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Prospective Memory Impairment in Children with Prenatal Alcohol Exposure

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Abstract

Background—Prenatal alcohol exposure (PAE) is linked to impaired performance on tests of retrospective memory, but prospective memory (PM; the ability to remember and act on delayed intentions) has not been examined in alcohol-exposed children. We investigated event-based PM in children with heavy PAE and the degree to which associations between PAE and PM are influenced by IQ, executive functioning (EF), retrospective memory, and attention deficit/hyperactivity disorder (ADHD).

Methods—We administered a computerized PM task to 89 children (*M*_{age}=11.1 years) whose mothers were recruited prenatally: 29 with fetal alcohol syndrome (FAS) or partial FAS (PFAS), 32 nonsyndromal heavily exposed (HE), and 28 controls. We examined effects of diagnostic group, cue focality, and task difficulty on PM performance. The association between a continuous measure of alcohol exposure and PM performance was also examined after controlling for sociodemographic confounders. Mediation of alcohol effects on PM by IQ, EF, and retrospective memory scores was assessed as was the effect of ADHD on PM performance.

Results—Children with FAS/PFAS made more PM errors than either HE or Control children. PAE was negatively related to PM performance even after adjusting for sociodemographic confounders, EF, and retrospective memory. This relation was only partially mediated by IQ. PAE was related to ADHD, but ADHD was not related to PM performance.

Conclusion—Fetal alcohol-related impairment in event-based PM was seen in children with FAS/PFAS. The effect of PAE on PM was not attributable to impaired EF and retrospective

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memory and was not solely attributable to lower IQ. Consistent with previous studies, we found no effect of ADHD on event-based PM performance at this age. This is the first study documenting PM impairment in children with heavy PAE and identifies a new domain of impairment warranting attention in diagnosis and management of FASD.

Keywords

fetal alcohol spectrum disorders; prenatal alcohol exposure; fetal alcohol syndrome; prospective memory; executive function; IQ; ADHD

INTRODUCTION

Prenatal alcohol exposure (PAE) is associated with adverse cognitive and behavioral outcomes throughout childhood and adolescence. Learning and memory are particularly vulnerable to PAE (e.g., Mattson and Roebuck, 2002; Kaemingk et al., 2003; Lewis et al., 2015). Research in this domain has, however, been limited primarily to the study of retrospective (i.e., the retention, recall and/or recognition of previously acquired information; e.g., Willoughby et al., 2008) and working memory (WM; i.e., temporarily storing and manipulating information; e.g., Burden et al., 2005). To our knowledge, this is the first study to examine prospective memory (PM)—the ability to remember and to execute delayed intentions—(Kliegel et al., 2008) in children with PAE.

Researchers have only recently begun to investigate PM in pediatric clinical samples, including children with attention deficit/hyperactivity disorder (ADHD; Kerns and Price, 2001; Kliegel et al., 2006; Talbot and Kerns, 2014). PM, which is integral to effective everyday functioning, is classified as being either time-based (i.e., remembering to execute delayed intentions at a specific time; e.g., remembering to take medication at a specific time) or event-based (i.e., remembering to execute delayed intentions when encountering a specific event, person, or place; e.g., remembering to get a letter signed when encountering a specific person; Einstein and McDaniel, 1996). Unlike retrospective memory tasks, which rely on external, direct prompting to retrieve the encoded information (e.g., in a free or cued-recall task, such as responding to questions like “What is the capital of France?”), prospective remembering requires an internal, self-initiated response (to a time- or event-based cue) that interrupts on-going activity so that a delayed intention may be recalled and completed effectively (Einstein and McDaniel, 1996; McDaniel and Einstein, 2000).

Previous research suggests that successful PM proceeds through four phases: intention formation, retention, intention initiation, and intention execution (Kliegel et al., 2002; 2011). Three of these four phases are closely related to aspects of executive functioning (EF), particularly when individuals are completing complex tasks: intention formation is related to planning abilities; intention initiation, to task switching; and intention execution, to response inhibition. These associations have been shown in both behavioral (Kliegel et al., 2002; Martin et al., 2003) and neuroimaging studies (Okuda et al., 2007; Simons et al., 2006), with the latter showing that activation of the prefrontal lobes (in particular, the anterior prefrontal cortex [Brodmann’s area 10]) is functionally significant when completing PM tasks successfully.

Empirical research has also demonstrated, however, that although PM is closely related to EF, the two are dissociable cognitive constructs, each with some unique variance (Schnitzspahn et al., 2013). At least some of this variance in PM is accounted for by the fact that the retention phase of PM is similar to cued-recall retrospective memory (and not at all similar to any aspect of EF) in that an individual has to remember both the content of intended action and the appropriate PM cue (Einstein and McDaniel, 1996). Hence, although retrospective and prospective remembering are two distinct cognitive processes, PM functioning has both retrospective and prospective remembering components, making it a cognitive construct that combines memory and EF processes (Einstein and McDaniel, 1996; Kliegel et al., 2008).

