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VISUOSPATIAL WORKING MEMORY IN SCHOOL-AGED CHILDREN EXPOSED *IN UTERO* TO COCAINE

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Objective: ***Among the neurocognitive impairments reported as associated with prenatal cocaine exposure, slower response time, and less efficient learning in school-aged children are common to findings from several laboratories. This study presents performance data on a spatial working memory task in 75 prenatally cocaine exposed (CE) and 55 nondrug-exposed (NDE) 8- to 10-year-old children.***

Methods: ***Children were administered a novel neuropsychological measure of immediate- and short-term memory for visuospatial information, the Groton Maze Learning Test© (GMLT), a computer-based hidden maze learning test that consists of a "timed chase test" (a simple measure of visuomotor speed), eight learning trials followed by a delayed recall trial after an 8-minute delay and a reverse learning trial. Performance is expressed as correct moves per second and number of errors per trial.***

Results: ***Across all trials, the cocaine-exposed group showed significantly slower correct moves per second and made significantly more errors. There were no significant main effects for amounts of alcohol, tobacco, or marijuana exposure. After an 8-minute delay and compared to the eighth trial, cocaine-exposed children showed less consolidation in learning compared to nonexposed children. When asked to complete the maze in reverse, cocaine-exposed children showed a greater decrement in performance (decreased correct moves per second and increased errors) compared to the eighth learning trial.***

Conclusions: ***Children exposed* in utero *to cocaine exhibit a possible impairment in procedural learning and diminished efficiency in creating and accessing an internal spatial map to master the hidden maze.***

Keywords: ***prenatal cocaine exposure, visuospatial working memory, delayed recall, spatial map***

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INTRODUCTION

Whether or not prenatal cocaine exposure has an enduring impact on the neurocognitive development of preschool and school-aged children is an area of active, and controversial, research (Brooks-Gunn, McCarton et al., 1994; Lester, Freier et al., 1995; Neuspiel, 1995; Bland-Stewart, Seymour et al., 1998; Chiriboga, 1998; Malakoff, Fay et al., 1999; Olson & Toth, 1999; Singer, Arendt et al., 1999; Tronick and Beeghley, 1999; Frank, Augustyn et al., 2001; Mayes & Fahy, 2001). Despite considerable variation regarding critical issues of exposure definition (e.g., quantity, frequency, and timing of exposure), accumulating findings from published studies to date suggest an association between prenatal cocaine exposure and neurocognitive deficits, under optimal testing conditions using narrow band assessments to test specific executive control functions such as task switching and inhibition. Collected findings include slower reaction times (Heffelfinger, Craft et al., 1997; Eghbalieh, Crinella et al., 2000), greater perseveration with diminished response inhibition (Bendersky, Gambini et al., 2003; Noland, Singer et al., 2003a, 2003b), increased errors of commission or omission on A-not-B or continuous performance tasks (Richardson, Conroy et al., 1996; Mayes, Grillon et al.,1998; Espy, Kaufmann et al., 1999; Eghbalieh, Crinella et al., 2000; Noland, Singer et al., 2003a, 2003b), diminished capacity for sustained attention (Bandstra, Morrow et al., 2001; Savage, Brodsky et al., 2005), and deficits in spatial learning (Schroder, Snyder et al., 2004). Several studies have also documented dose-response effects on attention control and a range of executive control functions (Coles, Platzman et al., 1992; Jacobson, Jacobson et al., 1996; Alessandri, Bendersky et al., 1998; Jacobson, Bihun et al., 1999; Swanson, Streissguth et al., 1999) as well as an interactive effect with the level of environmental risk (Bendersky, Gambini et al., 2003).

Among the neurocognitive impairments reported, slower response time, poor inhibitory control, diminished sustained attention, and less efficient learning are common to findings from several laboratories (Bendersky, Gambini et al., 2003; Noland, Singer et al., 2003; Schroder, Snyder et al., 2004; Chawarska, Mayes et al., 2005). Such findings may be consistent with the direct effect of cocaine on cortical morphology observed in preclinical models that include disrupted cortical lamination, reduction in cortical volume, and inappropriate positioning of cortical neurons; these morphological changes appear also associated with behavioral disruptions including impaired attention (Lidow & Rakic, 1995; Lidow & Wang, 1995; Lidow & Song, 2001; He, Bai et al., 2004). Further, electrophysiology data from humans has shown that cocaine-exposed children use more diffuse regions of the cortex compared to controls while completing simple neurocognitive tasks (e.g., Stroop color word tasks; Mayes, Molfese et al., 2005). With such direct effects on cortical morphology, neurocognitive deficits might be expected in even relatively nonchallenging or nonstressful conditions across a range of functions including slowed reactions times and slower consolidation of information (Lidow, 2003).

