Neurotoxicology and Teratology 34 (2012) 434–441

Contents lists available at SciVerse ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

Memory ability and hippocampal volume in adolescents with prenatal drug exposure

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ARTICLE INFO

Article history:
Received 12 January 2012
Received in revised form 15 May 2012
Accepted 21 May 2012
Available online 28 May 2012

Keywords:
Prenatal drug exposure
Memory
Hippocampus
Development
Adolescent brain

ABSTRACT

The objective of the present study was to examine the influence of prenatal drug exposure (PDE) on memory performance and supporting brain structures (i.e., hippocampus) during adolescence. To achieve this goal, declarative memory ability and hippocampal volume were examined in a well-characterized sample of 138 adolescents (76 with a history of PDE and 62 from a non-exposed comparison group recruited from the same community, mean age = 14 years). Analyses were adjusted for: age at time of the assessments, gender, IQ, prenatal exposure to alcohol and tobacco, and indices of early childhood environment (i.e., caregiver depression, potential for child abuse, and number of caregiver changes through 7 years of age). Results revealed that adolescents with a history of PDE performed worse on the California Verbal Learning Test—Child Version (CVLT-C), and story recall from the Children's Memory Scale (CMS), and had larger hippocampal volumes, even after covariate adjustment. Hippocampal volume was negatively correlated with memory performance on the CVLT-C, with lower memory scores associated with larger volumes. These findings provide support for long-term effects of PDE on memory function and point to neural mechanisms that may underlie these outcomes.

1. Introduction

Drug abuse among women of childbearing age is a serious public health problem as ramifications often extend beyond users themselves and impact the development of unborn children (Lester and Lagasse, 2010; Lester et al., 1998; Lester and Tronick, 1994). Results from the 2009–2010 National Survey on Drug Use and Health indicate that 16.2% of pregnant women aged 15 to 17, 7.4% of pregnant women aged 18 to 25, and 1.9% of pregnant women aged 26 to 44 are current illicit drug users (Substance Abuse and Mental Health Services Administration, 2011). However, these statistics likely underestimate actual prevalence, as self-report measures are subject to bias as a result of guilt, embarrassment, fear of reprisal, or loss of custody (Chasnoff and Griffith, 1989).

Prenatal drug exposure (PDE) to cocaine, heroin, methamphetamines, or multiple illicit substances may alter the course of development and adversely impact physical, cognitive, and socio-emotional development. The mechanisms underlying these effects are complex, as initial insults occur and effects cascade during a time of rapid neural development, ultimately disrupting and compromising brain function. For example, cocaine has been shown to impact signal transduction in dopaminergic pathways, which leads to alterations in cortical neuronal development and to permanent morphological abnormalities in multiple brain structures (see Harvey, 2004 for review). In addition, such prenatal mechanisms combine with postnatal risk factors (e.g., environmental conditions associated with continued drug use) to place individuals with a history of PDE at even higher risk for poor outcomes (Ackerman et al., 2010). For example, substance-abusing pregnant women are at an elevated risk for violence and sexual victimization (Hans, 1999), implying their children are at higher risk of being raised in a dysfunctional environment.

The majority of studies to date have focused on the impact of a particular substance (e.g., maternal cocaine use); however data from 8500 mothers in the Maternal Lifestyles Study showed that single drug use is very rare; most women ingest multiple substances (referred to as poly-substance use, Lester et al., 2001). Considering the effects of such poly-substance exposure is critical, as substances that may not be the focus of a particular investigation have known effects on fetal and infant development (e.g., tobacco and alcohol, Frank, 2001).

Longitudinal studies that have followed PDE cohorts from birth through middle childhood report mixed findings regarding the association between PDE and growth, cognitive ability, academic achievement, and language functioning during the school-age years (see Ackerman et al., 2010; Lester and Lagasse, 2010 for reviews). In particular, effects tend to be small and are commonly attenuated or moderated by child

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doi:10.1016/j.ntt.2012.05.054

or environmental variables (e.g., gender, race, birth weight, prenatal alcohol and/or tobacco exposure, non-maternal care, continued maternal drug use, caregiver mental health, and poverty).

In spite of this variability, evidence suggests that subtle effects of PDE in certain domains (i.e., sustained attention, inhibitory control, and behavioral regulation) persist into middle childhood even after rigorous control of confounding variables (Ackerman et al., 2010). These effects have been best documented in samples with prenatal cocaine exposure. Higher-order cognitive abilities and the brain networks that support them continue to develop and remain open to environmental influences throughout the adolescent years (Gogtay et al., 2006); for these reasons, we may not be able to detect subtle differences in functionality until the neural systems responsible for them have fully developed. This protracted development may be driven, in part, by the increasingly complex cognitive and social demands that children face as they transition from childhood to adolescence (Arnett, 1999). Given these continued changes, it is reasonable to expect that the effects of PDE may also change over time. Effects may decrease as maturation continues or they may increase as cognitive and social demands increase, along with environmental challenges and expectations (Yumoto et al., 2008). In order to fully characterize the effects of PDE, cohorts need to be followed through adolescence and into adulthood (Ackerman et al., 2010).