Relatively few studies have investigated PM in typically developing children and adolescents. Most have focused on time-based PM and the role of time-monitoring, which gradually improves with age (Mahy et al., 2014). By 10 years, children appear to have developed a reasonably sophisticated level of PM functioning (Kerns, 2000). In one of the few pediatric clinical studies, Kerns and Price (2001) found that 8- to 13-year-old children with ADHD made more time-based PM errors than controls and that those errors were due to inefficient time-monitoring strategies rather than attentional deficits. Given that children with FASD often present with attentional problems similar to those seen in ADHD (Coles et al., 1997; Mick et al., 2003; Jacobson et al., 2011), we compared the effects of heavy PAE and ADHD on PM performance in a cohort of children with FASD.

Many cognitive and behavioral deficits in FASD have been linked to key domains of EF: response inhibition (e.g., Burden et al., 2010), cognitive flexibility (e.g., Rasmussen and Bisanz, 2009), WM (e.g., Burden et al., 2005), and planning and problem solving (e.g., Kodituwakku et al., 1995). Moreover, impaired EF has been documented in cases with and without the characteristic FAS facial dysmorphism (Mattson et al., 1999), and adverse effects of PAE on EF persist after control for IQ (Noland et al., 2003). Because IQ scores are generally lower in FASD samples (Mattson et al., 1997), it is important to adjust statistically for IQ to determine whether PAE affects discrete cognitive domains, such as learning and memory (Lewis et al., 2015). Investigation of EF and retrospective memory as possible mediators of the effects of heavy PAE on PM is also important, as previous studies have revealed associations between PM and EF (Kliegel et al., 2002) and between PM and retrospective memory (Einstein and McDaniel, 1996).

The aims of this study were to determine (1) whether children with a history of heavy PAE have impaired PM performance, (2) the degree to which associations between PAE and PM performance are accounted for by fetal alcohol-related impairment in IQ, (3) the degree to which associations between PAE and PM performance are accounted for by fetal alcohol-related impairment in EF and retrospective memory, and (4) the degree to which associations between PAE and PM performance are attributable to the presence of ADHD.

METHODS

Participants

The sample consisted of 89 children who participated in the 10-year follow-up of the Cape Town Longitudinal Cohort (Jacobson et al., 2008) in Cape Town, South Africa, where the incidence of FAS, partial FAS (PFAS) and alcohol-related neurodevelopmental disorder (ARND) in the Cape Coloured (mixed ancestry) population is among the highest in the world (135.1 to 207.5 cases/1000; May et al., 2013). The mothers of the children were recruited between July 1999 and January 2002 to participate in a prospective longitudinal study investigating effects of PAE on growth and cognitive development.

Pregnant women were recruited from a local antenatal clinic that served an economically disadvantaged, predominantly Cape Colored community with known heavy alcohol use during pregnancy (Jacobson et al., 2008). At recruitment, the mother was interviewed regarding her drinking on a day-by-day basis during a typical 2-week period at time of conception and during the preceding 2 weeks, using a timeline follow-back interview (Jacobson et al. 2002). Volume was recorded for each type of beverage consumed each day and converted to oz absolute alcohol (AA). The mother was then asked whether her drinking had changed since conception and, if so, when the change occurred and how much she drank on a day-by-day basis. Pregnant women were invited to participate in the study if they reported drinking 1.0 oz AA/day ($\approx$ 2 standard drinks/day) or if they engaged in binge drinking (defined as >5 drinks/occasion). Alcohol-consuming women were advised to stop or reduce their alcohol intake and were offered referral for treatment. Controls were invited to participate if they reported abstaining or drinking no more than minimally during pregnancy. Among the control participants, all but two mothers (92.9%) abstained from drinking during pregnancy: one reported drinking 2 drinks on 3 occasions, and the other, 1 drink on 6 occasions.

The timeline follow-back interview was repeated in mid-pregnancy and again at 1 month postpartum to provide information about drinking during the latter part of pregnancy. Data from the three alcohol interviews were tabulated to provide three continuous measures of drinking during pregnancy: average oz AA/day, AA/drinking occasion, and frequency (days/week). Data regarding maternal drug use (i.e., marijuana, cocaine, methaqualone ("mandrax")) and smoking during pregnancy were summarized for each drug in terms of days/week; smoking, in cigarettes/day.

Women <18 years of age and those with diabetes, epilepsy, or cardiac problems requiring treatment were excluded. Religiously observant Muslim women were also excluded because their religious practices prohibit alcohol consumption, and they would, therefore, have been disproportionately represented among the controls. Infant exclusionary criteria were major chromosomal anomalies, neural tube defects, multiple births, and seizures.

