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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 Ross[b], Maureen M. Black[c,d], Tracy Riggins[a]

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

Author note

Correspondence concerning this article should be sent to Tracy Riggins, Department of Psychology, University of Maryland, College Park, MD 20742. Telephone: (301)405-5905. Email: riggins@umd.edu

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.

Key words: Memory; prenatal drug exposure; encoding; retrieval; fMRI

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, Riggins, & Black, 2010) and adolescence (Buckingham-Howes, Berger, Scaletti, & Black, 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 and colleagues (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.

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 & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Paz-Alonso, Bunge, Anderson, & Ghetti, 2013; Sastre III, Wendelken, Lee, Bunge, & Ghetti, 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 & Ghetti, 2013; DeMaster, Pathman, & Ghetti, 2013; Sastre III et al., 2016). For example, DeMaster, Pathman, and Ghetti (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 & 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, Prince, & Cabeza, 2004; Kim, 2011; Park & Rugg, 2008), which may reflect mind-wandering or brief lapses in attention (Christoff, Gordon, Smallwood, Smith, & Schooler, 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, Wheeler, Donaldson, & Buckner, 2000; Rugg & Vilberg, 2013). We examined effects of PDE on memory across the whole brain.

Methods

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, Nair, Black, & Kettinger, 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, Nair, & Black, 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.

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.

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)**	***p* < .001**
Prenatal exposure to tobacco (%,n)	**13.6 (3)**	**94.7 (18)**	***p* < .001**
Weight-for-length z-score	**-0.04 (1.33)**	**-1.33 (1.55)**	***p* = .042**
Length-for-gestational age z-score	**0.44 (1.12)**	**-0.84 (0.99)**	***p* = .007**

Head circumference-for-gestational age z-score	**1.06 (3.56)**	**-1.35 (1.35)**	***p* = .03**
Maternal education (years)	**12.09 (1.22)**	**11.08 (1.04)**	***p* = .04**
Apgar scores (1 min after birth)	8.09 (0.83)	8.23 (0.60)	*p* = .64
Apgar scores (5 min after birth)	8.91 (0.30)	8.92 (0.28)	*p* = .91
Adolescence			
Age at scan (years, SD)	**17.11 (1.13)**	**18.23 (0.91)**	***p* = .001**
Male (%, n)	40.9 (9)	42.1(8)	*p* = .94
Right-handed (%, n)	90.9 (20)	78.9 (15)	*p* = .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.

Experimental Design

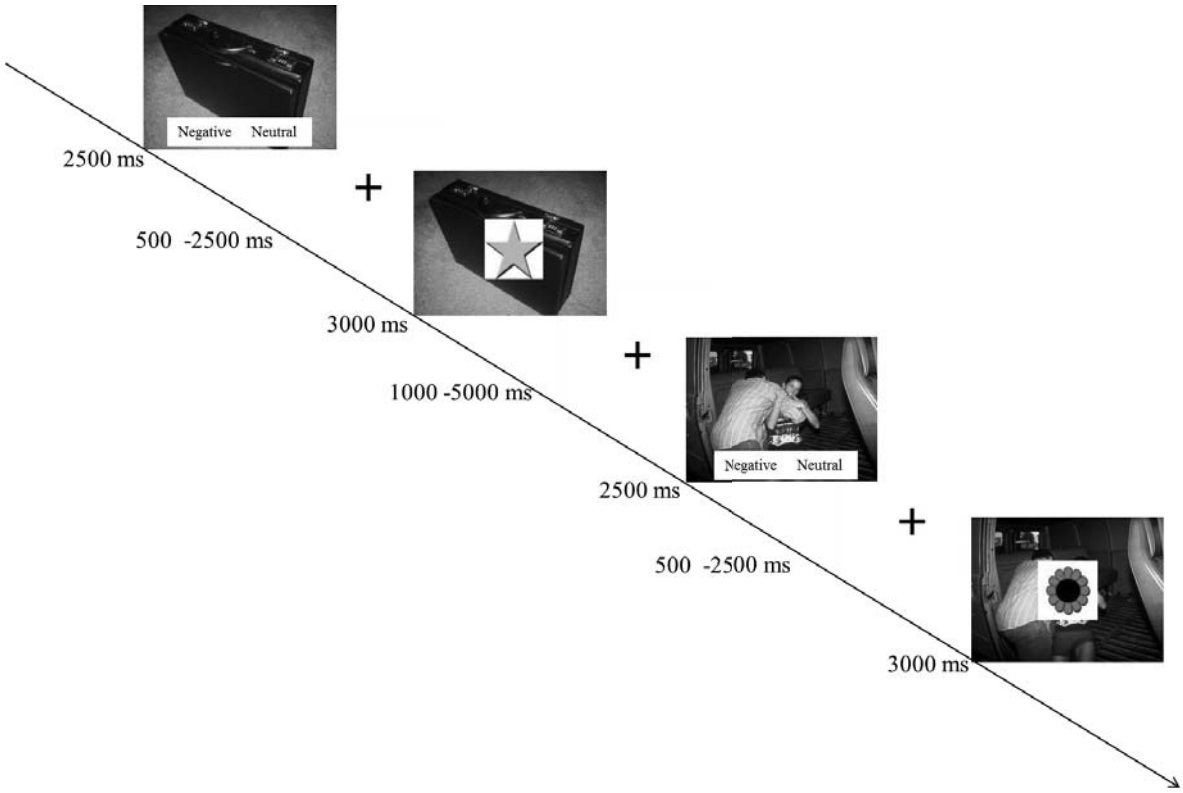
This study used an event-related fMRI emotion source memory paradigm adapted from (Erk, Martin, & Walter, 2005) to examine memory at encoding and retrieval. Stimuli consisted of 44 negative and 44 neutral pictures from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 1999) that served as background pictures. Neutral target items were colorful line drawings from the Snodgrass database (Rossion & Pourtois, 2004). The effect of emotion on memory was not tested due to small sample sizes (e.g., for fMRI data analysis, there were only 9 subjects for encoding and 7 for retrieval). In addition, no effect of emotion was found on memory performance both in the behavioral data analyses for this sample and an independent behavioral pilot study in typically developing adolescents. Therefore, only memory effects are reported in this study.