The present study compares the performance of prenatally cocaine-exposed children on a task of visuospatial learning and memory (Boulanger, Snyder et al., in press; Snyder, Werth et al., in press) to the performance of age and socioeconomic status (SES) matched controls. The children in the sample are part of an ongoing longitudinal study of prenatally cocaine-exposed and noncocaine-exposed school-aged children followed since birth. The current report extends an earlier preliminary study (Schroder, Snyder et al., 2004) on a small sample of prenatally cocaine-exposed children in which investigators discovered significant differences between cocaine-exposed 8- and 9-year-olds in several aspects of their

performance on the Groton Maze Learning Test (GMLT) when compared to SES and age-matched controls. Despite the small size of the control group, an evident association was found between prenatal cocaine exposure and decreased efficiency in creating and accessing an internal spatial map. The present study attempts to expand on these findings, which may suggest the emergence of a profile of possible impairments in visuospatial processing in children exposed *in utero* to cocaine. We hypothesized that children who were prenatally exposed to cocaine would have more difficulty learning the GMLT. That is, these children would show relative impairments in spatial working memory for the complex two-dimensional hidden maze, over successive learning trials as evidenced by fewer correct moves per second compared to children who were not exposed prenatally to cocaine.

METHOD

Participants

The present study includes data from 130 children who were drawn from a larger sample of 369 children who have been participating in a 12-year-longitudinal study of the effects of fetal cocaine exposure on physical, cognitive, social, and emotional development. Children (and their mothers) who were exposed to drugs other than cocaine (primarily alcohol, tobacco, and/or marijuana) were also enrolled in the study, as were nondrug-using control subjects. The sample was recruited at birth over a 5-year period and children and their parents are seen biannually. Families were originally recruited when they presented for prenatal care at the Women's Center of Yale-New Haven Hospital or, in the case of no prenatal care, when they were admitted to the postpartum ward. The larger sample from which the 130 children for this study were recruited consisted of 81 % African American, 6.5% Hispanic, and 12.5% Caucasian children, all of who come from the greater New Haven area. The present sample consists of 75 children who were identified as cocaine-exposed (CE) and 55 who were identified as noncocaine-exposed (NCE). These subjects were chosen for the present set of analyses only on the basis of their current age: all were aged between 8.0 and 9.0 years old at the time of their most recent assessment visit. Subjects in both groups were potentially exposed prenatally to varying amounts of alcohol, tobacco, and/or marijuana. The sample includes 69 males and 61 females, with a mean age of 8.22 years (SD = 0.32). There were no differences in age or gender between the CE and NCE groups but the CE group was comprised of proportionately more African American parents. However, there were no main effects for ethnicity in the analyses of maze performance. Demographic information for both subject groups is provided in Table 1.

Prenatal drug-exposure status was ascertained at the time of recruitment into the longitudinal follow-up study (either prenatally or at the time of delivery). For those women interviewed prenatallly, the majority were interviewed in their late second or third trimester. After obtaining verbal consent for an interview, all women were questioned about substance use in a detailed interview that covered lifetime use (prior to the current pregnancy) of cocaine, tobacco, alcohol, marijuana, and other drugs (e.g., sedatives, opiates), and frequency and amount of use of these agents during the preceding 30 days. Women interviewed prenatally were also interviewed again at the time of delivery either to confirm their continued use or to ascertain new use. For all women regardless of drug use history, a urine sample was obtained for toxicology. Standard urine screening for drug level or metabolites of cocaine (e.g., benzoylecognine), opioids, benzodiazepines, and tetrahydrocannabinol

Table 1 Demographic Characteristics for the Study Sample.

