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Prenatal Drug Exposure Moderates the Association between  
Stress Reactivity and Cognitive Function in Adolescence

Running head: Prenatal Drug Exposure and Stress Reactivity in Adolescence

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Key words: Hypothalamic-Pituitary-Adrenal axis, cortisol, psychobiology

1 Abstract

2 Prenatal drug exposure (PDE) can undermine subsequent health and development. In a  
3 prospective longitudinal study we examine whether PDE moderates the link between stress  
4 reactivity and cognitive functioning in adolescence. Participants were 76 prenatally drug exposed  
5 and 61 non-exposed (NE) community comparison African American youth (50% male, mean age  
6 14.17 years) living in an urban setting. All participants completed neuropsychological and  
7 academic achievement tests (Children’s Memory Scales, the California Verbal Learning Test-  
8 Children’s Version, and the Wide Range Achievement Test 4) over the course of one day in a  
9 laboratory setting. Two mild stressors (Balloon Analogue Risk Task-Youth and Behavioral  
10 Indicator of Resilience to Distress) were administered with saliva samples (assayed for cortisol)  
11 collected pre and post stress task. A higher percentage in the NE group, compared to the PDE  
12 group [26% vs. 12%,  $\chi^2(df=1, N=137)=4.70, p=.03$ ], exhibited task-related increases in salivary  
13 cortisol. PDE moderated the association between stress reactivity and 11 of 15 cognitive  
14 performance scales. In each case, the NE-stress reactive group had better cognitive performance  
15 than either the NE-lower cortisol reactive group or the PDE group regardless of stress reactivity  
16 status. Stress-related reactivity and regulation of the hypothalamic-pituitary-adrenal axis in  
17 adolescence may be disrupted by PDE, and the disruption may be linked to lower cognitive  
18 performance.

19 Prenatal drug exposure (PDE; cocaine/heroin) is a recognized public health problem with  
20 more than 4% of women between the ages of 15 and 44 reporting drug use while pregnant [1].  
21 **Recent developmental theories suggest that** prenatal stressors such as PDE may impact the  
22 building blocks of adult health and well-being through their influence on early brain  
23 development and the hypothalamic-pituitary-adrenal axis (HPA) [2-5]. In both human and  
24 animal studies, stress in various forms (e.g., psychopathology, natural disasters, pharmacological  
25 treatments, etc.) experienced by pregnant females increases activation of the HPA axis.  
26 Prolonged exposure to the chemical products (i.e., glucocorticoids) released by the HPA axis has  
27 the potential to alter fetal neurological and cognitive development [6,7], impacting brain regions  
28 that are involved in the development and regulation of the HPA axis (e.g., hippocampus,  
29 amygdala, and frontal cortex) and resulting in possible functional deficits in memory, learning,  
30 and executive functioning that can last a lifetime [3,4,6,8]. The association between stress and  
31 cognitive function is viewed as an inverted U-shape with moderate stress, versus low or high  
32 levels, as optimal [9], but chronic stress during the prenatal and postnatal period may lead to  
33 prolonged, repeated elevations in glucocorticoids resulting in the down-regulation of the HPA  
34 axis response. These disruptions may prevent an expected stress response, resulting in a blunted  
35 cortisol or atypical response to stress over time [10,11]. This process has been demonstrated in  
36 maltreated and deprived/neglected children [10-13] and in children with early life stress (e.g.,  
37 harsh parenting, poverty) [14-16].

38 PDE has subtle, measurable consequences on children's behavior and development  
39 through adolescence [17,18]. There is preliminary evidence that PDE is associated with  
40 compromised memory performance and academic achievement in adolescence [18]. In four of  
41 five recent studies, adolescents with PDE demonstrated worse performance on memory tasks



65 **Participants**

66 One hundred and thirty seven adolescents were recruited from a longitudinal  
67 investigation of the effects of PDE. The participants were a mean age of 14.17 ( $SD=1.17$ ; min-  
68 max=11.93-16.64 yrs), were evenly divided by gender with 50% male, and were 99% African  
69 American. Adolescents with PDE were significantly more likely than non-exposed adolescents to  
70 have been prenatally exposed to alcohol [54% vs. 18%,  $\chi^2(df=1, N=137) = 18.54, p<.01$ ] and  
71 tobacco [79% vs. 21%,  $\chi^2(df=1, N=137) = 45.16, p<.01$ ]. In the PDE sample, 33% were exposed  
72 to cocaine only, 13% to heroin only, and 54% to both cocaine and heroin.