An overview of the task is depicted in Figure 1. Prior to scanning, participants were introduced to the task and completed a short training to ensure understanding of the task. During

encoding, participants viewed and rated the emotional content of the IAPS background pictures using a button response box in their right hand. The response buttons were counterbalanced between participants such that some participants were instructed to press 1 for negative and 2 for neutral while other participants were given reverse instructions (i.e., 1 for neutral, 2 for negative). IAPS pictures were presented for 2.5 seconds in pseudorandom order with the constraint that no more than two pictures of the same valence occurred in succession. Following the rating, a fixation cross appeared for 500ms to 2500ms. The IAPS picture then reappeared with a neutral target item placed on top for 3 seconds. At that time, participants were instructed to think of a scenario/story to associate the two images together. This was done as a means to encourage the binding of item and background. During training, participants verbalized such scenarios to training items to ensure understanding of the task. No verbal responses were collected during scanning.

At retrieval (approximately 1 hour later), 88 old and 44 new neutral target items were presented individually for 3 seconds each, followed by a fixation cross for 1000-5000ms. Participants were instructed to respond as to whether the item was previously paired with a negative or neutral background or if the item was new using a button box in their right hand. Response buttons were counterbalanced between participants. For both encoding and retrieval phases, if participants did not respond within the designated timeframe, a reminder appeared on the screen and the trial was repeated.

Encoding


Negative Neutral
2500 ms
500 -2500 ms
3000 ms
1000 -5000 ms
Negative Neutral
2500 ms
500 -2500 ms
3000 ms

Retrieval

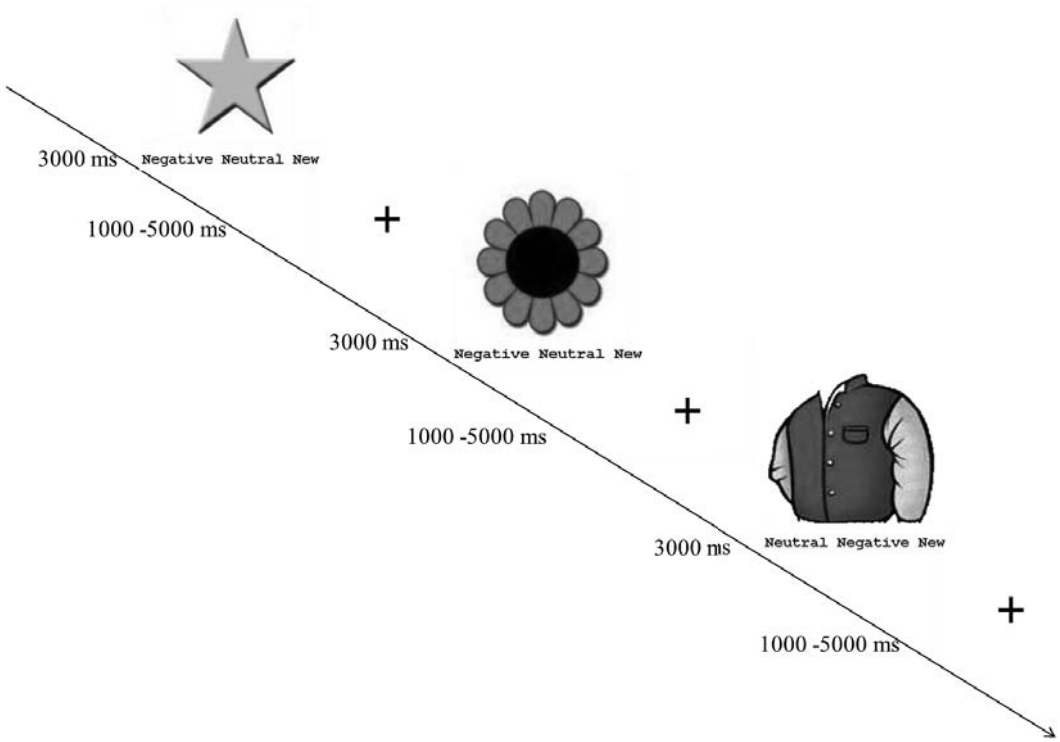

3000 ms
Negative Neutral New
1000 -5000 ms
3000 ms
Negative Neutral New
1000 -5000 ms
3000 ms
Neutral Negative New
1000 -5000 ms

Figure 1. Diagram of the experimental design. During encoding, participants rated the emotional content of pictures as negative or neutral. After fixation, a neutral item was superimposed onto the background picture and participants had to think of a sentence that combined the two pictures. During retrieval, old and new neutral items were presented and participants were instructed to respond if the picture was previously paired with a neutral or negative background or if it is a new picture.

Data Acquisition

Functional imaging data were acquired on a 3.0T Trio scanner (Siemens AG, Erlangen, Germany) with a 12 channel head coil. A whole-brain oblique axial T1-weighted structural image was obtained (MPRAGE) for registration purposes (1.0 × 1.0 × 1.0 mm voxel size; 1900 ms TR; 3.51ms TE; 900ms inversion time; 9° flip angle; pixel matrix= 256 x 192). Functional images were obtained using a gradient-echo, echo-planar sequence sensitive to blood oxygen level-dependent (BOLD) contrast (36 oblique interleaved slices; 3.43 x 3.43 x 4 mm voxel size; 2s TR; 27ms TE; 78° flip angle; 64x64 pixel matrix). If no trials were repeated, the encoding and retrieval phases were 12 minutes 13 seconds and 10 minutes 28 seconds respectively.