Dysmorphology Assessment—We organized a clinic in September 2005, in which the children were examined by two U.S.-based FAS dysmorphologists (H.E. Hoyme and L.K. Robinson) using a standard diagnostic protocol for growth and FAS anomalies (Hoyme et al., 2005). FAS, the most severe of the FASD, is characterized by distinctive facial

dysmorphology (short palpebral fissures, thin vermillion, flat philtrum), small head circumference and pre- and/or postnatal growth retardation; PFAS was diagnosed when there was a history of heavy prenatal maternal drinking, the presence of two of the principal alcohol-related facial anomalies, and small head circumference or growth retardation. There was substantial agreement between the two dysmorphologists on assessments of the dysmorphic features, including palpebral fissure length, philtrum and vermillion ratings based on the Astley and Clarren (2001) rating scales (r -values = 0.80, 0.84, and 0.77, respectively). There was also substantial agreement with the Cape Town FASD dysmorphologist (N. Khaole; median r = 0.78), who evaluated eight children who could not be scheduled for the clinic. FASD diagnosis was determined by consensus at case conferences conducted by the dysmorphologists HEH and LKR with SWJ, CDM, and JLJ (Jacobson et al., 2008).

Materials

For all neuropsychological tests, we compared raw test scores for participants with a history of heavy PAE to those of the control participants. We did not use published normative data in any way, largely because of the potential effects on test performance of socio-environmental and cultural differences between the current participants and normative samples.

Prospective Memory Test—The *Dresden Cruiser* (Voigt et al., 2011) is a computerized two-dimensional task based on Kerns' (2000) *CyberCruiser*, which uses a videogame format that appears to be ecologically valid and that is suitable for use with clinical pediatric populations (e.g., Kerns and Price, 2001; Kliegel et al., 2013). The participant drives a car using the arrow keys on a keyboard and is awarded points if s/he successfully steers the car around other cars on the road; points are lost for each car crash. Number of cars hit during this on-going task is used as a measure of attention.

The PM measure is embedded within the on-going task and consists of the participant's needing to refuel the car when a specific event occurs. In the *focal version*, the participant needs to refuel when s/he encounters a yellow car on the road (proximal cue); in the *non-focal version*, when s/he encounters yellow flowers on the roadside (distal cue). Focal PM cues are presumed to activate more automatic retrieval processes; non-focal PM cues, more strategic retrieval processes (McDaniel and Einstein, 2000). Participants are awarded bonus points for every successful refuel and are given five opportunities to refuel during each of the focal and non-focal versions. Number of correct refuels is used as the measure of PM performance. To assess the influence of retention of task instructions (i.e., immediate and delayed recall of instructions) and computer experience (both computer use and ease of access), these variables were measured using self-report questionnaires.

Mediating Variables—We assessed IQ using the *Wechsler Intelligence Scale for Children-Fourth Edition* (WISC-IV; Wechsler, 2003). The WISC-IV was translated by a native Afrikaans-speaking Master's-level child psychologist with extensive experience working with the children in this cohort and was back-translated by a second fluent Afrikaans speaker. The 10-year WISC-IV IQ scores for the 89 children in the sample were

strongly correlated with 5-year IQ on the Junior South African Individual Scale (Madge et al., 1981), which is normed for South African children, $r=0.76$, $p<0.001$.

We assessed four domains of EF using the following six neuropsychological tests: response inhibition—*Rubia Stop* (Rubia et al., 1998) and *Delis-Kaplan Executive Functioning System (D-KEFS) Color-Word Interference Test* (Delis et al., 2001); cognitive flexibility—*DKEFS Color-Word Interference Test* (Delis et al., 2001), *Children's Color Trails Test* (CCTT; Llorente et al., 2003), and *DKEFS Verbal Fluency* (Delis et al., 2001); WM—*WISC-IV Digit Span Backwards* (Wechsler, 2003); and planning and problem solving—*Tower of London* (ToL; Culbertson and Zillmer, 2001). Although the Rubia Stop task is not a standardized measure of response inhibition, the stop task paradigm is considered the gold standard and a valid measure of this cognitive domain in pediatric clinical samples (see Nigg, 2005). During this task, participants are required to inhibit a previously learned motor response and to self-monitor their behavior.

The *California Verbal Learning Test—Children's Version* (CVLT-C; Delis et al. 1994) is a list-learning task that has been used to document verbal learning and memory performance in children with moderate-to-heavy levels of PAE (e.g., Mattson & Roebuck, 2002; Lewis et al., 2015). We used number of words correctly recalled during the long-delay free recall trial as the indicator of retrospective memory.

ADHD Assessment—Each child was assessed for ADHD following research criteria developed in collaboration with two experts in ADHD research (Joel Nigg, Ph.D., and Rafael Klorman, Ph.D.) This diagnosis was based on (a) a maternal interview using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS; Kaufman et al., 1996) administered by CDM and (b) ratings by the child's classroom teacher on the Disruptive Behavior Disorders (DBD) Scale (Pelham et al., 1992). An ADHD classification was assigned if (a) at least 6 of the 9 inattention and/or 6 of the 9 hyperactivity/impulsivity symptoms were endorsed ("pretty much" or "very much true") by the teacher on the DBD or indicated by the parent on the K-SADS, and (b) some impairment was reported by age 7 years and in two or more settings.

Procedure

Approval for the study was obtained from the Wayne State University and University of Cape Town Faculty of Health Sciences research ethics committees. Informed consent and assent were obtained from the mothers and children, respectively. Except in the most severe cases of FAS, child examiners were blind regarding FASD diagnosis and PAE history.