	NCE (*N* = 55)	CE (*N* = 75)	
Child Age (Yrs)	8.2 (*SD* = 2.8)	8.2 (*SD* = 0.4)	*F*(1, 129) = 0.01
Sex (M:F)	33:22	36:39	X2 (1) = 1.8
Ethnicity			
% (*n*) African American	65.5% (36)	93.3% (70)	
% (*n*) Caucasian	21.8% (12)	4.0% (3)	X2 (2) = 16.4***
% (*n*) Hispanic	12.7% (7)	2.7% (2)	
Maternal Drug Use			
% Using Alcohol	43.6	62.7	X2 (1) = 4.6*
Days Alcohol use in month before interview	0.4 (*SD* = 0.5)	3.1 (*SD* = 5.7)	*F*(1, 129) = 12.0***
% Using Tobacco	10.9	66.7	X2 (1) = 40.2***
Average packs per day in month before interview	0.3 (*SD* = 0.6)	1.5 (*SD* = .85)	*F*(1, 129) = 78***
% Using Marijuana	9.1	48.0	X2 (1) = 22.2***
Days Marijuana use in month before interview	0.1 (*SD* = 0.3)	1.2 (*SD* = 4.0)	*F*(1, 129) = 4.5*
Years of cocaine use		5.5 (*SD* = 3.1)	
Days of cocaine use in month before interview		2.6 (*SD* = 7.1; range 1–30	

*$p \leq .05$; **$p \leq .01$; ***$p \leq .001$.

(THC) was performed using the Abbott TDx system and the recommended cutoff levels (Poklis, 1987). A urine sample was rated as positive if the quantity of drug or metabolite was >300 gms/ml. The TDx system is highly sensitive and specific for the detection of illicit drug use, and benzoylecognine is detectable for three days after use (Walters, 1987).

Prenatal cocaine-exposure status was determined by a combination of maternal report and urine toxicology from the prenatal or immediate postpartum period. Infants were considered cocaine-exposed prenatally if maternal self-reports were positive, even if urine toxicological results were negative. Conversely, if mothers reported that they did not use cocaine, but clinic or hospital urine toxicological results were positive, infants were also considered exposed. Every mother with a positive history and/or positive urine toxicology for cocaine use was invited to join the study. Noncocaine-exposed status was ascertained by negative urine toxicology and a negative maternal history of cocaine during pregnancy and at the time of delivery.

The 75 mothers for the present study sample who were identified as cocaine users had used cocaine at least since the beginning of their pregnancy (and the majority had used for months and years before their pregnancy) and the cocaine-using women did not stop their use before delivery. None had used cocaine only before but not during their pregnancy. No mother in the sample had used opiates. Thus, the terms cocaine-using and noncocaine-using refer to the presence of cocaine/crack, and not the use of alcohol, marijuana, or tobacco up to the time of delivery. The 75 cocaine-using mothers in this sample reported 5.5 years of lifetime cocaine use (*SD* = 3.1), 2.6 days of cocaine use during pregnancy in the 30 days prior to the interview (*SD* = 7.1), and 54.7% of mothers reported using 0.50 grams per day or more when they used (Table 1).

There were significant differences between the CE and NCE groups in the reported amount of other drugs used during pregnancy (Table 1). The CE group overall more often

reported using alcohol, tobacco, or marijuana during their pregnancy in addition to their cocaine use. Sixty-three percent (63%) of cocaine-using women compared to 44% of non-cocaine-using women also reported alcohol use during their pregnancy (chi-square = 5.1, $p = .2$). Similarly, 67% and 48% of cocaine-using women compared to 11% and 9% of noncocaine users reported tobacco (chi-square = 41, $p < .001$) or marijuana (chi-square = 22.8, $p < .001$) use respectively during their pregnancy. Cocaine-using women who also used tobacco reported an average amount of use of 1.5 packs per day ($SD = 0.85$) in the 30 days prior to the prenatal or immediate postnatal interview. Similarly, cocaine-using mothers who reported alcohol or marijuana use admitted to the use of these on at least 3.1 days ($SD = 5.7$) or 1.2 days ($SD = 4.0$), respectively, in the 30 days prior to the interview. In contrast, among the noncocaine-using mothers, those reporting tobacco use reported only 0.3 packs per day ($SD = 0.6$) in the 30 days prior to the interview (compared to the cocaine-using mothers, $F[1, 129] = 78$, $p < .001$). There were similar differences in days of alcohol (Mean = 0.4, $SD = 0.5$; $F[1, 129] = 12.3$, $p = .001$) and marijuana (Mean = 0.1, $SD = 0.3$; $F[1, 129] = 4.5$, $p = .04$) use for the noncocaine-using women. Thus, for all analyses comparing the CE and NCE groups, the reported amounts of alcohol, tobacco, and marijuana consumed were entered as covariates.