During the scan, participant head motion was monitored in real-time. If a participant exhibited excessive head motion (>3mm in any direction) during the first half of any block, the scan was restarted and the participant was reminded to stay as still as possible.

fMRI Analysis

fMRI preprocessing was carried out using SPM 8. The preprocessing steps included: slice timing correction, motion correction, coregistration, segmentation, normalization, and smoothing (Gaussian kernel FWHM=5mm).

Statistical analyses were carried out in AFNI. For the first level analyses, multiple regression analyses were carried out for both the encoding and retrieval phases. For the encoding phase, the rating and binding events were convolved with a model hemodynamic response function to create the four regressors of interest. The rating process contributed two regressors: negative and neutral pictures; the binding process contributed two regressors: subsequently remembered pictures (whether paired to correct or incorrect emotion) and subsequently forgotten pictures. For the retrieval phase, the events were convolved with a model hemodynamic response function to create four regressors: remembered pictures (whether paired to correct or incorrect emotion); forgotten pictures; new pictures with correct responses (correct rejection) and new pictures with wrong responses (false alarm). The regressors included in the models not only allowed us to test the memory effects but also separated the influence of other cognitive processes (e.g., emotion rating) on brain activation. The six motion correction curves were included as covariates to control for motion in all above models.

ROI analyses were carried out using hippocampus head, body, and tail from left and right hemisphere as seed regions. The ROIs were defined using left and right hippocampal templates from the AAL atlas (J. Lancaster, Summerln, Rainey, Freitas, & Fox, 1997; J. L. Lancaster et al., 2000; Tzourio-Mazoyer et al., 2002). The templates were then subdivided into head, body, and tail based on standard anatomical landmarks (with the uncal apex as the boundary between head and body MNI y = -20, and separation of the fornix as the boundary between body and tail MNI y = -35, see DeMaster & Ghetti, 2013 for details). The ROI parameter estimates were extracted and submitted to IBM SPSS Statistics 20 (IBM Corp., Chicago, IL) for repeated measures of ANOVA analyses. In these analyses, group differences during memory encoding were examined by comparing BOLD signal between items that were subsequently remembered versus those that

were subsequently forgotten (Subsequent hits versus Subsequent misses). Group differences during retrieval were examined by comparing BOLD signal between items that were remembered and those that were forgotten (Hits versus Misses). In both ANOVA analyses, subregion (head, body, and tail) and hemisphere (left, right) were included as within-subject factors, and age was included as covariate.

For the exploratory analysis, whole brain, voxel wise linear mixed effects (LME) models were conducted with the 3dLME program within AFNI. Group differences during memory encoding were examined by comparing BOLD signal between items that were subsequently remembered versus those that were subsequently forgotten (Subsequent hits versus Subsequent misses). Group differences during retrieval were examined by comparing BOLD signal between items that were remembered and those that were forgotten (Hits versus Misses). In both LME models, age was included as a covariate.

Multiple comparison correction

In order to correct for multiple comparison, Monte Carlo simulations were first carried out using 3dClustSim in AFNI to determine the minimum cluster size and threshold in order to maintain an overall alpha at $p < .05$. Based on the simulation results, clusters with a minimum of 19 voxels size and $p_{\text{uncorrected}} < .001$ were viewed as significant with multiple comparison correction ($p_{\text{corrected}} < .05$). Because of the small sample sizes in the present report, the power to detect significant results may be reduced.

Results

Behavioral Results

MANOVA tests were used to examine group differences in accuracy and reaction time for correct recognition of old items, correct rejections of new items, d'(sensitivity index), and response bias. Results indicated that CC subjects accurately recognized more old items (i.e., hits) than PDE subjects, see Table 2. However, no differences were apparent between the groups using d', which is a measure of memory sensitivity that is calculated as the standardized difference between hits and false alarms. There were no other group differences, main effects, or interactions.

Correlation analyses were conducted to examine if associations existed between indices of memory performance (hits, misses, correct rejection and d') and potential confounding factors between the groups. Only prenatal tobacco exposure was related to hit percentage, $r = -.48$, $p < .05$.

Table 2. Behavioral results

Group	CC (*n*=20)		PDE (*n*=13)		Group difference	Effect size
	Mean	*SD*	Mean	*SD*		
Hits (%)	**66.2**	**15.2**	**50.3**	**19.5**	***F* (1,31) = 6.87, *p* = .013**	**0.90**
Hit reaction time (ms)	1593.2	293.6	1556.2	206.5	F (1,31) = 0.16, p = .70	0.15
Miss reaction time (ms)	1323.5	259.3	1311.2	177.3	F (1,31) = 0.02, p = .88	0.06
Correct Rejections (%)	72.6	19.8	74.6	22.3	F (1,31) = 0.08, p = .79	0.10
d'	1.16	0.53	0.89	0.60	F (1,31) = 1.78, p = .19	0.48
Response bias	0.12	0.49	0.43	0.64	F (1,31) = 2.42, p = .13	0.54

Note. When only subjects who provided usable encoding fMRI data were examined, group differences in d' became marginally significant (F (1, 30) = 4.15, p = .05*;* CC group: mean = 1.18, SD = 0.53; PDE group: mean = 0.77, SD = 0.61). d' is a measure of sensitivity and is calculated as the standardized difference between hits and false alarms. Response bias measures the inclination of the subject to say "old" (or "new").

fMRI Results

Hippocampal ROI analyses

Encoding: subsequent memory effect

Subsequent memory effects were examined by contrasting activity at encoding between items that were subsequently remembered (subsequent hits) and items that were subsequently forgotten (subsequent misses). Results revealed a 4-way interaction between Condition × Hemisphere × Subregion × Group (F (2, 58) = 4.37, p = .019). Follow-up analyses indicated a 3-way interaction in the hippocampal tail between Condition × Hemisphere × Group (F (1, 29) = 6.30, p = .018). Both CC and PDE groups showed 2-way interactions between Condition and Hemisphere (F (1, 17) = 5.06, p = .038; F (1, 11) = 7.79, p = .018). However, the 2-way interaction in the CC group was driven by greater activation differences between subsequent remembered items and subsequent forgotten items in the left compared to the right hemisphere (solid circle), whereas the interaction in the PDE group was driven by greater differences between the two conditions in the right compared to the left hemisphere (dashed circle, see Figure 2).