Reports are beginning to appear regarding the effects of PDE in adolescence (Avants et al., 2007; Bandstra et al., 2011; Betancourt et al., 2011; Bridgett and Mayes, 2011; Chaplin et al., 2010; Delaney-Black et al., 2011; Fisher et al., 2011; Greenwald et al., 2011; Hurt et al., 2008; Li et al., 2009, 2011; Rao et al., 2007; Rivkin et al., 2008; Rose-Jacobs et al., 2011; Warner et al., 2011). Findings suggest that subtle effects of PDE are present during adolescence on select aspects of higher-order cognition and language (Bandstra et al., 2011; Bridgett and Mayes, 2011; cf. Betancourt et al., 2011). For example, Bandstra and colleagues report associations between PDE and lower functioning in expressive and total language abilities during adolescence, after statistically controlling for possible confounding variables (i.e., child's age at testing, gender, prenatal exposure to alcohol, marijuana, and tobacco, and additional medical and social-demographic covariates; Bandstra et al., 2011). Although the effects are small, over time there emerges a consistent pattern of differences between groups. These findings extend previous research documenting the effects of PDE on language function during childhood and suggest they continue to persist into adolescence (Bandstra et al., 2002, 2004).

In other cognitive domains, effects of PDE have been shown to emerge during adolescence. For example, one study examined effects of PDE on incidental memory (i.e., memory when participants were not aware their recall of the material would be examined) and showed that although there were no differences between PDE and non-exposed groups' performance in childhood, memory ability improved at a slower rate in the PDE group, resulting in differences in memory performance during adolescence (Betancourt et al., 2011). Thus, a memory effect arose during the course of development. This finding is consistent with non-human primate studies, which have been able to follow development into adulthood and have also documented impairments in memory abilities as a result of PDE (Hamilton et al., 2010).

Such emerging memory impairments have been interpreted in the context of recent neuroimaging data, which suggest that the hippocampus (a structure vital for memory) has a protracted developmental course and matures in a complex fashion throughout the teenage years (Gogtay et al., 2006) and is susceptible to influences from quality of care in early childhood (Belsky and de Haan, 2011; Luby et al., 2012; Rao et al., 2009). During adolescence, posterior subregions of the hippocampus show enlargement over time and anterior subregions show volume loss (Gogtay et al., 2006). Thus, normative development of the hippocampus includes both increases and decreases in volume. Better caregiving quality early in life has been associated with larger hippocampal volume during school age (Luby et al., 2012) and smaller hippocampal volume during adolescence (Rao et al., 2009).

The suggestion that PDE impacts neural development is consistent with results from recent neuroimaging studies showing that children and adolescents with a history of PDE show differences in brain structure and function, including lower mean cortical gray matter and total parenchymal volumes (Rivkin et al., 2008; Walhovd et al., 2007) and smaller volumes of subcortical structures (e.g., caudate) versus comparison groups (Avants et al., 2007; Walhovd et al., 2007). Effects of PDE on both global and local cerebral blood flow have also been reported during rest (Li et al., 2009; Rao et al., 2007) and during cognitive tasks (Li et al., 2009, 2011, cf. Hurt et al., 2008). For example, Li et al. (2011) reported stronger functional connectivity within the default mode network (DMN) at rest and less deactivation in DMN during a working memory task among prenatally cocaine exposed adolescents compared to non-exposed controls.

The current study sought to examine the effects of PDE (cocaine and/or heroin) as well as other prenatal and early environmental factors on declarative memory ability using intentional memory tasks (i.e., participants knew their memory for the information would be examined) and hippocampal volume in a well-characterized sample of adolescents with a history of PDE and a comparison group recruited from the same urban community. Previous research has shown that hippocampal volume is related to memory performance in typically developing groups, with smaller volumes associated with better memory performance (Sowell et al., 2001; Van Petten, 2004). Based on previous research, we hypothesized that adolescents with PDE would show worse memory performance compared to the community comparison group and that differences at the neural level would be apparent in hippocampal volume.

2. Method

2.1. Participants

Participants were part of a longitudinal follow-up of drug-using women and their infants (Nair et al., 2008). Recruitment procedures have been described in detail elsewhere (Schuler et al., 2002). Regarding the PDE group, women and their babies were recruited during their postnatal stay in a university hospital that served a largely inner-city, African American population. Eligibility criteria for the PDE group included prenatal exposure to heroin and/or cocaine (assessed via maternal report and/or positive maternal and/or infant toxicology screen), gestational age > 32 weeks, birth weight > 1750 g, and no congenital or medical problems requiring admission to the neonatal intensive care unit. Recruitment began in 1991 and continued for 30 months (Nair et al., 2008). Women who met the eligibility criteria were approached in the hospital shortly after delivery. A total of 265 participants completed the baseline evaluation two weeks after delivery. Their children were followed for evaluation visits through middle childhood (n = 144 at 6 years) and were re-contacted for follow-up during adolescence. The present analyses focus primarily on data collected during early adolescence.

Two non-exposed community comparison (CC) samples with no evidence of PDE were recruited from the university primary care clinic at the 5-year time point (n = 70) and early adolescence time point (n = 24). Medical records were reviewed to identify children who were born in the university hospital during the same period as children in the PDE group, had negative mother and infant toxicology screens, and had no evidence of drug use during pregnancy (Schuler et al., 2002). Participants were matched with the exposed sample for socioeconomic status, age of first pregnancy, and race.

Both the PDE and CC participants were contacted in early adolescence and recruited for the current phase of the evaluation. A total of 138 (PDE = 76, CC = 62) participants were available for assessment

Table 1
Participant characteristics.