Assessments

All subjects completed the Groton Maze Learning Test© (GMLT), a novel computer-based neuropsychological measure of immediate- and short-term memory for visuospatial information. The GMLT,[1] which is conceptually based on a hidden maze learning test developed by Barker (1931) and extended by Milner (1964, 1965), was developed by one of the authors of this study (P.J.S.) and has been found to be sensitive to the detection of subclinical perseverative error making and slowed information processing speed in healthy adults (Boulanger, Snyder et al., in press).

In order to familiarize subjects with the test format and the use of a 15-inch touch screen monitor, an untimed practice "chase test" (without any hidden maze) was first administered. During the practice test, subjects moved a blue square around a 10×10 grid of squares, with the objective of chasing and capturing a moving flag, represented by a black square. When the chaser captured the flag, the flag reappeared in a new location, never more than two squares away from the chaser. During this practice test, it was necessary for the subjects to learn two rules: 1) the only valid moves are vertical and horizontal; and 2) subjects may not skip over any square(s) when moving towards the flag. Once the experimenter was confident that each subject understood these two rules and could move easily around the grid, a "*timed* chase test" was administered. The objective of the "timed chase test" was to chase and to capture the moving flag, using the rules learned in the practice test. The subject was asked to make as many correct moves as possible while being timed for a short period (30 seconds).

Following the "timed chase test," the subject next began the first learning trial through a maze (28 moves with 11 turns) that was hidden under the same 10×10 grid of squares. To complete the maze, the subject had to follow a hidden pathway through the grid from the top left corner to a flag in the bottom right corner. Each subject completed one of 20 well-matched alternate forms, which had been randomly selected by the

[1]For more information about the GMLT, please contact Dr. P. J. Snyder by E-mail: peter.snyder@uconn.edu; the GMLT is available for use from CogState, Ltd. (www.cogState.com).

computer program. Message bars at the top and bottom of the screen informed the subject whether a move was correct. If the move was correct, the subject was prompted to "Go On" by the message bar and a musical tone. If the move was incorrect, the subject had to move back to the previous square and try a new way. All perseverative errors were recorded, and if the subject made a "rule-break" error, defined as three successive incorrect moves, the square upon which the last correct move was made began to flash, and the subject was required to touch it before continuing through the maze. When the subject reached the flag, the trial ended.

The experimenter was allowed to provide minimal directive assistance to subjects, during the first learning trial. For example, if the subject repeatedly made a perseverative error, the experimenter could remind the subject to try all possible moves. If judged necessary, the experimenter was also permitted to provide help during only the first four moves of the second trial. Thereafter, the experimenter could only remind the subject to read the cues on the computer screen and provide *nondirective* encouragement, which included statements such as "keep trying" and "good job." For each subject, eight successive learning trials on the same maze version were completed. We expected in the reverse trial that such cues would not be effective and hence the reverse trial would be a more direct assessment of spatial working memory. Then, following an 8-minute delay interval, the subject completed a single delayed-recall trial in which they were asked once again to complete the maze working from beginning to end. Subjects were then asked to complete the maze in reverse, that is, to begin at the end and work backwards. This "reverse trial" was included in order to diminish reliance on verbal cues (e.g., reminding oneself, for example, "three moves down, and then turn left…"). Each trial was timed (1/100ths of sec.), and timing began automatically when the subject made his or her first move on each trial.

Performance on the GMLT is expressed as correct moves per second (CMS) for each trial that was computed as the total number of correct moves to complete the maze ($n = 28$) divided by the time per trial to complete the maze. For the timed chase task, the measure of correct moves per second provides an index of the subject's simple visuomotor speed. Additionally, performance on the learning trials is captured by recording the total errors per trial. Errors may be further divided into perseverative and rule-break errors as defined above.

