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Long-term effects of prenatal drug exposure on the neural correlates of memory at encoding and retrieval

Fengji Geng[a], Betty Jo Salmeron[b], Thomas J. Ross[b], Maureen M. Black[c,d], Tracy Riggins[a,*]

[a] Department of Psychology, University of Maryland, College Park, MD, United States
[b] Neuroimaging Research Branch, National Institute on Drug Abuse, National Institutes of Health, Baltimore, MD, United States
[c] Department of Pediatrics and Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD, United States
[d] RTI International, Research Triangle Park, NC, United States

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ABSTRACT

The objective of the current study was to examine what stage of memory (encoding or retrieval) may be compromised in adolescents with a history of prenatal drug exposure (PDE) and how the effects of PDE on memory ability are substantiated at the neural level. To achieve this goal, we examined memory performance and associated brain activations in adolescents with and without a history of PDE via event-related fMRI during encoding and retrieval. Consistent with previous studies, we found that PDE subjects remembered fewer items than community comparison subjects. However, there were no differences in behavior after adjusting for correct rejections (i.e., d'). Novel extensions of previous work are findings that PDE is associated with changes in brain activation during memory encoding but not during retrieval. These results suggest that less optimal memory performance often observed in adolescents with a history of PDE may result from variations in encoding rather than retrieval processes.

1. Introduction

Prenatal drug exposure (PDE) is a public health concern as 14.6% of pregnant women aged 15 to 17, 8.6% of pregnant women aged 18 to 25, and 3.2% of pregnant women aged 26 to 44 are estimated to use illicit drugs (Substance Abuse and Mental Health Services Administration, 2014). The adverse effects of PDE extend beyond users to unborn children by altering the course of development and affecting physical, cognitive, and social-emotional development. These effects may arise as a direct effect of PDE or as indirect effects of the risk factors associated with drug use (e.g., violence and sexual victimization, Hans, 1999). Finally, the effects of PDE have been shown to persist into childhood (Ackerman et al., 2010) and adolescence (Buckingham-Howes et al., 2013). Thus, although the adverse effects of PDE on development may originate during the prenatal period, they remain a public health concern across development.

Adolescence is thought to be an important time to test the long-term effects of PDE due to maturational changes in brain and social development during this period (Buckingham-Howes et al., 2013). Throughout the adolescent years, higher-order cognitive abilities and the brain networks that support them undergo important developmental changes and remain open to environmental influences as well (Gogtay et al., 2006). In a recent systematic review, Buckingham-Howes et al. (2013) indicated that PDE is associated with subtle negative effects on a broad range of outcomes that, taken together, may increase risk for poor outcomes. Specifically, negative effects of PDE have been documented in multiple domains, including behavior regulation, cognitive ability/school performance, brain structure/functioning, and physiological responses.

Memory is one cognitive domain in which long-term effects of PDE have been consistently reported. In one study, Betancourt et al. (2011) traced memory development from childhood to adolescence using tasks in which the participants did not know that a recall memory test would be administered (i.e., incidental memory tasks). Results indicated that even after controlling for potentially confounding environmental factors, the participants with a history of PDE showed slower rates of developmental change and lower scores than participants in the comparison group from the age of 12 to 17 years. Similarly, in a sample of 14-year-olds, Riggins et al. (2012) showed that adolescents with a history of PDE performed worse on intentional memory tasks (i.e., California Verbal Learning Test - CVLT and Children's Memory Scale-CMS). In addition, adolescents in the PDE group had larger hippocampal volumes, which were negatively correlated with recall memory performance.

* Corresponding author at: Department of Psychology, University of Maryland, College Park, MD 20742, United States.
E-mail address: riggins@umd.edu (T. Riggins).

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Although these studies were informative regarding the long-term effects of PDE on cognition, these studies did not address 1) what stage of memory may be compromised in adolescents with a history of PDE or 2) how the effects of PDE on memory ability are substantiated at the neural level. Memory is comprised of multiple processes including: encoding, consolidation, storage, and retrieval. Previous studies have focused on outcomes at retrieval (Betancourt et al., 2011; Riggins et al., 2012); however, from these studies it is not clear which stage of memory contributed to these differences. Additionally, it is unknown whether the PDE-related changes in memory ability during adolescence are accompanied by differences at the neural level and if so, what regions are affected and how they are different. For example, it is not known whether adolescents with a history of PDE activate different brain regions to encode and retrieve stimuli relative to their peers or if they activate the same brain regions but to a different extent/degree.

The goal of the current study was to address these two open questions by examining memory performance and associated brain activations in adolescents with and without a history of PDE via event-related fMRI during encoding and retrieval. This approach allowed us to examine regions for which we had a priori hypotheses about differences between PDE and comparison groups as well as exploratory whole-brain analyses.

First, based on previous work Riggins et al., 2012 that showed differences in hippocampal volume and relations with memory performance, we hypothesized that hippocampal activation may differ between PDE and non-PDE adolescents. The hippocampus is one of the medial temporal lobe regions known to be critical for episodic memory (DeMaster and Ghetti, 2013; Ghetti et al., 2010; Paz-Alonso et al., 2013; Sastre et al., 2016). Recent research has documented that there is a functional dissociation along the long-axis of hippocampus during performing a memory task and such dissociation shows developmental changes (DeMaster and Ghetti, 2013; DeMaster et al., 2013; Sastre et al., 2016). For example, DeMaster et al. (2013) found that activity in the hippocampal head and body was associated with episodic retrieval in adults, but such association was not found in 8–11-year-old children. Thus, we examined effects of PDE on the subregions (head, body, and tail) of the hippocampus during memory formation and retrieval using a region of interest (ROI) approach.