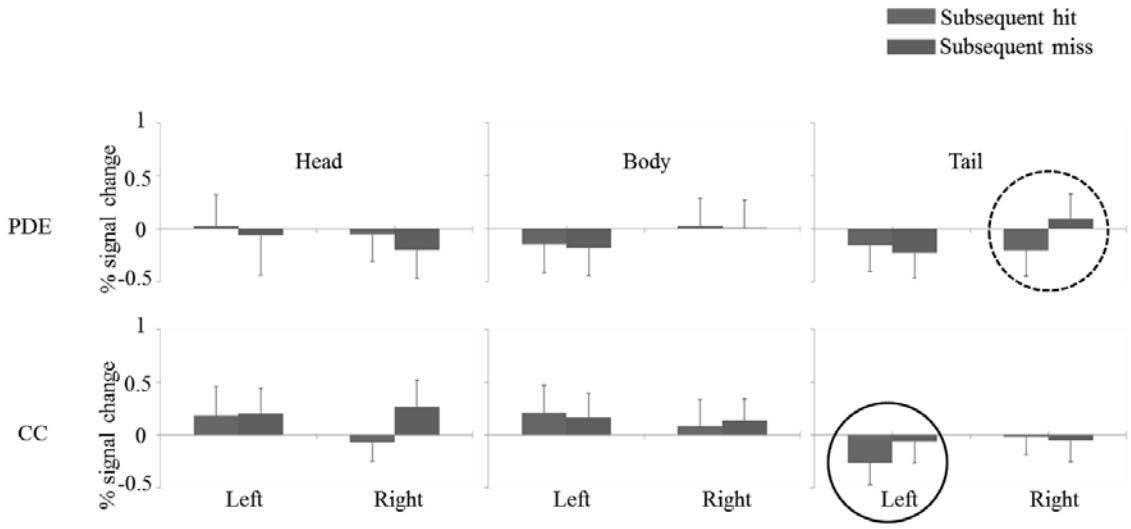


Figure 2. Brain activation in the subregions of hippocampus for subsequent hit trials versus subsequent miss trials. The error bars represent standard error of the mean. PDE stands for prenatal drug exposure.

Retrieval: memory effect

Memory effects were examined by contrasting activity at retrieval for remembered (hit) and forgotten items (miss). No main effects or interactions with group were observed. There was a 2-way interaction: Condition × Subregion (F (2, 56) = 3.58, p = .045). Follow-up analyses indicated that the interaction was mainly driven by greater condition differences in the hippocampal head than that in the hippocampal body and tail (see Figure 3).

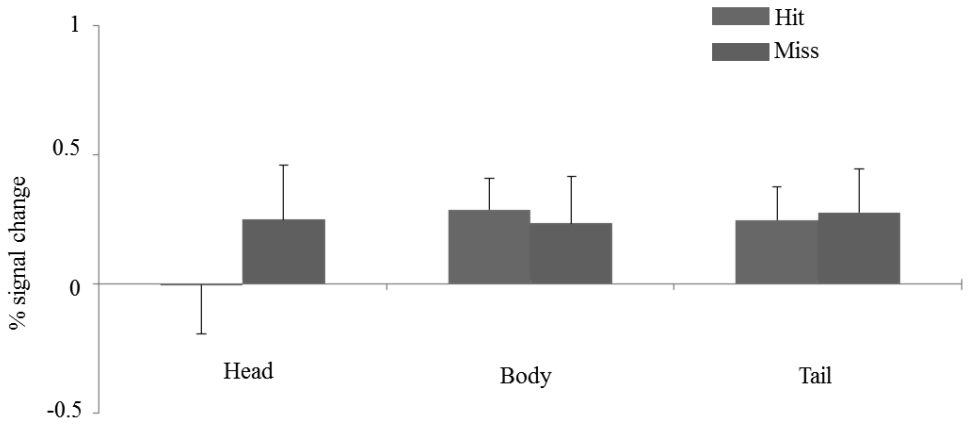


Figure 3. Brain activation in the subregions of hippocampus for hit trials versus miss trials. Activations are collapsed across groups because there were no differences between groups. The error bars represent standard error of the mean.

Whole brain analysis

Encoding: subsequent memory effect

There were no main effects or interactions involving group. A subsequent memory effect was observed in the anterior cingulate cortex (ACC), regardless of group status (see Figure 4).

Specifically, items that were subsequently remembered were associated with greater deactivation compared to items that were subsequently forgotten.