73 This study used existing data from a randomized, controlled trial of a home-based  
74 intervention for substance abusing women and their infants recruited at delivery from an urban  
75 University Hospital that catered to a largely African American population [29]. Eligibility  
76 criteria included gestational age  $\geq 32$  weeks, birth weight  $\geq 1,750g$ , no admission to the neonatal  
77 intensive care unit, and positive maternal and/or infant urine toxicology (cocaine and/or heroin)  
78 at delivery and/or maternal self-report of cocaine and/or heroin use during pregnancy. The study  
79 was conducted during a time when toxicology screens were conducted routinely during delivery.  
80 The study was approved by the University's Institutional Review Board. Seventy-two percent of  
81 potentially eligible mothers ( $N=265$ ) agreed to participate [30].

82 Two groups of non-exposed (NE) children and their caregivers were recruited to serve as  
83 community comparisons. The first group was recruited at age 5, ( $N=70$ ) [29,31] and the second  
84 group was recruited in early adolescence ( $N=24$ ). All NE participants were recruited from a  
85 primary care clinic serving the University Hospital. Medical records were reviewed to identify  
86 children delivered at the University Hospital at the same time period as children from the PDE  
87 group who had negative toxicology screens and no evidence of substance use. Participants in the

88 NE group resided in the same community as participants in the PDE group and were matched for  
89 socioeconomic status (e.g., maternal education), maternal age at first pregnancy, and child age,  
90 gender, and race [31].

## 91 **Procedures**

92 Participating families were re-recruited for assessments in adolescence. In the intervening  
93 years, there was a gap in funding, and many families were assigned to other health care providers  
94 through changes in Medicaid Managed Care, and there was significant housing  
95 relocation/demolition in the area. Families lost to follow up did not differ from retained families  
96 on birth weight, maternal education, maternal age at first pregnancy, maternal age at the target  
97 child's birth, neonatal abstinence scores, child gender, or receipt of public assistance.

98 The adolescent protocol took place in a university-based laboratory where each caregiver  
99 and adolescent completed a comprehensive protocol that included questionnaires,  
100 neuropsychological and cognitive tasks, and three assessments of cortisol (collected over a 4.5-6  
101 hour period). The adolescents fasted for three hours prior to their appointment, as cortisol can be  
102 influenced by glucose levels [32]. Participants and their caregivers were scheduled for morning  
103 appointments (85% arrived at 10:30 am or earlier). Experimenters established rapport, discussed  
104 consent forms, and collected the first cortisol sample (pre task;  $M=9:41$  am,  $SD=.85$  hrs).  
105 Participants then were presented with mild stressors on the computer and a questionnaire.  
106 Approximately 30 minutes after the mild stressors, the second cortisol sample was collected  
107 (post task;  $M=10:42$  am,  $SD=.86$  hrs). Both cortisol samples were collected before noon (99% of  
108 pre and 97% of post task collections before noon). After the completion of the pre and post task  
109 cortisol collections, adolescents received breakfast, completed structured tasks and assessments,  
110 had lunch, and completed more structured tasks. The third cortisol collection occurred at the end

111 of the visit. Since the focus of this investigation is the response to stress, only cortisol collections  
112 at pre and post task are used in the analyses.

### 113 **Measures**

114 **Mild stressors.** Two computer tasks were meant to impose mild stress and provoke an  
115 individual difference in stress reactivity measured by the change in salivary cortisol. Both tasks  
116 are impossible to complete at times. The first, the Balloon Analogue Risk Task-Youth (BART-  
117 Y) [33] was designed to measure risk-taking propensity from a cognitive decision making  
118 perspective, in a mildly stressful task. To earn a prize, the BART-Y requires respondents to  
119 inflate a computerized balloon over multiple trials to become as large as possible without  
120 breaking. Accumulated points are lost if the balloon explodes, and the balloon can explode at any  
121 time, making a loud bursting noise. Participants always received at least one small prize.  
122 The second task, the Behavioral Indicator of Resiliency to Distress (BIRD) [34] was developed  
123 based on the adult computerized distress tolerance task. Ten numbered boxes (1-10) are  
124 presented on a computer screen. To earn a prize, respondents use the computer's mouse to click a  
125 numbered box when a green dot appears above it, but before the green dot jumps to another box.  
126 The green dot moves quickly between the boxes, seemingly at random, and frequently changes  
127 speed.

128 **Prenatal alcohol and tobacco exposure.** For the PDE group, alcohol and tobacco  
129 exposure were determined through maternal self-report at delivery. In the NE group, alcohol and  
130 tobacco exposure were determined through retrospective self-report at recruitment. Youth  
131 received a "0" if they were not exposed and a "1" if they were exposed.