	Non-PDE comparison group (CC) (n = 62)	Prenatal drug-exposed group (PDE) (n = 76)	
	n (%)	n (%)	*p*-Value
Prenatal exposure to alcohol	**11 (18%)**	**41 (54%)**	**<.001**
Prenatal exposure to tobacco	**13 (21%)**	**60 (79%)**	**<.001**
Male	31 (50%)	38 (50%)	ns
Right-handed	54 (87%)	65 (86%)	ns
In maternal care at age 6 years	**62 (100%)**	**46 (61%)**	**<.001**
In maternal care at age 14 years	**61 (98%)**	**43 (57%)**	**<.001**
At birth	Mean ± SD	Mean ± SD	*p*-Value
Gestational age	**39.34 ± 1.45**	**38.49 ± 2.44**	**0.03**
Birth weight (g)	**3407.28 ± 597.98**	**2804.51 ± 521.50**	**<.001**
Weight-for-gestational age z-score[a]	**0.19 ± 1.17**	**−1.15 ± 1.18**	**<.001**
Weight-for-length/height z-score[a]	**−0.42 ± 1.38**	**−1.02 ± 1.71**	**0.04**
Birth length (cm)	**50.54 ± 2.73**	**48.00 ± 3.24**	**<.001**
Length-for-gestational age z-score[a]	**0.55 ± 1.44**	**−0.81 ± 1.68**	**<.001**
Birth head circumference (cm)	**34.94 ± 2.72**	**32.97 ± 2.58**	**<.001**
Head circumference-for-gestational age z-score[a]	**0.64 ± 2.17**	**−0.98 ± 2.15**	**<.001**
Maternal age at time of child's birth (years)	**24.48 ± 5.82**	**27.63 ± 4.78**	**<.001**
Maternal education at time of birth (years)	**11.89 ± 1.02**	**11.19 ± 1.51**	**.006**
Apgar scores (1 min after birth)	7.89 ± 1.25	7.99 ± 1.05	ns
Apgar scores (5 min after birth)	8.87 ± 0.46	8.88 ± 0.47	ns
6 years of age	Mean ± SD	Mean ± SD	*p*-Value
Caregiver depression (CES-D)	12.31 ± 10.22	12.59 ± 10.57	ns
Risk for child abuse (CAPI)	128.16 ± 95.66	141.24 ± 138.19	ns
Number of caregiver changes (through 7 years)	**0.03 ± 0.16**	**0.93 ± 1.16**	**<.001**
Adolescence	Mean ± SD	Mean ± SD	*p*-Value
Age at interview (years)	14.05 ± 1.20	14.26 ± 1.13	ns
Participant's IQ (WASI)	87.49 ± 12.76	86.72 ± 13.17	ns
Current caregiver IQ (WASI)	88.92 ± 11.98	85.18 ± 13.828	ns

Bold indicates significant group difference.
[a] Based on World Health Organization (WHO) growth standards.

(Table 1). These participants were compared to those who were lost to follow-up on the following 7 key variables: birth weight, maternal education, maternal age at first pregnancy, maternal age at the birth of the target child, neonatal abstinence scores, child gender, and receipt of public assistance. There were no differences between those lost and those retained for either the exposed or non-exposed groups. A subset of 52 adolescents (PDE = 28, CC = 24) were eligible and agreed to participate in an associated neuroimaging study (see below for details). The demographic characteristics of participants in the neuroimaging subset were similar to that of the larger sample.

2.2. Procedures

PDE was assessed at delivery through positive mother toxicology screen, positive infant toxicology screen, maternal self-report, and/or notation in the mother's chart (Black et al., 1993; Schuler et al., 2000). Participants who tested positive for or reported use of heroin and/or cocaine were considered drug exposed. Many of the drug-exposed participants also tested positive for or reported use of marijuana, tobacco, and alcohol. In addition to these substances, participants were tested for and queried about amphetamine, barbiturate, hallucinogen, and tranquilizer use. In the current sample, 33% of the infants were exposed to cocaine, 13% were exposed to heroin, and 54% were exposed to both cocaine and heroin. In most cases exposure to cocaine and/or heroin (84%) was "heavy" as defined by a positive toxicology screen at birth and/or maternal self-reported use of 2 times or more per week during the last 6 months of pregnancy (i.e., 48–180 days). Consistent with previous studies (Ackerman et al., 2010; Lester et al., 1998), the use of other drugs was common (i.e., cigarettes, alcohol); 87% were exposed to 3 or more substances.

Each child and current caregiver, completed a systematic protocol at our lab during middle childhood (mean age = 6 years) and early adolescence (mean age = 14 years). Data from the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff, 1977) and the Child Abuse Potential Inventory (CAPI Milner, 1986) obtained during middle childhood, and data from the Wechsler Abbreviated Scale of Intelligence (WASI, Wechsler, 1999), California Verbal Learning Test—Child Version (CVLT-C, Delis et al., 1994), and Children's Memory Scale (CMS, Cohen, 1997) obtained during early adolescence are reported here. The neuroimaging protocol included both structural and functional MRI scans and was completed by a subset of participants (n = 52; 28 PDE, 24 CC) who were interested in participating and met the eligibility criteria. These sessions occurred approximately 5 months after the lab visit (mean = 161 days, SD = 172 days, range = 7–918 days). There were no differences between groups in delay between the initial visit and scan $p = .51$. Data from the structural MRI are reported here.