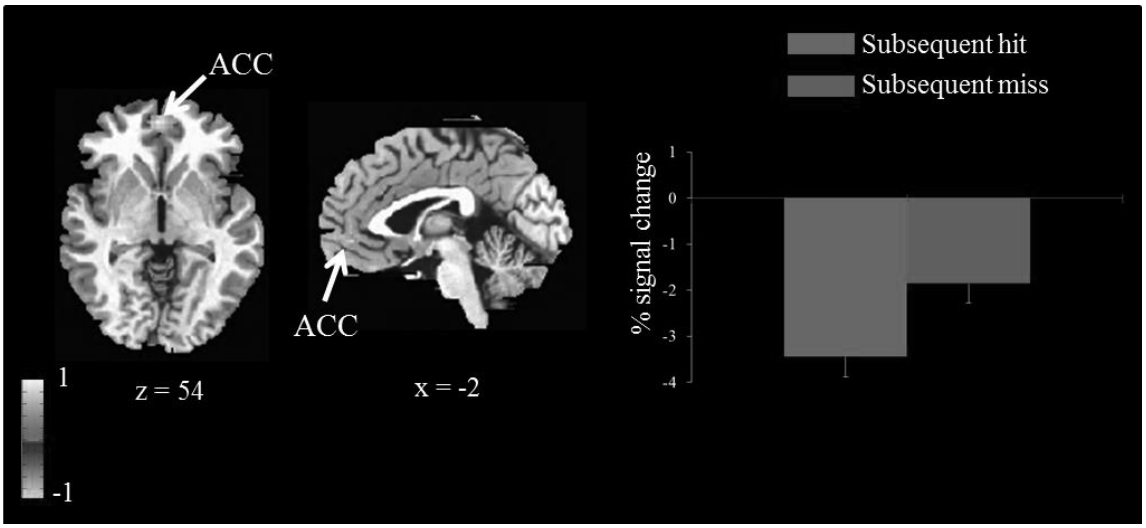


Figure 4. Brain activation in anterior cingulate cortex (ACC) for subsequent hit trials versus subsequent miss trials. The activation was collapsed across groups because there were no differences between groups. The error bars represent standard error of the mean.

Retrieval: memory effect

No significant differences between the groups or interactions with group were observed. However, memory effects were found in bilateral middle frontal gyrus (MFG), bilateral inferior parietal lobule (IPL), anterior cingulate (ACC), precuneus, right inferior frontal gyrus (IFG), and left middle temporal gyrus (MTG), see Figure 5. There was greater activation in the hit versus miss condition in all regions.

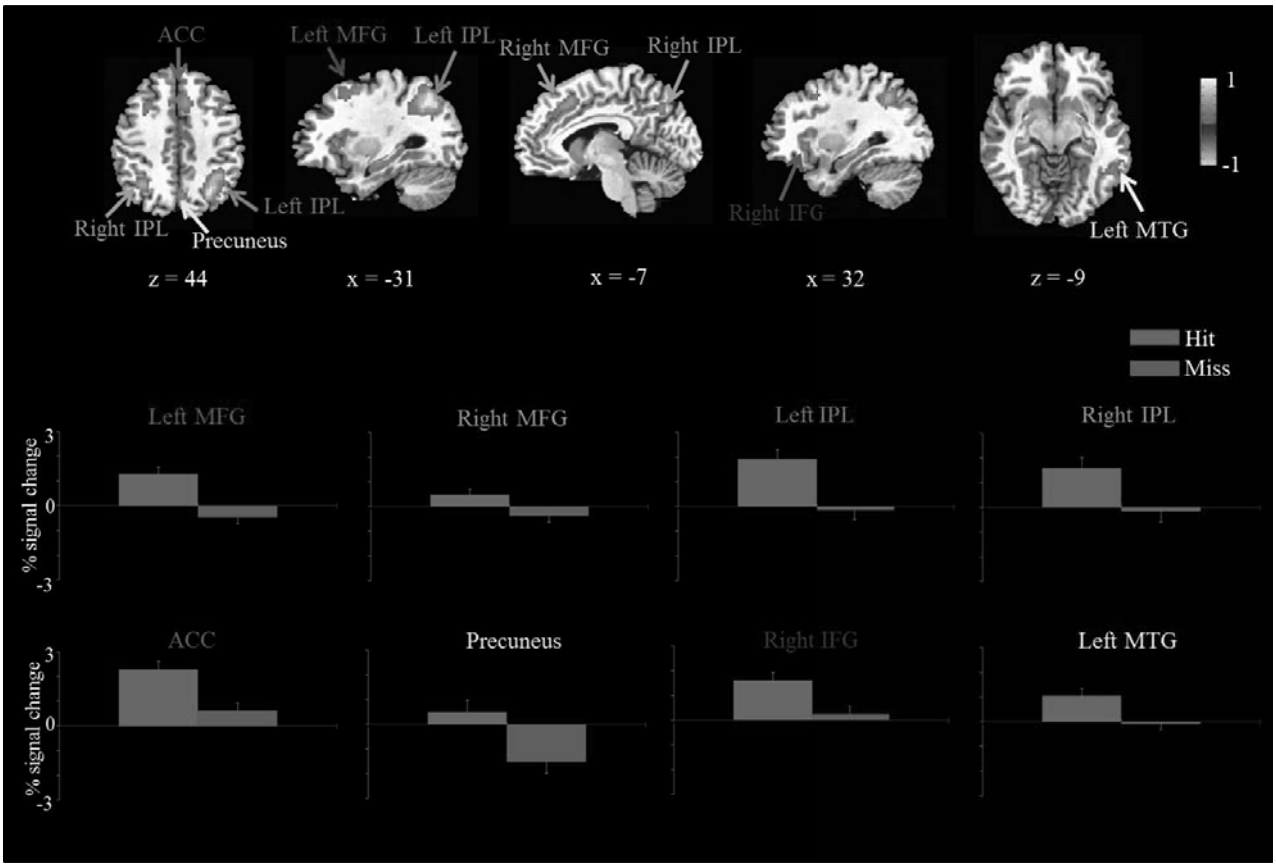


Figure 5. Brain activation differences between hit trials versus miss trials were found in these brain regions. The activation was collapsed across groups because there were no differences between groups. The error bars represent standard error of the mean. IFG: inferior frontal gyrus; IPL: inferior parietal lobule; ACC: anterior cingulate cortex; MFG:middle frontal gyrus; ITG: inferior temporal gyrus

Discussion and Conclusions

The current study sought to address what stage of memory may be compromised in adolescents with a history of PDE and how the effects of PDE on memory ability are substantiated at the neural level. Thus, 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 CC subjects did. However, there were no differences in behavior after adjusting for correct rejections (i.e., d'). A novel extension of previous work is the findings that PDE was associated with changes in brain activation during memory encoding but not during retrieval. These activation differences during encoding may help explain why PDE subjects remembered fewer items (i.e., lower hit percentage) than control subjects did in our study and in previous studies (Betancourt et al., 2011; Riggins et al., 2012). Although no differences in memory performance were observed in our sample after correcting for correct rejections(i.e., d'), it is possible that memory differences may ultimately emerge as a result of these encoding differences (as they did in Bentacourt et al., 2011 and Riggins et al., 2012).