Second, we also conducted whole-brain exploratory analyses, as memory engages widespread brain regions (i.e., prefrontal cortex, posterior parietal regions, and medial temporal lobe), which are known to show memory-related differences in activation in both typical adults and adolescents. During successful encoding, these regions generally show greater activation for later remembered versus forgotten items (Paller and Wagner, 2002). In contrast, unsuccessful encoding has been associated with increased activity in default-mode regions, such as medial prefrontal cortex and angular gyrus (Daselaar et al., 2004; Kim, 2011; Park and Rugg, 2008), which may reflect mind-wandering or brief lapses in attention (Christoff et al., 2009; Mason et al., 2007). During successful retrieval, widespread cortical regions and regions within the medial temporal lobe typically show greater activation for remembered versus forgotten or new items (Greenberg et al., 2005; Konishi et al., 2000; Rugg and Vilberg, 2013). We examined effects of PDE on memory across the whole brain.

2. Methods

2.1. Participants

Participants were recruited from a well-characterized cohort of non-drug exposed and drug exposed adolescents who were taking part in a longitudinal study examining the effects of PDE (see Table 1 for participant demographics; note: this cohort overlapped extensively with the cohort reported on in Riggins et al., 2012). The PDE group met the following criteria at the time of enrollment: prenatal exposure to heroin and/or cocaine, gestational age > 32 weeks, birth weight > 1750 g, and no congenital or serious medical problems requiring admission to the neonatal intensive care unit (see the detail of recruitment procedures in Schuler et al., 2000). These babies were followed for evaluation visits through middle childhood and were re-contacted for follow-up during adolescence. The community comparison (CC) group was recruited at either 5 years or 14 years of age from the same community as PDE samples (see Schuler et al., 2002 for recruitment details). Experimenters reviewed medical record to identify children who were born in the same hospital during the same period as PDE children. The mother and infant had negative toxicology screens and had no evidence of drug use during pregnancy. The CC group matched the PDE group for socioeconomic status, mother's age during first pregnancy, and race.

Table 1
Sample characteristics. Bold indicates significant difference between groups. CC = Community Comparison. PDE = Prenatal Drug Exposed.

Characteristic	CC (22)	PDE (19)	*p*-Value
At birth			
Prenatal exposure to alcohol (%,n)	**18.2 (4)**	**73.7 (14)**	$\mathbf{p < 0.001}$
Prenatal exposure to tobacco (%,n)	**13.6 (3)**	**94.7 (18)**	$\mathbf{p < 0.001}$
Weight-for-length z-score	**−0.04 (1.33)**	**−1.33 (1.55)**	$\mathbf{p = 0.042}$
Length-for-gestational age z-score	**0.44 (1.12)**	**−0.84 (0.99)**	$\mathbf{p = 0.007}$
Head circumference-for-gestational age z-score	**1.06 (3.56)**	**−1.35 (1.35)**	$\mathbf{p = 0.03}$
Maternal education (years)	**12.09 (1.22)**	**11.08 (1.04)**	$\mathbf{p = 0.04}$
Apgar scores (1 min after birth)	8.09 (0.83)	8.23 (0.60)	$p = 0.64$
Apgar scores (5 min after birth)	8.91 (0.30)	8.92 (0.28)	$p = 0.91$
Adolescence			
Age at scan (years, SD)	**17.11 (1.13)**	**18.23 (0.91)**	$\mathbf{p = 0.001}$
Male (%, n)	40.9 (9)	42.1(8)	$p = 0.94$
Right-handed (%, n)	90.9 (20)	78.9 (15)	$p = 0.28$

Note. Chi square testes were used to test group differences in prenatal exposure to alcohol and tobacco, as well as in gender and handedness. For the other variables, *t*-tests were used to test group differences. Age at scan was included as a covariate in whole-brain and ROI fMRI data analyses. Characteristics of the subsamples included in the behavioral and neuroimaging analyses were similar to that of the whole sample presented here.

A total of 41 participants underwent scanning (22 CC, 19 PDE). Data from some subjects were lost due to poor behavioral performance (i.e., hit rate – false alarm rate ≤ 0, $n = 2$ CC subjects and $n = 3$ PDE subjects), fewer than ten trials available for fMRI data analyses as a result of low performance ($n = 1$ CC subject for the encoding phase, $n = 1$ PDE subject for the retrieval phase), excessive motion (mean FD > 0.50 or/and rejected scans ≥ 30%; $n = 1$ PDE subject for the retrieval phase), and failure to complete the entire experimental task ($n = 3$ PDE subjects). For behavioral data analysis, a final sample of 33 subjects remained (20 CC subjects, 13 PDE subjects). For imaging data analysis, out of subjects who contributed usable behavioral data, a final sample of 32 subjects (19 CC subjects, 13 PDE subjects) contributed data for examination of the encoding phase and 31 subjects (19 CC subjects, 12 PDE subjects) contributed data for the retrieval phase. All participants gave written informed assent/consent along with guardians providing consent for minors. The study was approved by the National Institute on Drug Abuse Division of Intramural Research Program's Institutional Review Board (IRB) and the University of Maryland School of Medicine IRB.

2.2. Experimental design

This study used an event-related fMRI emotion source memory paradigm adapted from (Erk et al., 2005) to examine memory at encoding and retrieval. Stimuli consisted of 44 negative and 44 neutral pictures from the International Affective Picture System (IAPS) (Lang et al., 1999) that served as background pictures. Neutral target items