The study was approved by the Institutional Review Boards at University of Maryland Baltimore and National Institute on Drug Abuse Intramural Research Program. Informed consent was obtained from participant's caregivers and assent was obtained from all participants.

2.3. Cognitive assessments

An estimate of general intellectual ability (IQ)[1] was obtained using the Vocabulary and Matrix Reasoning subtests from the WASI. The Vocabulary subtest measures word knowledge, verbal concept formation, and fund of knowledge. The Matrix Reasoning subtest measures visual information processing and abstract reasoning skills. Reliability coefficients of the two subtest method for estimating full-scale IQ are .92–.95 (range indicates values for ages 11–16 years).

[1] IQ scores were not available for 3 adolescents (2 PDE, 1 CC) due to time limits during the testing session.

Memory was evaluated using both the CVLT-C and CMS. The CVLT-C measures strategies and processes involved in learning and recalling verbal material. Only the immediate recall portion was administered. In this task participants were asked to remember a shopping list of 15 items (List A). For the first five trials, the same list was read to participants and they were asked to recall words from the list after each presentation. A second interference list (List B), was then presented, and participants were asked to recall as many words from this list as possible. When the List B trial was completed, participants were again asked to recall words from List A without an additional presentation of List A. The 15 words on List A were categorized as fruits, clothing, or toys. These categories were used as cues to elicit words from the original list, for example, "Tell me all the things to wear." This assessment resulted in measures of immediate recall (List A — Trial 1), learning (List A — Trial 5), proactive interference (List B and percent change from List A — Trial 1 to List B — Trial 1), free recall (short-delay free recall), and cued recall (semantic and serial clustering).

The CMS measures learning and memory across a variety of memory dimensions. Only the story recall subtest was administered to assess free recall and recognition of story narratives. Participants were read two short stories and asked to recall them immediately and after a 15-minute delay. This assessment resulted in measures of immediate and delayed recall of verbatim and thematic information as well as delayed recognition.

2.4. Anatomical MRI

A 3-T Siemens Allegra scanner was used to acquire a whole-brain oblique axial T_1-weighted structural image (MPRAGE) for anatomical evaluation (1-mm^3 isotropic voxels: TR = 2.5 s; TE = 4.38 ms; FA = 80°). Cortical reconstruction and volumetric segmentation were performed using AFNI (Analysis of Functional Neuro-Imaging; Cox, 1996) and the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/). The technical details of the Freesurfer pipeline are described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000; Fischl et al., 2001; Fischl et al., 2002; Fischl et al., 2004a; Fischl et al., 1999a; Fischl et al., 1999b; Fischl et al., 2004b; Han et al., 2006; Jovicich et al., 2006; Ségonne et al., 2004, see: http://surfer.nmr.mgh.harvard.edu/ for overview). Briefly, this processing includes motion correction (Reuter et al., 2010) of volumetric T_1 weighted images, removal of non-brain tissue (Ségonne et al., 2004), automated Talairach transformation, segmentation of volumetric structures (Fischl et al., 2002, 2004a), intensity normalization (Sled et al., 1998), tessellation of the gray matter and white matter boundary, automated topology correction (Fischl et al., 2001; Ségonne et al., 2007), and surface deformation (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. They are not restricted to the voxel resolution of the original data and thus are capable of detecting submillimeter differences between groups. Freesurfer morphometric procedures have been demonstrated to show good test–retest reliability across scanner manufacturers and across field strengths (Han et al., 2006).

These procedures resulted in multiple measures; total cortical volume, whole brain gray matter, whole brain white matter, and left and right hippocampal volumes are reported. Freesurfer has been validated against hand measurements and has shown to be a reliable means of detecting differences in hippocampal volume (Morey et al., 2009).

2.5. Environment

Previous work has shown that the environment associated with PDE (e.g., quality and stability of maternal care, see Ackerman et al., 2010 for review) plays a critical role in interpreting the effects of PDE. Such environmental characteristics may also influence hippocampal development early in life (Belsky and de Haan, 2011; Rao et al., 2009). To index the environment, we drew on available data[2] in the longitudinal dataset for three different measures reflecting the early caregiving environment: depressive symptoms, child abuse potential, and caregiver changes. The children's primary caregivers completed the CES-D and the CAPI during assessments in the 6th year of the child's life. The CES-D is a short self-report scale designed to measure depressive symptomatology with higher scores indicating more depressive symptoms (Radloff, 1977). The CAPI is a screening tool for the detection of potential child abuse that encompasses the following six factors: distress, rigidity, unhappiness, problems with child and self, problems with family, and problems with others (Milner, 1986). Higher scores indicate higher risk for abuse. Finally, the number of caregiver changes through the 7th-year of life was also recorded. Caregiver changes were tracked via caregiver report at each assessment.