Analyses

Indices of performance (correct moves per second and total number of errors) were analyzed across trials using a repeated measures analysis of variance with exposure group as a between group variable and amounts of alcohol, tobacco, and marijuana use as covariates. Univariate analyses using analysis of covariance were performed for the "timed chase test" performance and for overall indices of performance across all trials. Effect sizes for key between-groups comparisons, reported below, are estimated with the Cohen's *d* statistic (Cohen, 1988). A moderate effect size (ES) is typically considered to fall between 0.3 to 0.7 (Cohen, 1988).

RESULTS

Table 2 shows the correct moves per second and total number of errors by trial for the CE and NCE groups. During the 30-second "timed chase test" (a measure of simple visuomotor speed), there was no significant difference in the performance of the CE and

Table 2 Performance on the GMLT.

	Correct Moves Per Second [Mean (*SD*)]		Total Number of Errors [Mean (*SD*)]	
	NCE *N* = 55	CE *N* = 75	NCE *N* = 55	CE *N* = 75
Timed Chase Trial Number	.77 (.29)	.69 (.23)		
One	.30 (.12)	.24 (.10)	21.7 (7.2)	27.8 (12.0)
Two	.45 (.14)	.40 (.14)	17.3 (6.2)	21.2 (10.3)
Three	.54 (.16)	.50 (.20)	15.1 (4.5)	18.2 (9.8)
Four	.58 (.20)	.53 (.21)	14.6 (7.2)	17.9 (10.1)
Five	.65 (.20)	.55 (.20)	12.3 (5.6)	17.0 (11.5)
Six	.67 (.25)	.59 (.24)	12.8 (8.2)	16.3 (10.5)
Seven	.70 (.25)	.62 (.24)	11.6 (7.3)	14.4 (8.3)
Eight	.77 (.28)	.64 (.24)	9.6 (6.2)	14.4 (10.1)
Average (CMS) or Sum (Errors) Across Trials	.50 (.13)	.44 (.14)	115.1 (36.4)	147.2 (64.7)
Reverse-Direction	.61 (.19)	.52 (.16)	13.2 (5.6)	17.0 (11.4)
Delayed-Recall	.79 (.28)	.69 (.23)	8.5 (5.3)	10.1 (8.8)

NCE groups suggesting equivalent visuomotor speed between the two groups (F[1, 126] = 1.1, *ns*). As expected and shown in Figures 1 and 2, both groups showed improved performance across trials as evidenced by faster performance (more correct moves per second [CMS]) and decreasing total numbers of errors across the eight trials (F for trial [7, 875] = 141.1, $p < .001$ for CMS, and 56, $p < .001$ for errors). After an 8-minute delay, both groups also showed a consolidation in learning as indicated by increased correct moves per second and fewer errors compared to the eighth learning trial (F[1, 123] = 6.4, $p = .01$ for CMS, and 17.6, $p < .001$ for errors). Also as expected, when asked to complete the

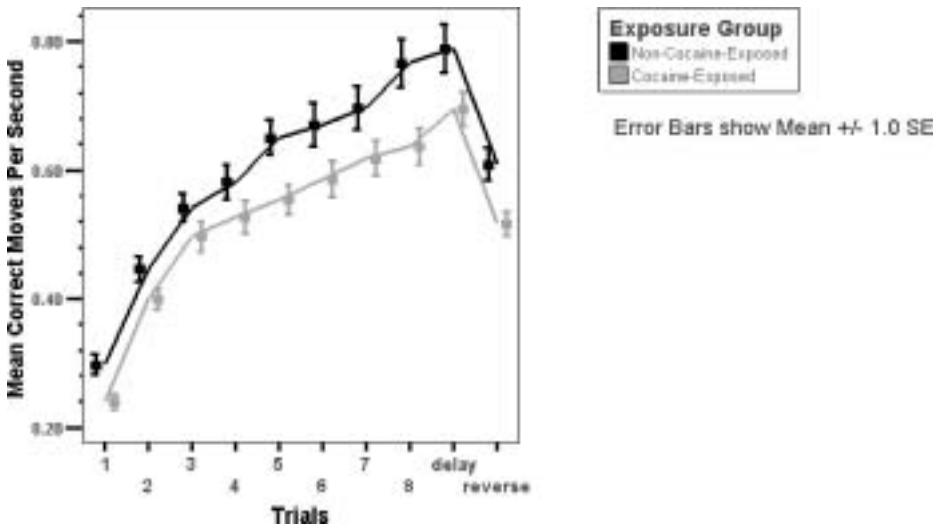

Figure 1 Correct moves per Second.