ROI analyses revealed that there was hemispheric difference in hippocampal activation between PDE and CC groups during memory encoding. The CC group showed greater activation differences between subsequently remembered items and subsequently forgotten items in the left compared to the right hemisphere, whereas the PDE group showed greater differences between the two conditions in the right compared to the left hemisphere. As the left hippocampal formation is thought to be involved in verbal information processing and the right processes nonverbal or spatial information (Abrahams, Pickering, Polkey, & Morris, 1997; Jones-Gotman, 1986; Maguire, Frackowiak, & Frith, 1997; Smith & Milner, 1981), the hemispheric differences between PDE and CC groups might imply that the two groups used different strategy to encode stimuli. PDE group might more rely upon nonverbal information, whereas CC group might more rely upon verbal information. This finding extended the finding of a previous study, which used an overlapping cohort of subjects at a younger age (14 years) and revealed that PDE subjects had greater hippocampal volumes than CC subjects. Together, these findings may suggest that PDE

places the hippocampus at risk for vulnerability during developmental both in terms of structure and function (Riggins et al., 2012).

ROI analysis of hippocampal subregions revealed that during the retrieval of old items, the hippocampal head showed greater activation differences between hit and miss conditions than in the body and tail. This finding suggests that there are functional differentiations along the anterior-posterior axis of during episodic retrieval task, which are consistent with previous studies in typically developing populations (e.g., Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Sastre III et al., 2016). However, the direction of the difference between hit versus miss conditions differed from previous findings (e.g., DeMaster & Ghetti, 2013), which could be due to differences in task designs and the age of participants between studies. Altogether, the findings from ROI analyses were not as strong as expected, which might be partially due to small sample size.

Whole-brain analysis of brain activation at encoding revealed greater deactivation for hit versus miss condition in ACC. This is consistent with previous findings that unsuccessful encoding was associated mostly with default-mode regions (Daselaar et al., 2004; Kim, 2011; Park & Rugg, 2008). The greater activity in default-mode network in an attentionally demanding task may suggest mind-wondering or brief lapses in attention (Christoff et al., 2009; Mason et al., 2007; Weissman, Roberts, Visscher, & Woldorff, 2006). Our results did not replicate the previous findings that suggested greater activation in prefrontal cortex during encoding for items subsequently remembered versus subsequently forgotten, possibly due to the differences in task design, relatively poor performance on the task, sample characteristics, or a combination of these factors (For reviews, see Blumenfeld & Ranganath, 2007; Paller & Wagner, 2002; Simons & Spiers, 2003). Additionally, whole-brain analyses revealed that during retrieval greater brain

activation was observed for hit versus miss trials at bilateral MFG, bilateral IPL, ACC, precuneus, right IFG, and left MTG. These brain regions were previously reported to engage in memory retrieval (Greenberg et al., 2005; Konishi et al., 2000; Lundstrom, Ingvar, & Petersson, 2005; Miyashita, 1993; Rugg & Vilberg, 2013).

It is important to highlight that the effect of PDE on memory was found during encoding but not during retrieval. The underlying mechanism for such a difference might be that as two independent phases of memory, encoding and retrieval engage different cognitive processes. For example, encoding engages item registration and maintenance, whereas retrieval occurs through the reactivation of representation created during encoding (Vilberg & Rugg, 2008). The difference between encoding and retrieval is also supported by the findings that there are different neural underpinnings involved in these two processes. For example, a meta-analysis study indicated that activations in left ventrolateral prefrontal and medial-temporal regions were only associated with encoding, whereas activations in left superior parietal and dorsolateral and anterior prefrontal regions were only associated with retrieval (Spaniol et al., 2009). Our results suggest that the influence of PDE is apparent on the pattern of hippocampal activation during encoding but not during retrieval.

It should be noted that the effects of PDE on memory encoding might be the direct result of PDE or the indirect result of PDE-associated factors across life or the combination of these two. For example, drug exposure has reported to be associated with the other environmental risk factors, including but not limited to the concurrent use of other drugs, poverty, violence exposure, and low quality of maternal care (Buckingham-Howes et al., 2014; Lambert & Bauer, 2012). In the current study, we found that compared to CC group, PDE group showed higher level of exposure to heroin, cocaine, alcohol, or tobacco. However, it is difficult to control for all these

factors associated with PDE in one study. In addition, the relatively small sample size of neuroimaging studies, such as the one in this report, precludes examination of multiple covariates (Buckingham-Howes et al., 2013). However, we attempted to examine the impact of confounding factors via correlational analyses. Only prenatal tobacco exposure was related to hit percentage (The results of ROI and whole brain analyses did not change with tobacco exposure included as a covariate). These findings help reduce the possibility that only these demographic factors explain the effect of PDE on memory observed in this study.

This is the first study, to our knowledge, to utilize fMRI to investigate the long-term effects of PDE on neural correlates of memory encoding and retrieval in adolescents. However, a few limitations should be noted. First, as mentioned above, the sample size is small. This is largely due to the nature of the sample and the longitudinal nature of the study design. Although the sample size of the current study is in line with other neuroimaging studies of adolescents with a history of PDE (Li et al., 2011; Liu, Cohen, Gongvatana, Sheinkopf, & Lester, 2011; Riggins et al., 2012), we were unable to test the influence of specific covariates or the effect of emotion on memory. However, PDE and CC subjects were fairly well matched in terms of race, gender and education, which help limit variability and increase control of confounding factors. In addition, the small sample sizes may reduce the power to detect condition or group differences. For example, small sample size might be part of the reason that there was no group difference in neural activation detected during retrieval. Despite small sample sizes, using fMRI to measure activation is a valuable method to test how PDE affects neural function. Second, CC subjects were recruited at either 5 years or 14 years of age, which is a potential limitation. Finally, the frequency of drug exposure during gestation was not available, thus it is unknown if there is dose-responsible relationship.