132 **Salivary cortisol.** Following Granger and colleagues [35,36], whole saliva samples were  
133 collected by passive drool and frozen at -20° C until transported on dry ice via overnight



134 delivery to Salimetrics Laboratories (State College, PA). Saliva samples were assayed in  
135 duplicate using a commercially available immunoassay specifically designed for use with saliva  
136 without modification to the manufacturers recommended protocol. Test volume was 25 ul and  
137 range of sensitivity was from .007 to 3.0 µg/dL. On average, intra- and inter-assay coefficients of  
138 variation were less than 5% and 15% respectively. All samples were assayed in duplicate and the  
139 average of the duplicate tests was used in the analyses. As expected, salivary cortisol values were  
140 skewed and kurtotic; therefore, pre and post task values were subjected to ln transformation.

141 **California Verbal Learning Test-Children's Version (CVLT-C).** The CVLT-C  
142 measures strategies and processes involved in learning and recalling verbal material. Participants  
143 were asked to remember a shopping list of 15 items (List A). The same list was recited to  
144 participants for 5 consecutive trials, and they were asked to recall words after each presentation.  
145 An interference list (List B), was then presented, and participants were asked to recall words  
146 from List B. Participants were then asked to recall List A words without an additional  
147 presentation of List A. The 15 words on List A were categorized as fruits, clothing, or toys. For  
148 the final recall, these categories were used as cues to elicit words from List A. This assessment  
149 resulted in measures of immediate recall (List A–Trial 1), learning (List A–Trial 5), proactive  
150 interference (List B and percent change from List A–Trial 1 to List B–Trial 1), free recall (short-  
151 delay free recall), and cued recall (short delay cued recall and semantic and serial clustering)  
152 [37]. Higher scores are optimal on all subscales except serial clustering.

153 **Children's Memory Scales (CMS).** Memory was evaluated using CMS Stories subscale.  
154 The CMS measures learning and memory across a variety of memory dimensions to assess free  
155 recall and recognition of story narratives [38]. Experimenters read two short stories to  
156 participants who were asked to recall them immediately and after a 15-minute delay. This

157 assessment resulted in measures of immediate and delayed recall of verbatim and thematic  
158 information as well as delayed recognition. The authors report adequate reliability coefficients  
159 (Cronbach's alpha=0.76-0.81) for children ages 11 to 16 [38].

160 **Wide Range Achievement Test 4 (WRAT).** The WRAT measures basic skills in  
161 reading and arithmetic [39]. The Word Reading and Math Computation subscales were  
162 administered to adolescents. Raw scores are converted into standard scores ( $M=100$ ,  $SD=15$ ).  
163 The WRAT 4 is correlated with the Wechsler Individual Achievement Test II and the Woodcock  
164 Johnson III. Authors report the reliability coefficients for this test as high for 11 to 16 year-olds  
165 (Word Reading: 0.96-0.97; Math Computation: 0.94-0.95). Higher scores are optimal.

#### 166 **Analytic Strategy**

167 Two cortisol reactivity variables were calculated, one continuous (a change score) and  
168 one dichotomous. Duplicate samples were assayed with "reactivity" defined following Granger  
169 and colleagues' methods [35]. First, a 10% difference between pre and post task cortisol levels  
170 was required because this is twice the intra-assay coefficient of variation (i.e., the error inherent  
171 in the assay when comparing results from the same samples assayed twice). Second, an absolute  
172 difference of at least 0.02  $\mu\text{g/dL}$  between pre task and post task cortisol collections was required  
173 (i.e., the lower limit of salivary cortisol assay sensitivity). If participants met both conditions,  
174 they were coded as "reactive;" otherwise they were coded "less reactive." In psychological  
175 science, the use of mild to moderate stressors typically produces 20-30% of participants who  
176 have a salivary cortisol increase from time 1 to time 2 of at least 10% [35]. The dichotomous  
177 variable representing reactive (1) or less reactive (0) was used to determine participant reactivity  
178 to the mild stressors and to describe the sample. To test whether adolescents with PDE are less

179 reactive to mild stressors than NE adolescents, a chi square analysis was conducted using the  
180 dichotomous cortisol stress reactivity variable.

181 Following data transformation, a continuous cortisol stress response change score was  
182 calculated for each participant by subtracting pre task cortisol from post task cortisol so that a  
183 higher positive change score indicates a larger salivary cortisol reaction to the mild stressors.

184 Using this variable, we tested whether PDE modified the association between cortisol stress and  
185 cognitive performance during adolescence by following procedures for testing interactions  
186 described in Aiken and West [40] and Holmbeck [41], adjusting for covariates. After the cortisol  
187 change variable was centered [40], each criterion variable was regressed upon the predictor, the  
188 moderator variable, the covariates, and the interaction term of the predictor and the moderator  
189 [40,41]. When the interaction term was statistically significant ( $p<.05$ ) or marginally significant  
190 ( $p<.10$ ), the outcome variables were plotted in bar graphs by PDE status and reactivity status  
191 [40,41].