The *Dresden Cruiser*, IQ, EF, and retrospective memory assessments were administered to each child during 2 testing days. Each child was first given general instructions for the *Dresden Cruiser* task, which did not involve the PM refuelling task. A 1-minute practice trial was administered to familiarize the child with the task. The child was then administered the PM refueling instructions and asked to recall the PM and on-going task instructions. Following a filled delay of 15 minutes, the child completed the first 4-minute trial, during which there were five opportunities to refuel when the PM cue was encountered. No further reminder of the task instructions was provided. Thereafter, another 15-minute filled delay

occurred, followed by the child's completing the second trial. Once finished, the child's retrospective memory for the on-going and PM task instructions was assessed via questionnaire, enabling us to assess whether failures were due to poor recall of the instructions.

The child was administered the focal version of the PM task on Day 1 of testing, and the non-focal version on Day 2. Ongoing task difficulty was examined by differences in number of cars on the road to rule out ceiling effects on both focal and non-focal versions of the task. The high-difficulty version required increased attention to avoid crashing into the cars. All responses were recorded automatically and imported from the electronic database into SPSS version 22.0 (2013, IBM Corp., Armonk, NY, USA) for analysis.

Data Analysis

Because the continuous predictor variable (oz AA/day) was positively skewed, it was normalized using a natural log transformation ($\ln[x + 1]$). The following measures each had 1–2 outliers (>3 *SD* beyond the mean): maternal parity and smoking during pregnancy; hit count scores on the PM focal (easy and difficult versions) and non-focal (easy version) tasks, CCTT Total Time, ToL Total Move Count, CVLT-C long-delay free recall, and the following composite scores derived as described below: Phonemic and Category Verbal Fluency, Cognitive Flexibility, and PM. Outliers were recoded to 1 point above or below the next lowest or highest observed value (Winer, 1971).

Six potential confounders were considered: maternal SES (Hollingshead, 2011), IQ (based on Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn and Dunn, 1981) and Raven Progressive Matrices (Raven, 1996)), and smoking during pregnancy; and child sex and age at testing. Shapiro-Wilk tests indicated that the distributions of maternal SES ($W(87)=0.95$), IQ ($W(89)=0.96$) and smoking during pregnancy ($W(89)=0.83$) deviated significantly from normal, all $p < .01$. Any control variable related (assessed using Pearson r or Spearman ρ) even weakly (at $p < .10$) to PM performance was identified as a potential confounder and controlled statistically in the regression analyses of effects on this outcome. None of the mothers reported using methaqualone, and prenatal exposure to marijuana ($n=6$) and cocaine ($n=1$) were too rare for statistical adjustment. Any association between prenatal alcohol use and the outcome was, therefore, rerun omitting children with either prenatal marijuana or cocaine exposure.

We examined the relation of diagnostic group to PM performance using a mixed-design factorial analysis of variance (ANOVA) with two within-subjects factors—cue focality (focal vs. non-focal) and ongoing task difficulty (low vs. high)—and one between-subjects factor, FASD diagnosis—FAS/PFAS, heavily-exposed (HE) nonsyndromal, and non-exposed Control. *Post-hoc* analyses were performed using Least-Significant Difference (LSD) tests. Differences in PM performance between easy and difficult versions were assessed using matched pair t -tests. To determine whether attention, retention of task instructions, or previous computer usage influenced on-going task performance, we examined between-group differences in on-going task absorption (i.e., number of car crashes) using analysis of covariance (ANCOVA), and in retention of task instructions and previous computer usage using chi-square tests.

A principal components analysis (PCA) with varimax rotation was run to investigate the factor structure underlying the PM and EF measures. The variables loading most strongly on each of the factors were converted to *z*-scores and averaged to create composite scores reflecting each of the underlying domains.

Mediation by IQ was examined in a hierarchical multiple regression analysis in which the PM composite score from the factor analysis served as the dependent variable. AA/day was entered at the first step and WISC-IV IQ at the second. The Sobel Test (Baron and Kenny, 1986) was used to test whether the IQ scores significantly mediated the effect of AA/day on the PM composite. Mediation by EF was assessed in a series of multiple regression analyses examining the PM composite score in relation to AA/day and each of the EF composite scores, and mediation was again tested using the Sobel Test. A similar regression was run to examine the relation of AA/day and retrospective memory to PM performance, followed by the Sobel test.

The relation of FASD diagnosis to ADHD (present vs. absent) was examined using χ^2 , and the association of a continuous measure of PAE with ADHD diagnosis and with inattentive and hyperactive symptoms was examined using Pearson correlation. The relation of ADHD to PM performance was examined using an independent samples *t*-test, and the association of inattentive and hyperactive symptoms using Pearson correlation.