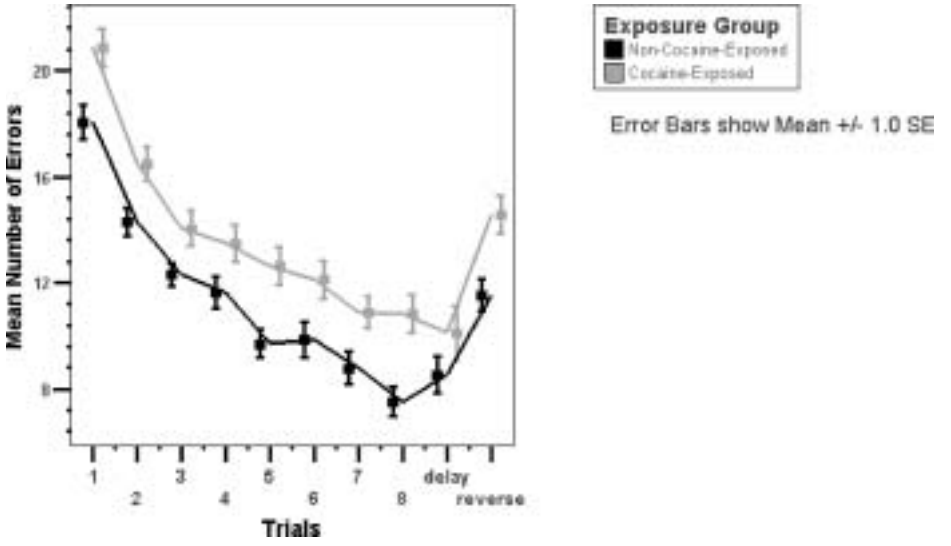

Figure 2 Total Errors.

maze in reverse, both groups showed marked decrement in performance (decreased CMS and more errors) in comparison to the eighth learning trial (F[1, 123] = 39.9, $p < .001$ for CMS, and 13.0, $p < .001$ for errors).

As also shown in Table 2 and Figures 1 and 2, when comparing CE and NCE groups, across all trials, the CE group showed significantly slower correct moves per second and made significantly more errors (F[1, 126] = 4.3, $p = .04$, ES = .44 for CMS, and 9.4, $p = .003$, ES = –0.59 for errors). There were no significant main effects for amounts of alcohol, tobacco, or marijuana exposure. After an 8-minute delay and compared to the eighth trial, CE children showed less consolidation in learning compared to NCE children (F[1, 125] 3.5, $p = .06$, ES = .40 for CMS and 3.5, $p = .06$, ES = –0.21 for errors). When asked to complete the maze in reverse, CE children showed a greater decrement in performance (decreased CMS and increased errors) compared to the eighth learning trial (F[1, 125] = 6.6, $p = .01$, ES = .52 for CMS and 5.8, $p = .02$, ES = –0.40 for errors). For five of the six between-groups comparisons listed above, all effect sizes for these significant differences fall within the moderate range (Cohen 1988), with the exception of the last comparison of total number of errors on the delayed-recall trial.

In terms of incidence of perseverative or rule-break errors, although these were not common observations for either group (for all subjects: mean total number of perseverative errors = 2.6 [SD = 2.3] and mean number of rule breaks = 1.3 [SD = 1.4]), CE children still produced significantly more perseverative errors (F[1, 126] = 10.7, $p < .001$) and more rule breaks (F[1, 126] = 8.4, $p = .004$). The relationship between the reported amount of cocaine exposure and GMLT performance was examined for the CE group separately, and although a trend-level correlation between the amount of cocaine exposure and total number of errors was found (r = .19, $p = .10$), no relationship was found for the working memory measure of correct moves per second (r = –.04).