192 Covariates were selected based on their theoretical and statistical associations to cortisol.  
193 There is a wide range of ages in this sample, and adolescents with PDE were significantly more  
194 likely than NE adolescents to have been prenatally exposed to alcohol and tobacco. Also, the  
195 time of the first cortisol sample collection varied (see Procedures), and the time of day saliva is  
196 collected can affect cortisol concentrations because cortisol follows a diurnal rhythm over the  
197 course of a day [35]. Finally, there is a theoretical difference between males and females in their  
198 responses to stress and their cortisol response [42,43]. In this sample, males were significantly  
199 more reactive to the stressor than females [25% vs. 12%,  $\chi^2(df=1, N=137)=3.80, p=.05$ ].  
200 Therefore, covariates for all regression analyses were gender, adolescent age, prenatal tobacco  
201 exposure, prenatal alcohol exposure, and time of first cortisol collection (pre task).

## Results

### Cortisol Production and Stress Reactivity

There were no group differences in cortisol levels at pre or post task. For pre task, the NE group mean cortisol value was 0.23  $\mu\text{g/dL}$  ( $SD=0.16$ ) and for the PDE group was 0.23  $\mu\text{g/dL}$  ( $SD=0.19$ ). For post task, the mean was 0.19  $\mu\text{g/dL}$  ( $SD=0.20$ ) for the NE group and 0.15  $\mu\text{g/dL}$  ( $SD=0.12$ ) for the PDE group. Overall, 19% of the sample demonstrated a measurable reaction to the mild stressors. A higher percentage in the NE group exhibited stress reactivity, compared to the PDE group [26% vs. 12%,  $\chi^2(df=1, N137)=4.70, p=.03$ ].

### Cognitive Performance

Similar to findings in Riggins et al. [20] using the same participants as the current study, compared to the NE group, adolescents with PDE scored significantly to marginally lower on 7 of 15 cognitive tests in raw comparisons (Table 1). After the inclusion of covariates, only the CVLT-C list B to A percent change score remained significant,  $F(1,129)=5.83, p=.02$ . Across both groups, most cognitive test mean scores were low. CMS scores were at the 25<sup>th</sup> percentile and WRAT math computation scores were at near the 35<sup>th</sup> percentile (Table 1). For the PDE group, WRAT mean word reading scores were at the 35<sup>th</sup> percentile, with slightly higher scores for the NE group (Table 1).

### PDE Moderates the Association between Stress Reactivity and Cognitive Functioning

PDE either significantly or marginally moderated the association between stress reactivity and 11 of the 15 analyses of cognitive performance. In each case, stress reactivity predicted academic achievement and memory performance, but the findings and direction varied by PDE status (Table 2). In academic achievement, the stress reactivity and PDE interaction significantly predicted word reading and math computation scores on the WRAT 4 (Table 2;

225 Figure 1). In memory performance, the interaction significantly predicted immediate recall,  
226 delayed recall, delayed recognition, immediate thematic memory, and delayed thematic memory  
227 on the CMS (Table 2; Figure 2). Finally, the stress reactivity and PDE interaction significantly  
228 predicted the short delay and cued recall scores on the CVLT, and marginally predicted  
229 performance on list A trials 1-5 and serial clustering (Table 2; Figure 3). In Figure 3, a constant  
230 of 10 was added to the cued recall, delayed recall, and serial clustering scores for graphing  
231 clarity. Interactions were probed to examine the effects of stress reactivity on cognitive  
232 performance in each drug exposure group.

233 **Probing the interactions.** In the NE group, stress reactivity (versus NE less reactivity)  
234 significantly predicted higher CMS immediate recall ( $b=4.36, p=.01$ ), delayed recall ( $b=4.03,$   
235  $p=.02$ ), delayed recognition ( $b=5.11, p=.002$ ), immediate thematic ( $b=4.89, p=.002$ ), delayed  
236 thematic ( $b=3.47, p=.03$ ), and CVLT short delay cued recall ( $b=1.22, p=.01$ ) memory scales. No  
237 other associations were detected in the NE group. In the PDE group, cortisol stress reactivity  
238 (versus PDE less reactivity) predicted lower recall scores on trials 1-5 ( $b=-10.81, p=.04$ ), lower  
239 short delay free recall ( $b=-.96, p=.05$ ), and higher (less optimal) serial clustering ( $b=.89, p=.03$ )  
240 on the CVLT, and marginally predicted lower WRAT 4 math computation ( $b=-13.48, p=.06$ ). No  
241 other associations were detected in the PDE group.