RESULTS

Sample Characteristics

Mothers in the FAS/PFAS group were older and had more live births than mothers in the HE and Control groups, all $ps < .05$ (Table 1). They were also less educated and had lower PPVT and Raven IQ scores than mothers in the HE and Control groups, all $ps < .01$. Mothers in the FAS/PFAS and HE groups were somewhat more economically disadvantaged than Controls, $ps < .05$ (on average, Hollingshead Level V—Unskilled Laborers, lowest of five levels, vs. Level IV—Semiskilled Workers, respectively). The proportion of married mothers was higher in the Control group than in either exposure group.

There was a dose-dependent effect of PAE for both average amount of alcohol consumed/day and frequency of drinking days/week, with mothers of children in the FAS/PFAS group consuming more alcohol than mothers in the HE and Control groups, and mothers in the HE group consuming more than Controls, all $ps < .05$ (Table 1). Although mothers in the FAS/PFAS and HE groups drank similar amounts of alcohol per occasion, mothers of the FAS/PFAS children drank, on average, 1.5 times more often than mothers of the HE children.

Mothers in the FAS/PFAS group smoked more than mothers in the Control group during pregnancy, $ps < .05$ (Table 1), but there were no HE versus Control group differences regarding smoking, $p > .20$. Only one mother in the FAS/PFAS group reported using cocaine during pregnancy (mean=2.6 times/week); six (3 FAS/PFAS, 2 HE, 1 Control) reported using marijuana during pregnancy (mean=1.3 times/week, range=0.03–3.1).

On average, children in the HE group were slightly older than those in the FAS/PFAS and Control groups, $p < .05$ (Table 1). There were no significant between-group differences for sex distribution, computer experience or number of days/week games played. As expected, children in the FAS/PFAS group had lower WISC-IV IQ scores than children in both the HE and Control groups, $p < .01$. Neither the incidence of ADHD nor reports of hyperactive and/or inattentive symptoms differed between FASD diagnostic groups.

Prospective Memory Performance

There were no significant between-group differences in terms of accuracy of immediate or delayed (retrospective) recall of PM task instructions, with frequencies of correct responses ranging from 95.4–100%, median=98.7%.

As expected, task performance for the sample as a whole was poorer in the non-focal ($M=3.2$, $SD=1.1$) than in the focal condition ($M=3.8$, $SD=1.3$), $F(1,83)=18.45$, $p < 0.001$. Unexpectedly, however, children performed more poorly on the easy ($M=3.4$, $SD=1.1$) than on the difficult ($M=3.6$, $SD=1.0$) task versions of the *Dresden Cruiser*, $F(1,83) = 7.18$, $p < 0.01$. This unanticipated result may be due to practice effects: on Day 1 of the study protocol, the easy version was always administered before the difficult version. On Day 1, refuelling performance improved significantly, $t(85)=-3.61$, $p < 0.01$, from the easy ($M=3.6$, $SD=1.4$) to the difficult ($M=4.0$, $SD=1.4$) version. On Day 2, building on the benefit of Day 1 practice, refuelling performance was at a ceiling for both easy ($M=3.2$, $SD=1.2$) and difficult ($M=3.2$, $SD=1.2$) versions, $t(88) = -0.21$, $p > 0.20$. Thus, although both the focal and non-focal versions of the task had a maximum of five refuel opportunities, the distribution of refuel scores was negatively skewed towards refuelling a maximum of four times during the non-focal task, with 54 (60.7%) and 52 (58.4%) children refuelling four times on the easy and difficult version of the non-focal task, respectively.

This practice effect interpretation is further supported by the fact that the factorial ANOVA detected a significant cue focality $\times$ ongoing task difficulty level interaction, $F(1,83)=8.30$, $p < 0.01$. This interaction suggests that within-diagnostic group differences between mean PM performance scores on the easy and difficult tasks were greater in the case of the focal task, which was the first task administered and, in practice, on which there were more refuelling opportunities, than the non-focal task (Table 2).

There was a significant main effect of FASD diagnosis on PM performance across all conditions, $F(2,83)=6.55$, $p < 0.01$ (Table 2), with children in the FAS/PFAS group refuelling fewer times than those in the HE and Control groups, $p < 0.01$. There were no significant differences in refuel count for children in the latter two groups, $p > 0.20$. There were also no significant interactions of diagnostic group with either cue focality or ongoing task difficulty, $p > 0.20$.

There were, however, significant between-group differences in on-going task absorption (measured by number of car crashes), with children in the FAS/PFAS group having more car crashes than those in the HE group, $p < 0.01$ (Table 2). There were no significant differences in task absorption between the HE and Control groups, $p > 0.20$. However, the effect of FASD

diagnosis on PM performance remained significant after controlling for on-going task performance, $F(2, 82)=3.98, p<.05$.

Principal Components Analysis (PCA): PM and EF Composites

The PCA generated four factors with eigenvalues >1 (Table 3), which jointly accounted for 61.8% of the variance. Performance on the four PM variables loaded onto one factor labeled “prospective memory”. Performance on the EF composites loaded on the other three factors: D-KEFS verbal fluency tasks loaded on one of these factors labeled “verbal fluency”; performance on the D-KEFS tasks of inhibition and set-shifting and the CCTT loaded on another factor labeled “cognitive flexibility”; and performance on the ToL, WM, and inhibition loaded on the last factor labeled “self-monitoring and planning.” Importantly, and consistent with previous literature, the analysis showed that PM represents a factor that is separate from and independent of the three EF components.