In conclusion, results from this longitudinal study suggest that the subtle effects of PDE on memory performance in adolescents may result from variations in encoding rather than retrieval processes. Additionally, fMRI results showing differences in hippocampal activation during encoding, which may suggest differences in encoding strategies between groups. These findings not only contribute to the accumulating evidence suggesting the subtle yet long-lasting effects of PDE on memory ability but also promote the understanding of the underlying cognitive and neural mechanisms of these effects during adolescence. These results imply that interventions designed to improve the memory ability of PDE adolescents should focus on encoding rather than retrieval.

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References

Abrahams, S., Pickering, A., Polkey, C. E., & Morris, R. G. (1997). Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. *Neuropsychologia, 35*(1), 11-24. doi: http://dx.doi.org/10.1016/S0028-3932(96)00051-6

Ackerman, J. P., Riggins, T., & Black, M. M. (2010). A Review of the Effects of Prenatal Cocaine Exposure Among School-Aged Children. *Pediatrics, 125*(3), 554-565. doi: 10.1542/peds.2009-0637

Administration., S. A. a. M. H. S. (2014). Results from the 2013 NSDUH: Summary of National Findings, NSDUH series H-48, HHS publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration, .

Betancourt, L. M., Yang, W., Brodsky, N. L., Gallagher, P. R., Malmud, E. K., Giannetta, J. M., . . . Hurt, H. (2011). Adolescents with and without gestational cocaine exposure: Longitudinal analysis of inhibitory control, memory and receptive language. *Neurotoxicology and Teratology, 33*(1), 36-46. doi: http://dx.doi.org/10.1016/j.ntt.2010.08.004

Blumenfeld, R. S., & Ranganath, C. (2007). Prefrontal cortex and long-term memory encoding: An integrative review of findings from neuropsychology and neuroimaging. *The Neuroscientist, 13*(3), 280-291. doi: 10.1177/1073858407299290

Buckingham-Howes, S., Bento, S. P., Scaletti, L. A., Koenig, J. I., Granger, D. A., & Black, M. M. (2014). Prenatal Drug Exposure Moderates the Association between Stress Reactivity and Cognitive Function in Adolescence. *Developmental Neuroscience, 36*(3-4), 329-337.

Buckingham-Howes, S., Berger, S. S., Scaletti, L. A., & Black, M. M. (2013). Systematic Review of Prenatal Cocaine Exposure and Adolescent Development. *Pediatrics*. doi: 10.1542/peds.2012-0945

Christoff, K., Gordon, A. M., Smallwood, J., Smith, R., & Schooler, J. W. (2009). Experience sampling during fMRI reveals default network and executive system contributions to mind wandering. *Proceedings of the National Academy of Sciences, 106*(21), 8719-8724. doi: 10.1073/pnas.0900234106

Daselaar, S. M., Prince, S. E., & Cabeza, R. (2004). When less means more: deactivations during encoding that predict subsequent memory. *NeuroImage, 23*(3), 921-927. doi: http://dx.doi.org/10.1016/j.neuroimage.2004.07.031

DeMaster, D., & Ghetti, S. (2013). Developmental differences in hippocampal and cortical contributions to episodic retrieval. *Cortex, 49*(6), 1482-1493. doi: http://dx.doi.org/10.1016/j.cortex.2012.08.004

DeMaster, D., Pathman, T., & Ghetti, S. (2013). Development of memory for spatial context: Hippocampal and cortical contributions. *Neuropsychologia, 51*(12), 2415-2426. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2013.05.026

Erk, S., Martin, S., & Walter, H. (2005). Emotional context during encoding of neutral items modulates brain activation not only during encoding but also during recognition. *NeuroImage, 26*(3), 829-838. doi: http://dx.doi.org/10.1016/j.neuroimage.2005.02.045

Ghetti, S., DeMaster, D. M., Yonelinas, A. P., & Bunge, S. A. (2010). Developmental differences in medial temporal lobe function during memory encoding. *The Journal of Neuroscience, 30*(28), 9548-9556.

Gogtay, N., Nugent, T. F., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., . . . Thompson, P. M. (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus, 16*(8), 664-672. doi: 10.1002/hipo.20193

Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., & LaBar, K. S. (2005). Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. *Neuropsychologia, 43*(5), 659-674. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2004.09.002

Hans, S. L. (1999). Demographic and psychosocial characteristics of substance-abusing pregnant women. *Clinics in perinatology, 26*(1), 55-74.

Jones-Gotman, M. (1986). Right hippocampal excision impairs learning and recall of a list of abstract designs. *Neuropsychologia, 24*(5), 659-670. doi: http://dx.doi.org/10.1016/0028-3932(86)90005-9

Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI studies. *NeuroImage, 54*(3), 2446-2461. doi: http://dx.doi.org/10.1016/j.neuroimage.2010.09.045

Konishi, S., Wheeler, M. E., Donaldson, D. I., & Buckner, R. L. (2000). Neural Correlates of Episodic Retrieval Success. *NeuroImage, 12*(3), 276-286. doi: http://dx.doi.org/10.1006/nimg.2000.0614

Lambert, B. L., & Bauer, C. R. (2012). Developmental and behavioral consequences of prenatal cocaine exposure: a review. *J Perinatol, 32*(11), 819-828.

Lancaster, J., Summerln, J., Rainey, L., Freitas, C., & Fox, P. (1997). The Talairach Daemon, a database server for Talairach atlas labels. *NeuroImage, 5*(4), S633.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., . . . Fox, P. T. (2000). Automated Talairach Atlas labels for functional brain mapping. *Human Brain Mapping, 10*(3), 120-131. doi: 10.1002/1097-0193(200007)10:3<120::aid-hbm30>3.0.co;2-8

Lang, P. J., Bradley, M. M., & Cuthbert, B. N. (1999). International affective picture system (IAPS): Instruction manual and affective ratings. *The center for research in psychophysiology, University of Florida*.