## 242 **Discussion**

243 Our observations suggest that PDE and stress-related change in the activity of the HPA  
244 axis interact to predict cognitive performance. The findings are particularly noteworthy given the  
245 effects of PDE were observed when individuals reached adolescence, and that the nature of the  
246 effects manifested across a range of cognitive performance scales. Small but significant

247 differences in the effects of PDE on adolescent cognitive performance may, at least partially, be  
248 attributable to the effects of PDE on individual differences in biological sensitivity to context.  
249 Previous reviews have identified the need to explore the distal effects of PDE on functioning,  
250 with an emphasis on examining mechanisms [18,44,45]. PDE is an established prenatal  
251 teratogen, but the process of how it affects later development is not fully understood. It is  
252 thought that stressors during pregnancy, such as PDE, alter the fetal development of  
253 physiological systems such as the HPA axis, which may influence later stress reactivity [2-7]. In  
254 the current study, although there were no differences between the PDE and NE groups on  
255 cortisol levels at pre or post task, there were differences in reaction to the presentation of mild  
256 stressors, with more adolescents in the NE group demonstrating the expected reactivity,  
257 compared to the PDE group. Together with the lack of association between stress reactivity and  
258 cognitive performance in the PDE group, the results support the findings of earlier studies  
259 [24,25,27] and suggest the possibility of dysregulation of the HPA axis in adolescents with PDE.  
260 These findings also support current developmental theories [2-5] and expand them to include the  
261 special population of youth with PDE.

262         The dysregulation of the HPA axis has serious consequences for development throughout  
263 the lifespan. Prior research suggests that early life stressors compound the effects of prenatal  
264 stressors by chronically over-activating physiological systems such as the HPA axis, eventually  
265 leading to down-regulation of the response until an individual demonstrates a blunted response  
266 [10-16]. Two recent studies found that the effects of poverty, financial instability, and caregiver  
267 instability accumulated over time resulting in a decline in cortisol [14] and time in poverty along  
268 with household chaos were associated with a flattened cortisol change trajectory [16]. PDE is  
269 often associated with multiple stressors such as non-supportive or absent caregivers, few

270 financial resources, neighborhood and/or home violence exposure, continued caregiver drug use,  
271 multiple out-of-home placements, and increased likelihood of various forms of abuse [46].  
272 Therefore, the significant stressors often associated with PDE may have compounded the  
273 prenatal effects of PDE. Future research could address this possibility as an additional  
274 explanatory mechanism.

275         In the brain, an extensive circuitry coordinates the HPA axis in response to stressors with  
276 the hippocampus, amygdala, and prefrontal cortex playing major parts. These areas of the brain  
277 are also integral to functions such as cognition, emotion, and impulse control because they help  
278 to interpret events on the basis of prior experience, determining whether an event is, in fact,  
279 stressful [8]. When there is repeated activation of this circuitry, glucocorticoid levels increase  
280 which can disrupt the functioning of the hippocampus (i.e., glucocorticoid neurotoxicity) [8,43].  
281 Both the CMS and CVLT were designed to assess skills that are regulated by the hippocampus,  
282 amygdala, and prefrontal cortex (e.g., memory and attention) [37,38]; thus, disruption to the  
283 HPA axis should be detectable. Furthermore, the WRAT 4 assesses academic achievement which  
284 is dependent upon skills such as memory and attention. In previous research on this sample,  
285 hippocampal volume in the PDE group was larger compared to the NE group, and this was  
286 associated with poorer memory performance [20] and is consistent with other research on  
287 hippocampal volume and memory performance [47]. The findings in the current study suggest  
288 that PDE, acting as a stressor, may have an effect on brain development (as measured through  
289 assessments such as the CMS, CVLT, and WRAT 4) that has lasting psychobiological and  
290 cognitive consequences.

291         Examination of the cortisol response across the cognitive functioning domains revealed  
292 that the NE stress reactive group performed better on each cognitive task than the NE less

293 reactive group and the PDE groups, regardless of reactivity. Three cognitive tests with a total of  
294 15 subscales were examined measuring rote memorization with immediate and delayed recall  
295 and recognition (CVLT), recall of stories and story themes (CMS), and academic skills (WRAT  
296 4), and the pattern held across each type of cognitive performance. In the PDE group, there were  
297 no consistent patterns with the scores varying between the two reactivity groups, possibly  
298 reflecting individual variability in the development of stress-related reactivity and regulation of  
299 the HPA axis. Findings are similar to those of children from other types of disadvantaged  
300 backgrounds [10,11]. Because these findings indicate a robust association between a  
301 dysregulated HPA axis and multiple domains of cognitive functioning, there is an implication for  
302 the impacts on other areas of functioning. A dysregulated HPA axis has been associated with  
303 negative physical health consequences [43,48] and poor performance on memory and cognitive  
304 tasks [9]. Over time, individuals with a dysregulated HPA axis often experience increased risk of  
305 metabolic and cardiovascular diseases as well as lowered life expectancy and cognitive  
306 impairments [49]. These associations have negative biomedical and quality of life implications.

