNAP")	None	Caudate was smaller in PCE group compared to children in NE group.	The caudate (a major dopaminergic area and an area implicated in attention) appears to be negatively affected by PCE. No covariate control.
Neuroimaging	Rivkin et al., 2008 Cohort 3	n=35 child age 12 low income, urban, AA; GA > 36 weeks ; PCE Assessment: TOX measures (mother & infant urine, meconium) and maternal report	PLF PCE=14 PCE, NE=21 From initial sample of 252 (14%)	Volumes of cortical gray matter, white matter, subcortical gray matter, cerebral spinal fluid, and total parenchyma; HC	ALC, CIG, and MAR exposure; Child age, gender, total intracranial volume	PCE group had reduced cortical gray, total parenchymal volumes, and HC. However, this result was not due to PCE alone. As the number prenatal substance exposures increased, cortical gray, total parenchymal and HC declined. The smallest volumes were found in children with exposure to all 4 substances.	Intrauterine exposures to COC, ALC, & CIG were related to reduced HC, cortical gray, and total parenchyma at school age. These substances may act both individually and cumulatively during gestation to exert effects on brain size/volume.
Neuroimaging	Hurt et al., 2008 Cohort 8	n=34 child age 14 low income, urban, AA; GA > 34 weeks; maternal care status not reported; PCE Assessment: TOX measures (mother & infant urine) and maternal report	PLF PCE = 17, NE = 17 From initial sample of 224 (15%)	Behavioral accuracy to non-spatial working memory task & mean blood oxygen level- dependent (BOLD) signal from fMRI	Discrimination scores from behavioral task; participants matched by sex and IQ	There were no group differences on behavioral performance on the non- spatial working memory task or on mean activation the two a priori regions of interest in the prefrontal cortex (Brodmann area 10 & 46) or five functional regions of interest (cingulate, right dorsolateral prefrontal cortex, left dorsolateral prefrontal cortex, right parietal, left parietal).	PCE and NE were similar in performance on non-spatial working memory task and in fMRI activation of 7 regions of interest during task performance.

Abbreviations: PCE, prenatal cocaine exposure; NE, non-exposed; COC, cocaine; HER, heroin; ALC, alcohol; CIG, cigarette or tobacco; MAR, marijuana; TOX, toxicology report; BW, birthweight; HC, head circumference; SES, socio-economic status; AA, African American; PLF, prospective longitudinal follow-up; HPD, historical prospective design; WISC, Wechsler Intelligence Scale for Children; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; CPT, Continuous Performance Test; CBCL, Child Behavior Checklist (parent form); TRF, Achenbach Teacher Report Form; HOME, Home Observation for Measurement of the Environment; CELF, Children's Evaluation of Language Fundamentals; CPT, Continuous Performance Task; fMRI, functional magnetic resonance imaging; CBF, cerebral blood flow; GLM, general linear modeling; GEE, generalized estimating equations; sig, significant.