2.6. Analytic approach

Group differences in memory abilities and brain volumes were evaluated using a series of analyses of covariance (ANCOVAs). First, group differences on scaled scores from the memory assessments (CVLT-C and CMS) were examined without covariates (Model 1). Second, to examine the hypothesis that memory differences were specific to PDE, age, gender, and IQ were entered as covariates (Model 2). Third, gestational exposure to alcohol and tobacco were entered as covariates, as previous research suggests these factors exert influences on cognitive outcomes (e.g., Cornelius et al., 2001; Huizink and Mulder, 2006; Lewis et al., 2007) and brain structure (Coles and Li, 2011; Lebel et al., 2011) (Model 3). Fourth, because aspects of the early caregiving environment, such as parental nurturance and environmental stimulation have been shown to influence cognitive abilities (e.g., Farah et al., 2006, 2008) and their neural correlates (including the hippocampus, Bredy et al., 2003; Meaney, 2001; Rao et al., 2009) analyses were re-conducted with maternal depression (CES-D), potential for child abuse (CAPI) and stability of early care (as indexed by the number of caregiver changes) as covariates (Model 4). A hierarchical approach was taken such that significant covariates from each step were included in subsequent models.

Measures of brain volume (total gray matter, total white matter, subcortical gray matter, intracranial volume, left hippocampus, right hippocampus) were analyzed with the same four models and hierarchical approach. Total gray matter was also included as a covariate in each model examining differences in left and right hippocampal volumes to ensure that differences were specific to the hippocampus and not due to differences in brain size overall.

3. Results

3.1. Environment

We examined group differences in total scores on the CES-D and CAPI and on the number of caregiver changes (see Table 1). There were no differences between groups on the CES-D or CAPI. The PDE group experienced more caregiver changes in the first 7 years of life compared to the CC group.

3.2. Cognitive assessments

The initial between-groups ANOVA indicated that there were differences between PDE and CC on two measures of the CVLT-C

[2] CES-D was missing for 33 individuals (7 PDE, 26 CC), CAPI was missing for 34 individuals (10 PDE, 24 CC), caregiver changes were missing for 29 individuals (5 PDE, 24 CC). These individuals were omitted from analyses that required these measures.

Table 2
Summary of standard scores on the CVLT-C and scaled scores on the CMS for PDE and CC groups (n = 138). Summary of brain volume measures for subset of PDE and CC groups who underwent neuroimaging protocol (n = 52). Results regarding group differences from ANCOVA models with measures of memory performance and brain volume as dependent variables. Group difference *p* values are represented.

	Non-PDE comparison group (CC)	Prenatal drug-exposed group (PDE)	*p*-Value			
CVLT-C	Mean ± SD	Mean ± SD	Model 1	Model 2	Model 3	Model 4
List A — Trial 1	−0.19 ± 1.03	−0.18 ± 0.90	ns	ns	ns	ns
List A — Trial 5	−0.40 ± 1.04	−0.34 ± 1.17	ns	ns	ns	ns
List B	−0.25 ± 1.07	−0.70 ± 1.05	**.02**	**.03**	.21	.17
Percent change	−0.06 ± 1.22	−0.47 ± 1.03	**.03**	.06	.06	.19
Short delay — free recall	−0.42 ± 0.86	−0.36 ± 1.01	ns	ns	ns	ns
Semantic clustering	0.20 ± 1.06	0.30 ± 1.07	ns	ns	ns	ns
Serial clustering	−0.53 ± 0.68	−0.39 ± 0.87	ns	ns	ns	ns
CMS	Mean ± SD	Mean ± SD	Model 1	Model 2	Model 3	Model 4
Immediate recall	8.61 ± 3.38	7.50 ± 2.68	**.03**	**.03**	ns	ns
Immediate thematic	8.00 ± 3.14	6.70 ± 2.76	**.01**	**.01**	.17	ns
Delay recall	8.21 ± 3.30	7.09 ± 2.63	**.03**	**.02**	.12	ns
Delay thematic	7.62 ± 3.17	6.69 ± 2.80	.07	.08	ns	ns
Delay recognition	7.59 ± 3.31	7.11 ± 3.30	ns	ns	ns	ns
Whole brain	Mean ± SD	Mean ± SD	Model 1	Model 2	Model 3	Model 4
Intracranial volume	1,290,832.33 ± 175,035.90	1,273,308.39 ± 210,959.36	ns	ns	ns	ns
Total gray matter	460,453.19 ± 41,042.05	460,774.83 ± 38,234.44	ns	ns	ns	ns
Total white matter	412,024.65 ± 41,766.86	417,663.25 ± 42,461.69	ns	ns	ns	ns
Total subcortical gray	181,948.25 ± 20,414.85	185,454.21 ± 20,699.06	ns	ns	ns	ns
Hippocampus[a]	Mean ± SD	Mean ± SD	Model 1	Model 2	Model 3	Model 4
Left hippocampus	3810.88 ± 327.61	4046.7143 ± 409.68	**<.001**	**<.001**	**<.001**	**.01**
Right hippocampus	3877.42 ± 346.46	4081.25 ± 381.31	**.02**	**.01**	**.01**	ns

Bold indicates significant group difference, ns indicates no significant difference.
Model definitions:
Model 1 covariates — none.
Model 2 covariates — age, gender, IQ.
Model 3 covariates — significant covariates from Model 2 and gestational exposure to tobacco and alcohol.
Model 4 covariates — significant covariates from Models 2 and 3 and early childhood environment: CES-D, CAPI, and number of caregiver changes.
[a] Total gray matter was also included as a covariate in all models.