Prenatal Alcohol Exposure and PM Performance

The continuous measure of PAE was significantly related to the PM composite score, $r=-0.34, p=0.001$. Maternal IQ and SES were identified as potential confounders of the effect of PAE on PM performance, $r_s=0.21$ and $.31$, respectively, and both $p_s<0.01$. PAE retained a significant effect on PM performance when these potential confounders were entered into the model, $\beta=-0.23, p<0.05$. The magnitude of the effects on PM performance remained virtually unchanged when data from the 6 children exposed to marijuana and the 1 exposed to cocaine were removed, $\beta_s=-0.40$ and $-0.38, p_s<0.001$, respectively.

Mediation by IQ, EF and Retrospective Memory

Table 4 summarizes results from the mediational analyses examining the effects of PAE and each of five potential mediators on PM performance. After adjustment for WISC IQ, the effect of PAE on PM performance fell just short of significance, and the significant Sobel Test confirmed that WISC IQ score partially mediated the alcohol effect on PM. By contrast, the effect of PAE on PM performance remained significant after adjustment for the three EF composite scores and retrospective memory performance. In addition, WISC IQ, cognitive flexibility, and retrospective memory each significantly predicted PM performance after inclusion of PAE in the model.

Prenatal Alcohol Exposure and ADHD in PM

Although incidence of ADHD did not differ among the FASD diagnostic groups (Table 1), the continuous measure of PAE was significantly related to ADHD status, $r=0.22, p<0.05$. PAE was also related to the number of inattentive ADHD symptoms, $r=0.36, p<.001$; the relation to hyperactivity symptoms was smaller, $r=0.20, p<.057$. There were, however, no significant associations between number of inattentive or hyperactive symptoms and the PM outcome, $p_s>0.20$, nor were there PM performance differences in children diagnosed with ADHD versus those without the diagnosis, $t(87)=0.79, p>.20$.

DISCUSSION

This is the first study to document prospective memory impairment in children with heavy PAE. In our sample, children in the FAS/PFAS group performed more poorly than children in the nonsyndromal HE and Control groups on both focal and non-focal versions of the *Dresden Cruiser*; those in HE and Control groups performed similarly. A continuous measure of PAE collected from the mother during pregnancy was related to poorer PM performance. This association was not attributable to differences in sociodemographic background or previous computer experience. Although children in the FAS/PFAS group showed poorer on-going task absorption, this indicator of attention did not account for the adverse effect of PAE on PM performance.

The lack of event-related PM deficits in the nonsyndromal exposed children suggests that those children appear to have mastered use of external cues by 11 years and that the test may not have been sufficiently challenging for them at this age. This interpretation is supported by evidence of ceiling effects in *Dresden Cruiser* performance: on the non-focal task, 22 HE children (68.80%) and 21 Controls (75.0%) refuelled 4 times (the maximum attained) during the easy version and 20 HE (62.50%) and 20 Controls (71.40%) refuelled four times during the difficult version.

Although previous studies report no relation between PM performance and IQ in children with IQs > 70 (e.g., Kerns and Price, 2001), we found a positive association between PM and IQ in our sample, which included children with a broader range of IQ scores. Further support for the positive association between PM and IQ in our sample is provided by the finding that the effect of PAE on PM performance was partially mediated by alcohol-related deficits in IQ. Thus, the PM performance impairments observed in heavily-exposed syndromal children are, at least in part, due to the effect of PAE on general intellectual functioning.

Consistent with previous research (Kerns and Price, 2001; Kliegel et al., 2006), event-based PM performance was not related to the presence of ADHD symptoms, nor were there performance differences when comparing children with and without ADHD. By contrast time- but not event-based PM tasks have been related to ADHD (e.g., Zinke et al., 2010; however, see Talbot and Kerns, 2014). This differential pattern of impairment is consistent with Barkley et al.'s (2001) proposal that impaired time estimation is a key element of ADHD. Kerns and Price (2001) suggest that time-based PM tasks may be more demanding of prefrontal activation than event-based tasks, which could account for the finding that time-based tasks are more sensitive to PM deficits in children with ADHD. In fact, time- and event-based PM paradigms may even be characterized by different patterns of prefrontal activation, a suggestion supported by research on young adults with acquired frontal lobe damage (Kinsella et al., 1996). Hence, one interpretation is that our findings of event-based PM deficits in children with FAS/PFAS are likely due to a pattern of prefrontal impairment different from that seen in the time-based PM deficits in children with ADHD.

In our study, PM performance was not mediated by PAE-related deficits on tasks used commonly to assess different aspects of EF. The absence of such a mediating effect suggests

that performance on the *Dresden Cruiser* is relatively independent of EF performance, and that PAE impacts on event-based PM via mechanisms other than executive control. These findings are consistent with recent research demonstrating convergent and discriminant validity for PM in young and older adults (Schnitzspahn et al., 2013). The absence of a mediating EF effect may be indicative of the relatively low cognitive demand of the event-based *Dresden Cruiser* task that draws more on automatic/spontaneous retrieval processes than the more complex strategic monitoring that recruits EF capabilities during some time-based PM tasks (McDaniel and Einstein, 2000).