307 This study has several limitations to acknowledge. Future research could examine the  
308 temporality of dysregulated stress reactivity and subsequent memory and cognitive functioning  
309 to develop a greater understanding of the specificity of effects on these functions in a PDE  
310 sample. **The sample size is small and racially homogenous, limiting generalizability.**  
311 **Additionally, we did not collect data regarding participant waking time, and this information**  
312 **should be collected in future research to control for the natural diurnal rhythm.** Finally, findings  
313 may be influenced by the poverty present in both groups [50]. Poverty and associated stresses  
314 have been shown to impact both the development of the HPA axis and cognitive development



315 [6,7]. Performance scores for both groups were extremely low with means below the 50<sup>th</sup>  
316 percentile and some as low as the 25<sup>th</sup> percentile [37,38].

317         This study has several strengths to note. First, this multi-method study and its hypotheses  
318 were informed by **current developmental theories** [2-5] and examined the psychobiological  
319 mechanisms underlying cognitive performance among a high risk sample of adolescents  
320 followed since birth. The findings support the hypothesized association between stress reactivity  
321 and cognitive performance, and the extension to an additional at-risk population, children with  
322 PDE. Second, findings were replicated across three objective measures of cognitive functioning,  
323 yielding similar patterns within the stress reactivity groups. This replication indicates robustness  
324 in the association between stress reactivity and cognitive function. Finally, the current study  
325 provides a psychobiological explanation for the individual differences in cognitive functioning,  
326 particularly memory, that may extend to other areas of functioning.

327         In conclusion, this investigation demonstrated dysregulation of the HPA axis in a sample  
328 of adolescents with PDE and an association with poor cognitive performance. Due to the  
329 negative consequences of a dysregulated HPA axis and PDE, further investigations of protective  
330 mechanisms that may reduce either the dysregulation of the HPA axis or the consequences of  
331 dysregulation are warranted.

Table 1. Comparison of Raw Means (Standard Deviations) of Adolescent Memory and Academic Performance

	Overall	Drug Exposed	Non-Drug Exposed	<i>p</i>
<b>School Achievement</b>				
WRAT Math Computation	91.02 (14.47)	90.36 (14.60)	91.81 (14.04)	ns
WRAT Word Reading	93.83 (15.06)	91.47 (13.80)	96.56 (16.09)	.04
<b>Memory Performance</b>				
CMS Immediate Recall	7.99 (3.05)	7.50 (2.68)	8.61 (3.38)	.03
CMS Delayed Recall	7.60 (2.98)	7.09 (2.63)	8.21 (3.30)	.03
CMS Delayed Recognition	7.33 (3.29)	7.11 (3.30)	7.59 (3.31)	ns
CMS Immediate Thematic	7.28 (2.99)	6.70 (2.76)	8.00 (3.14)	.01
CMS Delayed Thematic	7.11 (2.99)	6.69 (2.80)	7.62 (3.17)	.06
CVLT Trials 1-5	46.39 (10.66)	46.22 (11.16)	46.61 (10.08)	ns
CVLT Trial 5	-0.37 (1.11)	-0.34 (1.17)	-0.41 (1.05)	ns
CVLT B vs. A % change	-7.06 (39.20)	-13.99 (35.77)	1.57 (41.83)	.02
CVLT List B	-0.50 (1.08)	-0.70 (1.05)	-0.25 (1.08)	.02
CVLT Short Delay Free Recall	-0.38 (.95)	-0.36 (1.01)	-0.42 (0.87)	ns
CVLT Short Delay Cued Recall	-0.40 (1.04)	-0.45 (1.07)	-0.33 (1.02)	ns
CVLT Serial Cluster	-0.45 (0.79)	-0.39 (0.87)	-0.53 (0.69)	ns
CVLT Semantic Cluster	0.25 (1.06)	0.30 (1.07)	0.19 (1.07)	ns