DISCUSSION

When children who were prenatally exposed to cocaine are compared to age- and SES-matched controls, significant differences are observed in several aspects of their performance on the GMLT. These differences may aid in our understanding of the long-term effects of prenatal cocaine exposure on the domains of procedural learning, information processing, and visuospatial memory. Across all trials, including the delayed-recall and reverse-direction trials, the CE group showed significantly fewer correct moves per second and made significantly more errors than the NCE group, and nearly all of these differences reflect moderate effect sizes (Cohen, 1988), providing some confidence that these observed between-groups differences do not reflect a Type I error. These results suggest relative impairments in children who are exposed to cocaine *in utero* (and all tested between 8 and 9 years old) on a measure of spatial working memory and delayed-recall. The noncocaine exposed children showed a relative superiority in performance, suggesting that they are better able to efficiently and to correctly create and then use the internal spatial map of the hidden maze that subjects rely on over the successive learning trials. It is also possible that over successive trials, the NCE group became more facile with the test demands, and that this group difference reflects a relative impairment in procedural learning for the CE group (Boulanger, Snyder et al., 2001).

After an 8-minute delay interval, and compared to the eighth learning trial, the CE children were slower in terms of the number of correct moves made per second, and they made more errors; suggesting that the CE group were less skilled than the NCE children in consolidating the hidden maze path for short-term recall. When asked to complete the same maze in the reverse-direction, the CE group again made fewer correct moves per second and more errors compared to the eighth learning trial. This result suggests a relative deficit in visuospatial working memory for children exposed prenatally to cocaine. Unlike findings reported previously by our group (Schroder, Snyder et al., 2004), the CE group made significantly more errors (including both perseverative and rule-break errors) than the NCE group across all trials. This pattern of results suggests that even after repeated exposures, the CE children were not able to learn the maze as efficiently as the NCE children.

A number of findings from other laboratories may converge on the results of this study. Singer and colleagues reported poorer visual recognition memory among cocaine-exposed one-year-olds (Singer, Eisengart et al., 2005). Espy and colleagues found cocaine-exposed toddlers to show poor emotional regulation that may interfere with performance in any learning task (Espy, Kaufmann et al., 1999). Other investigators have also demonstrated a cocaine-related impact on learning through impaired sustained or selective attention (Gaultney, Gingras et al., 2005; Noland, Singer et al., 2005; Savage, Brodsky et al., 2005), and preclinical models report long-term effects on learning and memory (Morrow, Elsworth et al., 2002). More specifically, several laboratories have reported an association between prenatal cocaine exposure and impaired spatial learning and memory in preclinical models (Inman-Wood, Williams et al., 2000; Melnick, Kubie et al., 2001). Further, data from the Maternal Lifestyle Study show that cocaine-exposed infants require longer to habituate to a novel stimulus, as compared to the nonexposed infants (Chawarska, Mayes et al., 2005). This finding suggests that the effects of cocaine exposure may also manifest early in infancy in decreased efficiency of information processing. The results from the present study also corroborate unpublished findings from the larger cohort of children in the ongoing longitudinal study from which this sample was

drawn. For example, in the test battery for the larger cohort, children complete a cancellation task, a computerized continuous performance task designed for preschool-aged children, and The Beery-Buktenica Development Test of Visual Motor Integration (VMI) (Beery & Buktenica, 1982) consisting of 24 geometric designs that the child copies that are all arranged in order of increasing difficulty. Each of these tasks require intact visuomotor skills, the capacity for sustained attention, simultaneous information processing, and in the case of the VMI integrating and processing sensory input into discrete motor plans. Compared to the NCE children, the CE children show slower response times on average for each task and make more errors. These findings parallel the present findings that the CE group took longer to complete the maze and may provide evidence of convergent validity for the finding of slowed information processing and/or procedural learning in the CE children.

Importantly, our findings on increased time to complete the maze may seem in contrast to other reports of impaired inhibitory control among cocaine-exposed toddlers and school-aged children (Espy, Kaufmann et al., 1999; Bendersky, Gambini et al., 2003). The apparent contrast in results may in large part be due to the different demands of the tasks used to measure inhibitory control and the present task designed to measure efficiency of learning that does not require children to inhibit a response or conversely does not pull for quick responding. However, convergence with the findings on inhibitory control may be reflected in the continued increased error rates across the learning trials for the cocaine-exposed children, suggesting that despite repeated trials they had difficulty inhibiting responses they had previously learned to be incorrect. Such a hypothesis is partially supported by the finding of increased rule-break and perseverative errors among the cocaine-exposed children inasmuch as perseveration may be functionally related to impaired inhibitory control (van der Ven, 1998).