(Model 1, see Table 2 and Fig. 1). Specifically, List B recall (an index of proactive interference) was lower in the PDE compared to the CC group, $F(1, 136) = 6.10$, $p = .02$. Z-scores for percent change between List B versus List A recall, which also characterizes the extent of proactive interference, were also significantly lower in the PDE compared to the CC group, $F(1, 136) = 4.74$, $p = .03$. There was a 14% decrease in the PDE group, compared to a 1% increase in the CC group. As suggested by the percent change score, there were no differences between groups in scaled scores for List A recall at Trial 1 (a measure of immediate recall), $p = .96$. When age, gender, and IQ were entered into the analysis as covariates (Model 2) differences in List B recall remained, $F(1, 130) = 4.66$, $p = .03$, but differences in z-scores for percent change between List B versus List A recall became marginal, $F(1, 130) = 3.48$, $p = .06$. Both age, $F(1, 130) = 4.02$, $p = .05$, and IQ, $F(1, 130) = 6.60$, $p = .01$, were significantly associated with List B performance and were therefore included in subsequent models. When exposure to alcohol and tobacco were added as covariates (Model 3), the difference in List B recall was no longer apparent ($p = .21$) however, z-scores for percent change between List B versus List A recall remained marginally different between groups, $F(1, 129) = 3.74$, $p = .06$. When measures of the early caregiving environment were added as covariates (Model 4), differences in both List B recall and differences in z-scores for percent change between List B versus List A recall were no longer apparent, $ps = .17$ and .19 respectively.

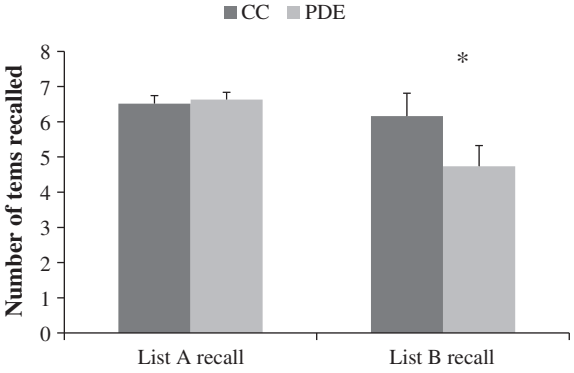

Fig. 1. CVLT-C raw scores for PDE and CC groups. * $p < .05$.

Overall, findings for the CVLT-C followed the same pattern in the subset of participants who underwent neuroimaging. There was a marginal difference between PDE and CC on scaled scores for List B recall, $F(1, 50) = 3.71$, $p = .06$, and a significant difference on scaled scores (z scores) for percent change between List B versus List A recall, $F(1, 50) = 4.67$, $p = .04$, with the pattern of PDE showing worse performance than CC. Given the reduced sample size, other models were not examined.

On the CMS, significant group differences, with the CC group performing better than the PDE group, were found for immediate recall scaled scores, $F(1, 135) = 4.56$, $p = .03$, immediate recall thematic scaled scores, $F(1, 135) = 6.67$, $p = .01$, and delayed recall scaled scores, $F(1, 134) = 4.86$, $p = .03$[3] (see Table 2 and Fig. 2). There was a marginal difference for delayed recall thematic scaled scores, $F(1, 134) = 3.29$, $p = .07$. There was no difference between groups in delayed recognition scaled scores, $p = .40$. This pattern of findings was identical when age, gender, and IQ were entered into the analyses (Model 2). There were significant differences between groups on immediate recall scaled scores, $F(1, 29) = 4.91$, $p = .03$, immediate recall thematic scaled scores, $F(1, 129) = 6.80$, $p = .01$, and delayed recall scaled scores,

[3] The CMS was not completed by 1 adolescent (in the CC group); 3 other adolescents are missing data for various portions of the task (3 PDE, 1 missing delay recall, thematic, and recognition, 2 missing delay recognition).

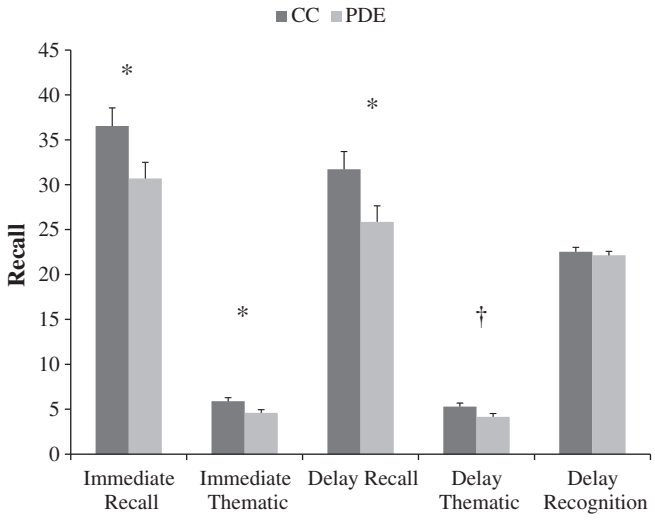

Fig. 2. CMS story recall raw scores for PDE and CC groups. * $p<.05$, † $p<.10$.

$F(1, 128)=5.35$, $p=.02$. There was a marginal difference between groups on delayed thematic scaled scores, $F(1, 128)=3.22$, $p=.08$, and no difference on delayed recognition scaled scores, $p=.39$. IQ was significantly associated with performance on all 5 CMS measures, $F(1, 126–129)=19.85–33.21$, $ps<.001$, and was included in subsequent models. When gestational exposure to alcohol and tobacco were added in the analysis as covariates (Model 3), no significant differences between groups remained. When measures of the early caregiving environment were added as covariates (Model 4), no significant group differences emerged. In addition to IQ, CES-D $F(1, 91)=4.05$, $p=.05$ was a significant predictor of immediate recall.