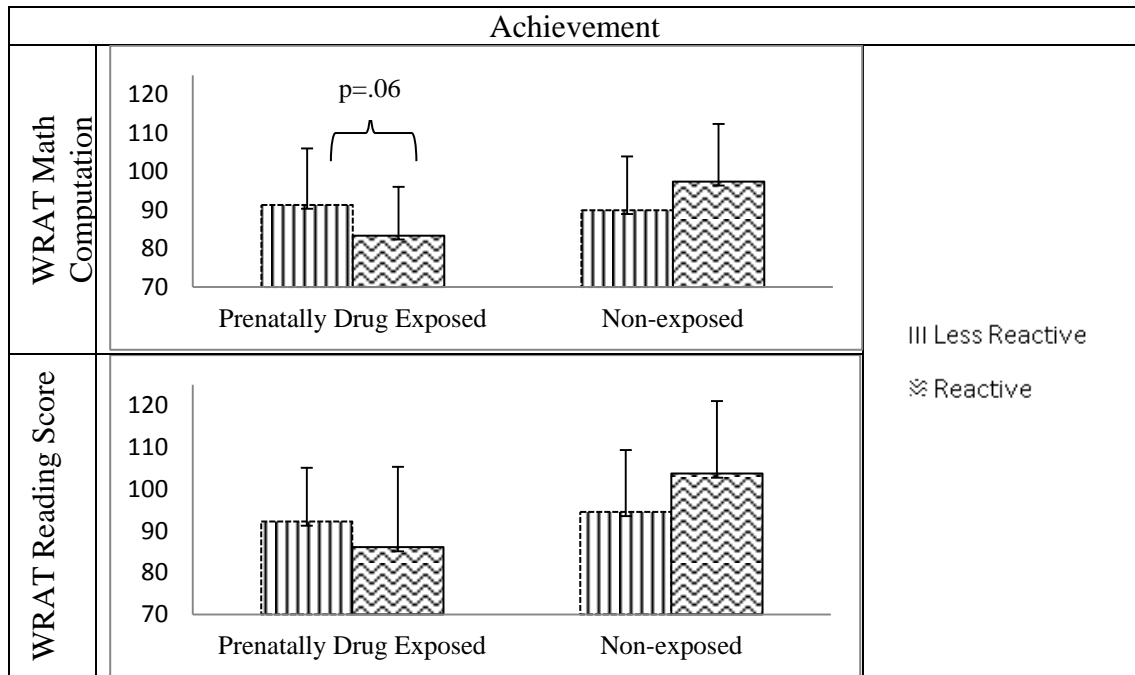
Note. WASI=Wechsler Scales of Intelligence; IQ=intelligence quotient; WRAT=Wide Range Achievement Test; CMS=Children's Memory Scales; CVLT=California Verbal Learning Test

Table 2. *Prenatal Drug Exposure Interacts with Cortisol Change from Pre task to Post task to Predict Cognitive Outcomes*

Outcome Variable of PDE by Cortisol Change Score Interaction	b	t	p	Effect Size ( $f^2$ )
<b>School Achievement</b>				
WRAT Math Computation	28.15	2.98	.003	.07
WRAT Reading Score	22.99	2.28	.02	.04
<b>Memory Performance</b>				
CMS Immediate Recall	6.25	3.12	.002	.08
CMS Delayed Recall	5.41	2.76	.01	.06
CMS Delayed Recognition	4.97	2.27	.03	.04
CMS Immediate Thematic	5.68	2.92	.004	.07
CMS Delayed Thematic	5.52	2.76	.01	.06
CVLT Trials 1-5	-13.38	-1.92	.06	.03
CVLT Trial 5	-0.34	-0.47	ns	--
CVLT B vs. A % change	-10.08	-0.39	ns	--
CVLT List B	-1.01	-1.45	ns	--
CVLT Short Delay Free Recall	-1.37	-2.21	.03	.04
CVLT Short Delay Cued Recall	-1.88	-2.72	.01	.06
CVLT Serial Cluster	0.92	1.74	.08	.02
CVLT Semantic Cluster	-0.26	-0.36	ns	--