Li, Z., Santhanam, P., Coles, C. D., Lynch, M. E., Hamann, S., Peltier, S., & Hu, X. (2011). Increased "default mode" activity in adolescents prenatally exposed to cocaine. *Human Brain Mapping, 32*(5), 759-770. doi: 10.1002/hbm.21059

Liu, J., Cohen, R. A., Gongvatana, A., Sheinkopf, S. J., & Lester, B. M. (2011). Impact of Prenatal Exposure to Cocaine and Tobacco on Diffusion Tensor Imaging and Sensation Seeking in Adolescents. *The Journal of Pediatrics, 159*(5), 771-775. doi: http://dx.doi.org/10.1016/j.jpeds.2011.05.020

Lundstrom, B. N., Ingvar, M., & Petersson, K. M. (2005). The role of precuneus and left inferior frontal cortex during source memory episodic retrieval. *NeuroImage, 27*(4), 824-834. doi: http://dx.doi.org/10.1016/j.neuroimage.2005.05.008

Maguire, E. A., Frackowiak, R. S. J., & Frith, C. D. (1997). Recalling Routes around London: Activation of the Right Hippocampus in Taxi Drivers. *The Journal of Neuroscience, 17*(18), 7103-7110.

Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering Minds: The Default Network and Stimulus-Independent Thought. *Science, 315*(5810), 393-395. doi: 10.1126/science.1131295

Miyashita, Y. (1993). Inferior temporal cortex: Where visual perception meets memory. *Annual Review of Neuroscience, 16*, 245-263. doi: 10.1146/annurev.ne.16.030193.001333
Paller, K. A., & Wagner, A. D. (2002). Observing the transformation of experience into memory. *Trends in Cognitive Sciences, 6*(2), 93-102. doi: http://dx.doi.org/10.1016/S1364-6613(00)01845-3
Park, H., & Rugg, M. D. (2008). Neural correlates of successful encoding of semantically and phonologically mediated inter-item associations. *NeuroImage, 43*(1), 165-172. doi: http://dx.doi.org/10.1016/j.neuroimage.2008.06.044
Paz-Alonso, P. M., Bunge, S. A., Anderson, M. C., & Ghetti, S. (2013). Strength of Coupling within a Mnemonic Control Network Differentiates Those Who Can and Cannot Suppress Memory Retrieval. *The Journal of Neuroscience, 33*(11), 5017-5026. doi: 10.1523/jneurosci.3459-12.2013
Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences, 17*(5), 230-240. doi: http://dx.doi.org/10.1016/j.tics.2013.03.005
Riggins, T., Cacic, K., Buckingham-Howes, S., Scaletti, L. A., Salmeron, B. J., & Black, M. M. (2012). Memory ability and hippocampal volume in adolescents with prenatal drug exposure. *Neurotoxicology and Teratology, 34*(4), 434-441. doi: http://dx.doi.org/10.1016/j.ntt.2012.05.054
Rossion, B., & Pourtois, G. (2004). Revisiting Snodgrass and Vanderwart's Object Pictorial Set: The Role of Surface Detail in Basic-Level Object Recognition. *Perception, 33*(2), 217-236. doi: 10.1068/p5117
Rugg, M. D., & Vilberg, K. L. (2013). Brain networks underlying episodic memory retrieval. *Current Opinion in Neurobiology, 23*(2), 255-260. doi: http://dx.doi.org/10.1016/j.conb.2012.11.005
Sastre III, M., Wendelken, C., Lee, J. K., Bunge, S. A., & Ghetti, S. (2016). Age- and performance-related differences in hippocampal contributions to episodic retrieval. *Developmental Cognitive Neuroscience, 19*, 42-50. doi: http://dx.doi.org/10.1016/j.dcn.2016.01.003
Schuler, M. E., Nair, P., & Black, M. M. (2002). Ongoing Maternal Drug Use, Parenting Attitudes, and a Home Intervention: Effects on Mother-Child Interaction at 18 Months. *Journal of developmental and behavioral pediatrics : JDBP, 23*(2), 87-94.
Schuler, M. E., Nair, P., Black, M. M., & Kettinger, L. (2000). Mother-Infant Interaction: Effects of a Home Intervention and Ongoing Maternal Drug Use. *Journal of Clinical Child Psychology, 29*(3), 424-431. doi: 10.1207/s15374424jccp2903_13
Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. [10.1038/nrn1178]. *Nat Rev Neurosci, 4*(8), 637-648.
Smith, M. L., & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia, 19*(6), 781-793. doi: http://dx.doi.org/10.1016/0028-3932(81)90090-7
Spaniol, J., Davidson, P. S. R., Kim, A. S. N., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: Meta-analyses using activation likelihood estimation. *Neuropsychologia, 47*(8–9), 1765-1779. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2009.02.028
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., . . . Joliot, M. (2002). Automated Anatomical Labeling of Activations in SPM Using a

Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *NeuroImage, 15*(1), 273-289. doi: http://dx.doi.org/10.1006/nimg.2001.0978
Vilberg, K. L., & Rugg, M. D. (2008). Memory retrieval and the parietal cortex: A review of evidence from a dual-process perspective. *Neuropsychologia, 46*(7), 1787-1799. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2008.01.004
Weissman, D. H., Roberts, K. C., Visscher, K. M., & Woldorff, M. G. (2006). The neural bases of momentary lapses in attention. [10.1038/nn1727]. *Nat Neurosci, 9*(7), 971-978.

Highlights

Long-term effects of prenatal drug exposure on memory in adolescence were examined
Prenatal drug exposure was related to decreased memory performance
Prenatal drug exposure was related to altered brain activation during memory encoding
Results suggest prenatal drug exposure has long-term consequences for memory ability