While the amount of cocaine exposure did not appear related either to correct responses per second or to the number of errors, it is important to underscore that this is a polydrug-exposed cohort and there were significant differences between the amount of tobacco, alcohol, and marijuana use between the CE and NCE groups. Hence, caution is critical in attributing any of these findings directly to the effects of cocaine alone on the developing brain, especially since alcohol, tobacco, and marijuana have also been associated with a range of deficits in postnatal development, some similar to those observed in the present cohort (Olds, 1997; Fried, Watkinson et al., 1998; Wasserman, Liu et al., 2001; Rauh, Whyatt et al., 2004). Indeed, moderate prenatal alcohol exposure has been shown to impact both verbal and visuospatial learning in school-aged children and adolescents (Kaemingk, Mulvaney et al., 2003; Willford, Richardson et al., 2004) and these findings are paralleled by similar impairments in spatial navigation learning in rats (Cronise, Marino et al., 2001). Prenatal nicotine exposure also seems to impact similar capacities. In preclinical models, prenatally nicotine exposed animals show decreased learning in a maze learning task (Vaglenova, Birru et al., 2004). Prenatal nicotine exposure has also been linked to higher incidence of ADHD in school-aged children (Linnet, Dalsgaard et al., 2003; Thapar, Fowler et al., 2003), a deficit that may in turn impair learning through the effect on sustained attention. At the same time, findings from a well-characterized, carefully studied cohort of school-aged children (Alessandri, Bendersky et al., 1998) suggest that the effects of prenatal nicotine exposure may be expressed in those aspects cognitive functioning that are more dependent on auditory processing, a feature not characteristic of the GMLT. Prenatal marijuana exposure also appears to impact functions that may directly or indirectly relate to learning. Fried and colleagues have shown that prenatal marijuana exposure negatively impacts a number of executive control function tasks

that require inhibitory control and with deficits in sustained attention (Fried, Watkinson et al., 1998; Fried, Watkinson et al., 2003; Smith, Fried et al., 2004) though not an effect specifically on visuospatial performance (Fried & Watkinson, 2000). Thus, given the apparent similar effects of prenatal alcohol, nicotine, and marijuana on common aspects of learning, and especially visuospatial learning, we cannot rule out interactive effects between prenatal cocaine and other drug exposures in this sample and thus are cautious about attributing any findings directly to the impact of prenatal cocaine exposure even though all analyses were controlled for amounts of exposure to alcohol, tobacco, and marijuana.

The present findings suggest that children exposed to cocaine and other drugs prenatally take longer to create a working schema of a spatial map. Their capacity to consolidate that working map appears also delayed as evidenced by continued increased errors and fewer correct moves per second in the delay period. These findings have important implications for prenatally cocaine-exposed children's adjustment to the classroom. It is not that they are unable to learn or to process new information but rather that it may take them more exposures and more time to consolidate that which they have learned. It is also possible that cocaine-exposed children may learn more efficiently in a classroom with either slower presentation of material or more reinforced repetition. Each of these options suggests classroom instructional changes that may need to be individualized for each child and, importantly, that curricular changes are not labeled as specific to cocaine-exposed children but rather to any child requiring more time and more reinforced repetition of material to learn.

In conclusion, continued study of prenatally cocaine-exposed children over time with more narrow band measures of specific executive control functions in addition to the spatial working memory explored in this study will permit characterization of developmental trajectories and problems experienced by children with prenatally conveyed neuropsychological vulnerabilities who are also subjected to varying degrees of social-environmental discord. Candidate executive control functions deserving further study in this preadolescent age group include those reported in studies of younger children to be delayed in cocaine-exposed children. These include response inhibition and capacity for task switching (Eghbalieh, Crinella et al., 2000; Noland, Singer et al., 2003a, 2003b), areas for which there is an emerging literature in younger children (Bendersky, Gambini et al., 2003). As has been observed in preclinical models, it may also be that some neurocognitive effects first appear (while others may attenuate) as children near or reach puberty (Smith, Mattran et al., 1989; Spear, Frambes et al., 1989; McMillen, Johns et al., 1991; Bilitzke & Church, 1992; Molina, Wagner et al., 1994; Spear, Campbell et al., 1998). Thus, it is especially important to focus on exposed children as they reach puberty and also on the longer term trajectory on learning with the attendant implications for academic achievement and overall adjustment.

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