Cognitive flexibility composite scores were a significant predictor of PM performance. These data are consistent with the suggestion that cognitive flexibility supports the stage of intention initiation during successful prospective remembering (Kliegel et al., 2002, 2008).

The finding that retrospective memory performance predicts PM performance is consistent with the suggestion that retrospective memory supports the PM stage of intention retention (Kliegel et al., 2002, 2008). The fact that retrospective memory, on its own, predicted PM performance is most likely due to performance differences seen on the CVLT-C (viz., children in the FAS/PFAS group recalled fewer words than children in the HE or Control groups). These PAE-related impairments in delayed recall performance are consistent with previous research documenting verbal learning and memory impairments in FASD (e.g., Lewis et al., 2015). This finding should, however, be interpreted in light of the fact that most children in this sample recalled on-going and PM task instructions accurately. PM failures cannot, therefore, be attributed solely to failures at the level of intention retention.

Limitations—Given the lack of differences in event-based PM performance between the HE and Control groups, it is possible the event-based *Dresden Cruiser* task was not sufficiently complex to elicit PM deficits in the nonsyndromal children at this age. Time-based PM measures might detect PM dysfunction in those children. More challenging time-based PM tasks might also allow identification of the stage(s) (i.e., intention formation, intention retention, intention initiation, or intention execution) of PM that might be particularly vulnerable to effects of PAE.

We did not counter-balance presentation of the *Dresden Cruiser* tasks (i.e., the focal task was always administered before the non-focal task) because of a concern that if there were an interaction between order and exposure group, it would be more difficult to detect an exposure effect.

Conclusions

This study documented PM impairment in children with a history of heavy PAE. These findings contribute to the growing body of work attempting to define a cognitive-behavioral phenotype for FASD and to document the distinctive profile seen in alcohol-exposed children with attention problems compared to those with idiopathic ADHD. The fetal alcohol-related PM deficits were not attributable to sociodemographic influences, EF, or retrospective memory and were only partially mediated by IQ. These results support the inclusion of PM-targeted interventions in treatment programs designed for children with a

history of heavy PAE. Intact PM is necessary for optimal functioning in the school and home environment, and it is important, therefore, that appropriate compensatory strategies be developed in children who display PM impairments.

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Table 1Sample characteristics ($N = 89$)

	FAS/PFAS ($n = 29$)	Heavy exposed ($n = 32$)	Control ($n = 28$)	F or χ^2
Age at delivery (years)	29.1 (7.4)	25.2 (4.8)	25.7 (3.9)	4.26 *
Parity	2.8 (1.8)	1.7 (1.0)	1.9 (1.1)	5.88 **
Maternal education (years) ^a	7.3 (2.5)	9.2 (2.4)	10.1 (1.6)	11.13 **
Peabody Picture Vocabulary Test—Revised ^b	50.2 (13.4)	62.9 (15.6)	71.4 (19.5)	11.50 ***
Raven Progressive Matrices ^c	24.2 (9.8)	32.6 (11.3)	32.4 (8.8)	6.41 **
Socioeconomic status (SES) ^d	17.6 (8.0)	21.7 (10.3)	27.4 (10.8)	7.01 **
Marital status (% married)	41.4	34.4	67.9	7.30 *
Prenatal alcohol exposure				
AA/day (oz) ^e	1.2 (1.4)	0.5 (0.5)	0.001 (0.003)	13.92 ***
AA/occasion (oz)	3.7 (2.2)	3.1 (2.3)	0.06 (0.2)	32.13 ***
Frequency (days/week)	2.1 (1.4)	1.4 (0.7)	0.01 (0.03)	26.99 ***
Smoking during pregnancy (cigarettes/day)	7.8 (5.7)	5.9 (5.8)	3.6 (6.5)	3.47 *
Child's age at testing (years)	11.0 (0.5)	11.2 (0.4)	10.9 (0.3)	4.77 **
Sex (% male)	55.2	59.4	50.0	0.53
Computer experience (% yes) ^f	69.0	87.1	75.0	2.93
Frequency of computer use (days/week) ^g	2.6 (2.4)	3.1 (2.4)	2.4 (2.3)	0.69
WISC-IV IQ	64.5 (10.8)	74.9 (11.8)	75.6 (12.0)	8.40 ***
ADHD n (%)	9 (31.0)	7 (21.9)	6 (21.4)	0.92
Inattentive ADHD symptoms	3.6 (3.4)	3.0 (3.0)	2.7 (3.0)	0.62
Hyperactive ADHD symptoms	3.2 (3.4)	2.8 (2.8)	2.8 (3.0)	0.16

Note. Means are presented with standard deviations in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal; SES = Socioeconomic status; AA = absolute alcohol; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition; ADHD = attention deficit/hyperactivity disorder. Test statistics were either F or χ^2 depending on whether the variable under consideration was continuous or categorical.