Findings from the CMS for the neuroimaging subset were in the same direction, with a marginal difference between PDE and CC on immediate thematic scaled scores $F(1, 50)=3.49$, $p=.07$. Given these findings and the reduced sample size, other models were not examined.

3.3. Anatomical MRI

The initial ANOVA revealed no differences between PDE and CC groups in total intracranial volume, total cortical gray matter, total white matter volume, and total subcortical gray matter volume, $ps>.54$ (Table 2). No group differences emerged after statistically controlling for variables in Models 2, 3, or 4, $ps>.15$. Age was significantly associated with total intracranial volume, total cortical gray matter, and total subcortical gray matter volume, $F(1, 47)=6.32–9.11$, $ps<.05$, and gender was associated with total intracranial volume, total cortical gray matter, total white matter volume, and total subcortical gray matter volume, $F(1, 47)=9.14–71.03$, $ps<.01$.

The initial ANCOVA with total cortical gray matter entered as a covariate revealed significant differences between PDE and CC in both the left, $F(1, 49)=9.63$, $p=.003$, and right hippocampus, $F(1, 49)=5.59$, $p=.02$. Total cortical gray matter was significantly associated with both left and right hippocampal volumes, $F(1, 49)=21.73$ and 46.48, $ps<.001$, respectively and was included in subsequent models. Hippocampal volume was larger in the PDE compared to the CC group, see Fig. 3. These differences remained after statistically controlling for age, gender, IQ and total cortical gray matter (Model 2), left: $F(1, 46)=10.58$, $p=.002$, right: $F(1, 46)=6.66$, $p=.01$. Differences remained after controlling for prenatal exposure to tobacco and alcohol as well as total cortical gray matter (Model 3), left: $F(1, 47)=10.11$, $p=.003$, right: $F(1, 47)=6.02$, $p=.02$. Differences also remained for the left hippocampus after controlling for the early caregiving environment and total cortical gray matter (Model 4), $F(1, 36)=7.86$, $p=.008$; however differences were no longer apparent for the right hippocampus, $F(1, 36)=0.66$, $p=.42$. Measures of caregiver depression (CES-D) were significantly associated with left hippocampal volume, $F(1, 36)=7.17$, $p=.01$.

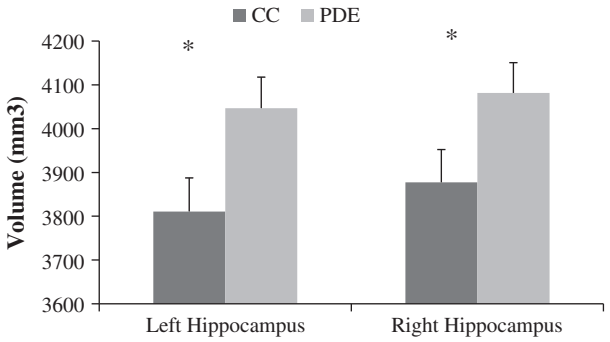

Fig. 3. Hippocampal volume for PDE and CC groups. * $p<.05$.

3.4. Associations between hippocampal volume and memory performance

Nonparametric correlations (Spearman's rho) were conducted between measures of memory performance that differed between groups and hippocampal volume adjusted for total cortical volume. On the CVLT-C, scaled scores (z scores) for percent change between List B versus List A recall were negatively correlated with both left, $r(52)=-.33$, $p=.02$, and right, $r(52)=-.28$, $p=.05$ hippocampal regions, such that larger hippocampal volume was associated with worse performance on the task (i.e., more proactive interference). No significant correlations were observed between hippocampal volume and CMS.

4. Discussion

In this study, we report differences in memory ability and bilateral hippocampal volume during adolescence in a PDE sample. Differences in hippocampal volume were related to memory ability; consistent with previous findings, smaller hippocampi were related to better performance (Sowell et al., 2001; Van Petten, 2004). These findings are also consistent with previous research showing differences between PDE and non-exposed adolescents' performance on incidental memory tasks (Betancourt et al., 2011) and findings of memory impairments in adult non-human primates with histories of PDE (Hamilton et al., 2010).

In our sample, small to moderate differences were found on multiple memory measures, including a list learning task and a story recall task. In the former, although there were no differences in memory for the initial list presented (CVLT-C List A), there were differences on subsequent lists (CVLT-C List B). This pattern of performance may reflect proactive interference, or difficulty in learning new information because of already existing information; suggesting that although memory impairment may not be apparent on simple tasks, it may emerge under increased task demands. In general, these differences remained even after statistically controlling for other factors, including: age, gender, and IQ (Model 2). However these differences were diminished when gestational exposure to alcohol and tobacco (Model 3), and early childhood environment (Model 4) were controlled. Together with previous literature (Betancourt et al., 2011), these results suggest both direct effects and indirect effects (through characteristics that are associated with or commonly co-occur with PDE, such as use of multiple substances, low-quality caregiving) of PDE on memory. Specifically, results from this study suggest that PDE may increase susceptibility to proactive interference, which arises through atypical development of the hippocampus, as hippocampal volume was negatively correlated with performance on the CVLT-C. However, a direct test of this mediation model was precluded by the small sample size.

In the story recall task, differences were apparent in recall measures but not recognition measures both before and after controlling for age, gender and IQ (Model 2). However, these differences were diminished after gestational exposure to alcohol and tobacco (Model 3) and the early caregiving environment (Model 4) were controlled. These results suggest that PDE may impact recall memory indirectly through characteristics that are associated with or commonly co-occur with PDE. Findings from both the CMS and CVLT-C suggest that although PDE may exert an influence on memory, other factors also contribute to the severity of these effects. In particular, measures of maternal depression emerged as a significant predictor of recall ability. One possibility is that a low-quality early caregiving environment (i.e., as characterized by caregiver depression and multiple caregiver changes) did not foster cognitive development. Thus, one way to improve outcomes in recall memory in children with a history of PDE would be to promote and support maternal functioning and the early caregiving environment.

It is notable that scores for both groups of children on the CMS were quite low (near the 25th percentile for the test). This is likely due to the low-quality environment associated with poverty/low-SES environments that are characteristic of the neighborhoods in which our participants were raised that have been shown to have a particularly strong impact on memory abilities (National Institute of Child Health and Human Development Early Child Care Research Network, 2005; Farah et al., 2006). This finding highlights why it is essential that the comparison group used in studies such as ours that are designed to detect effects of PDE over and above other environmental factors (such as poverty) includes participants from the same communities/SES. In the present study we did include participants from the same community and with similar SES. Differences between groups in terms of memory scores were significant, yet constitute small to medium effect sizes. This finding is consistent with the majority of previous studies on PDE indicating that although long-term effects exist, they yet are subtle (Ackerman et al., 2010; Lester and Lagasse, 2010).

Findings from the MRI portion of the study indicated that hippocampal volumes were larger in the PDE group. This effect remained after controlling for differences in age, gender, and IQ (Model 2) gestational exposure to other substances (Model 3), and the early caregiving environment (albeit in the left hemisphere only, Model 4). In contrast to previous research (Rao et al., 2009) these findings suggest an effect of PDE on hippocampal volume. These effects were quite robust, particularly in the left hemisphere, as they remained after statistically controlling for multiple confounding variables. Moreover, these differences appear to have consequences for cognitive behavior, as hippocampal volume was negatively correlated with performance on the CVLT-C subtest measuring susceptibility to interference. This finding is consistent with previous research that has suggested that larger hippocampal volume is associated with poorer memory performance in children and adolescents (Van Petten, 2004), as well as research that suggests volumetric abnormalities in the hippocampus may represent a developmental vulnerability (Whittle et al., 2011).

Determining the mechanism(s) and/or pathways through which PDE exerts its effects is challenging, as brain development and cognition are influenced by bidirectional processes, including the early caregiving environment (Rao et al., 2009). Given the dynamic and complex development of the hippocampus during adolescence (Gogtay et al., 2006), the processes that are at the root of these differences remain unknown — but neuronal proliferation, synaptogenesis and synaptic pruning are likely candidates.

Strengths of this work include multiple methods of data collection (i.e., a combination of MRI, self-report, and objective neuropsychological tests) and inclusion of multiple covariates (i.e., age, gender, IQ, prenatal exposure to alcohol and tobacco, maternal depression, potential for abuse, and caregiver changes) to examine long-term effects of PDE with a high level of specificity. There are also limitations that should be noted. The CC group was recruited to provide a community standard. However, they differ from the children in the PDE group on dimensions that could influence performance, such as number of caregiver changes. In addition, although we adjusted for alcohol and tobacco, children in the PDE group may have been exposed to other substances; thus, our findings cannot be linked to exposure to a specific drug. However, 85% of longitudinal studies of PDE consist of poly-substance exposed individuals, which is characteristic of typical substance use behavior (e.g., Lester et al., 1998). Thus, findings from our sample have high ecological validity and can be generalized to samples in the majority of other studies on PDE. Most women used illegal substances multiple times per week, making it difficult to examine if there was a dose–response relationship. Gradations of frequency of exposure during gestation were not available. Although we included premature and low birth-weight infants, we excluded infants with medical problems and those admitted to the neonatal intensive care unit, thus limiting our sample to relatively healthy infants. Finally, our sample was homogenous in terms of race and SES. Although homogeneity is advantageous in limiting variability and increasing control of confounding factors, it limits the generalizability of our findings to this demographic group.

In summary, we report negative effects of PDE on memory and hippocampal volume in adolescence, some of which persist after accounting for early environmental influences that also affect memory function and hippocampal volume. These findings contribute to the accumulating evidence suggesting subtle effects of PDE on cognition, and memory in particular (i.e., Betancourt et al., 2011), in adolescence, which may operate through neural mechanisms. In addition, these results suggest that continued examination of longitudinal cohorts with histories of PDE enables a comprehensive understanding of the mechanisms underlying the impact PDE on developing children. Such information has the potential to significantly influence interventions that promote early development, improve the caregiving environment, and enable children to overcome some of the potentially negative effects of PDE.

Conflict of interest statement

No conflicts of interest to declare.

Acknowledgments

We thank the parents and children for their participation in this longitudinal study; Elliot Stein, Ph.D., Kim Slater, and the Neuroimaging Research Branch of NIDA-IRP for support with data collection and analysis; Prasanna Nair, M.D., and the F.U.T.U.R.E.S. team for participant recruitment and testing. This research was supported in part by the Intramural Research Program of the NIH, NIDA, and grants DA07432-05 (Nair), DA02105-09 (Black), and DA029113 (Riggins).

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