^aData missing for one mother in the HE group and one mother in the Control group

^bData missing for one mother in the FAS/PFAS group, two mothers in the HE group, and three mothers in the Control group.

^cData missing for two mothers in the HE group and three mothers in the Control group.

^dBased on Hollingshead Four Factor Index (2011). Data missing for one mother in the HE group and one mother in the Control group.

^e 1 oz AA/day $\approx$ about 2 standard drinks

^f Number of children reporting computer and/or video game experience; data missing for one subject in the HE group.

^g Data missing for one subject in the HE group and two subjects in the Control group.

*
 $p < .05$;

**
 $p < .01$;

 $p < .001$.

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Table 2Effects of FASD diagnosis on prospective memory performance ($N = 89$)

	FAS/PFAS ($n = 29$)	HE ($n = 32$)	Control ($n = 28$)	F
Focal PM Task	3.2 (1.6)	4.2 (1.0)	4.0 (1.0)	5.26 ^{**}
Refuel Count, Easy ^a	2.9 (1.7)	4.1 (1.1)	3.7 (1.3)	
Refuel Count, Difficult ^b	3.5 (1.8)	4.3 (1.0)	4.2 (1.0)	
Non-Focal PM Task	2.8 (1.2)	3.3 (1.1)	3.5 (0.8)	4.35 [*]
Refuel Count, Easy	2.7 (1.5)	3.3 (1.2)	3.6 (0.8)	
Refuel Count, Difficult	2.8 (1.3)	3.4 (1.1)	3.5 (1.1)	
Ongoing Task Absorption				
Focal Hit Count	24.7 (9.9)	19.2 (9.7)	21.0 (6.9)	2.88 [†]
Non-Focal Hit Count	21.9 (9.5)	15.9 (8.1)	17.8 (7.8)	3.91 [*]
Mean Hit Count	22.9 (8.0)	17.5 (8.2)	19.1 (6.3)	3.92 [*]

Note. Means are presented with *SDs* in parentheses. FAS = fetal alcohol syndrome; PFAS = partial FAS; HE = heavily exposed nonsyndromal.

^aData missing for one child in the FAS/PFAS group and for one child in the Control group.

^bData missing for one child in the Control group.

[†] $p < .10$;

^{*} $p < .05$;

^{**} $p < .01$.

Table 3Varimax rotated factors ($N = 70$)

Outcome Variables	Prospective memory (1)	Verbal fluency (2)	Cognitive flexibility (3)	Self-monitoring and planning (4)
Dresden cruiser (refuel count)				
Focal, easy	.68	.09	.24	-.15
Focal, difficult	.64	.25	.40	-.01
Non-Focal, easy	.72	-.07	-.41	-.17
Non-Focal, difficult	.81	-.08	-.32	.11
D-KEFS verbal fluency				
Phonemic	-.06	.74	-.09	-.37
Category	.07	.66	-.31	.03
Switch	.06	.90	-.09	.02
D-KEFS color-word interference test				
Interference	.03	-.15	.63	.01
Set-Shift	-.05	-.33	.55	.33
Children's Color Trails Test 2 (time)	-.10	-.18	.67	.34
Tower of London (total moves)	.16	.20	.15	.80
WISC-IV Digit Span, Backwards	.18	.38	-.15	-.57
Rubia stop (SSRT)	-.30	-.21	.08	.60
Eigenvalue	2.00	3.47	1.50	1.08
Variance explained (%)	15.21	26.72	11.50	8.32

Note. D-KEFS = Delis-Kaplan Executive Functions System; SSRT = Stop Signal Reaction Time; WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition.

Table 4

Mediation of effect of prenatal alcohol exposure on prospective memory by IQ, executive function, and retrospective memory

	Prenatal alcohol exposure			Mediator variable		
	N	r ₁	β ₁	r ₂	β ₂	Sobel z
Mediator						
WISC-IV IQ	89	-.34**	-.20 [†]	.44***	.36**	-2.72**
Executive function						
Verbal fluency	84	-.29**	-.24*	.24*	.17	-1.35
Cognitive flexibility	88	-.31**	-.26*	-.27**	-.21*	-1.52
Self-monitoring and planning	89	-.34**	-.34**	-.07	-.08	0.31
Retrospective memory	82	-.27**	-.22*	.27**	.22*	-1.43

Note. WISC-IV = Wechsler Intelligence Scale for Children—Fourth Edition. Each row summarizes results from a multiple regression analysis examining the effect of prenatal alcohol exposure and the indicated mediator variable on prospective memory (PM) performance. *r*₁ indicates the unadjusted correlation between prenatal alcohol exposure and PM performance and β₁ indicates the standardized beta value for prenatal alcohol exposure when the mediator variable is entered into the regression model; whereas *r*₂ indicates the unadjusted correlation between the mediator variable and PM performance and β₂ indicates the standardized beta value for the mediator variable when prenatal alcohol exposure is entered into the regression model.

[†] *p* < .10;

* *p* < .05;

** *p* < .01;

*** *p* < .001.