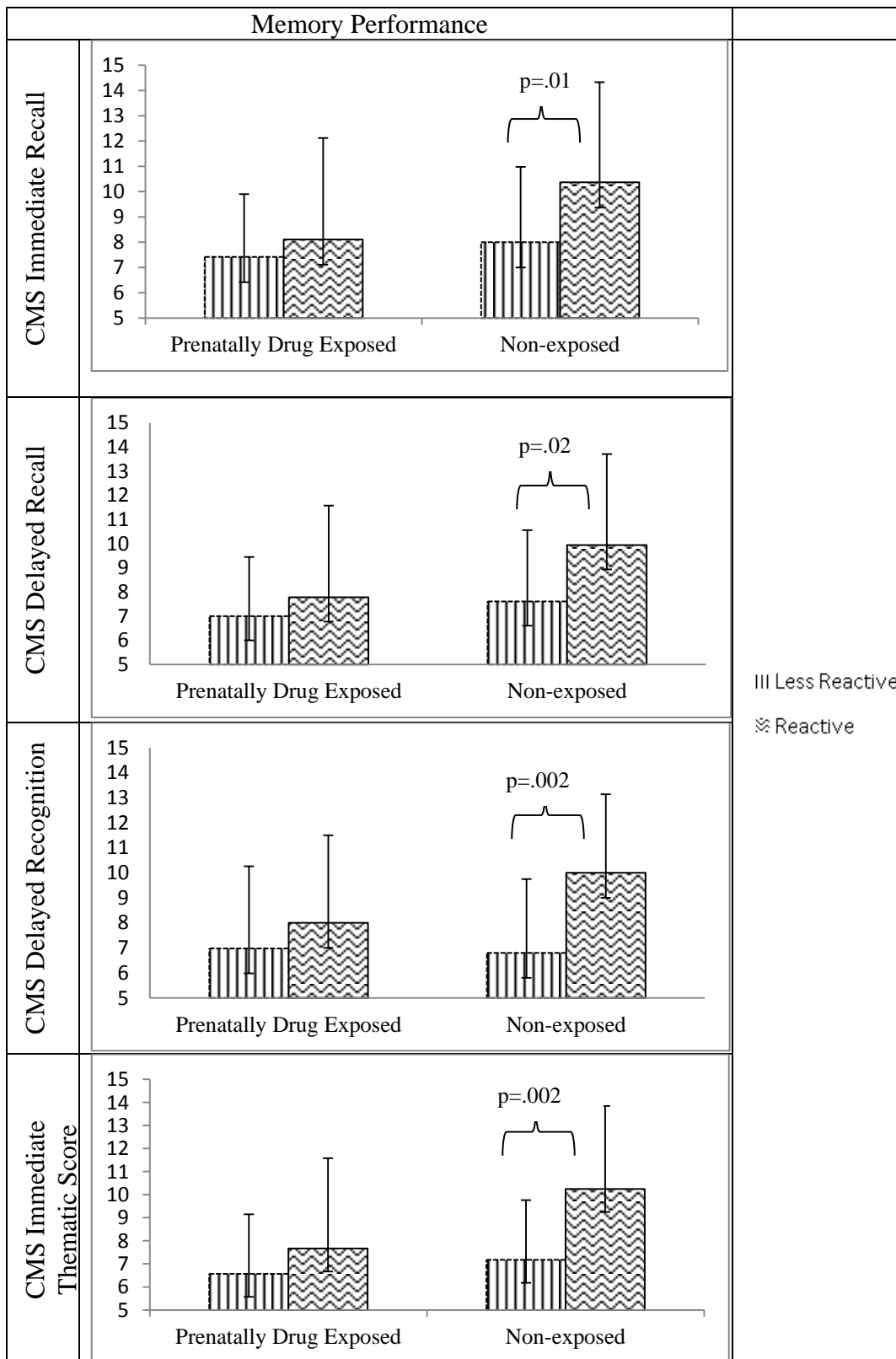
Note. PDE = Prenatal Drug Exposure; WASI=Wechsler Scales of Intelligence; IQ=intelligence quotient; WRAT=Wide Range Achievement Test; CMS=Children's Memory Scales. All regression equations included gender, adolescent age, prenatal tobacco exposure, prenatal alcohol exposure, and time of first cortisol sample collection as covariates.

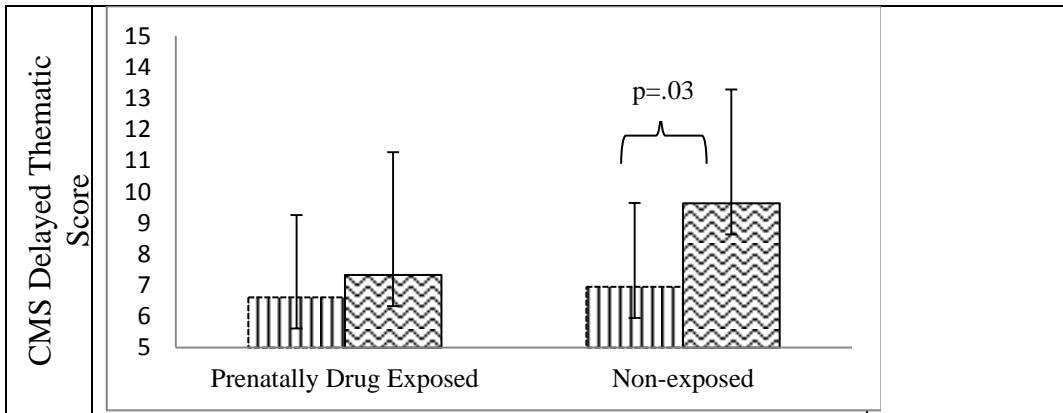
332 Figure 1. *Prenatal Drug Exposure Moderates the Association between Stress Reactivity and*  
 333 *Academic Achievement*



334 Note. WRAT = Wide Range Achievement Test

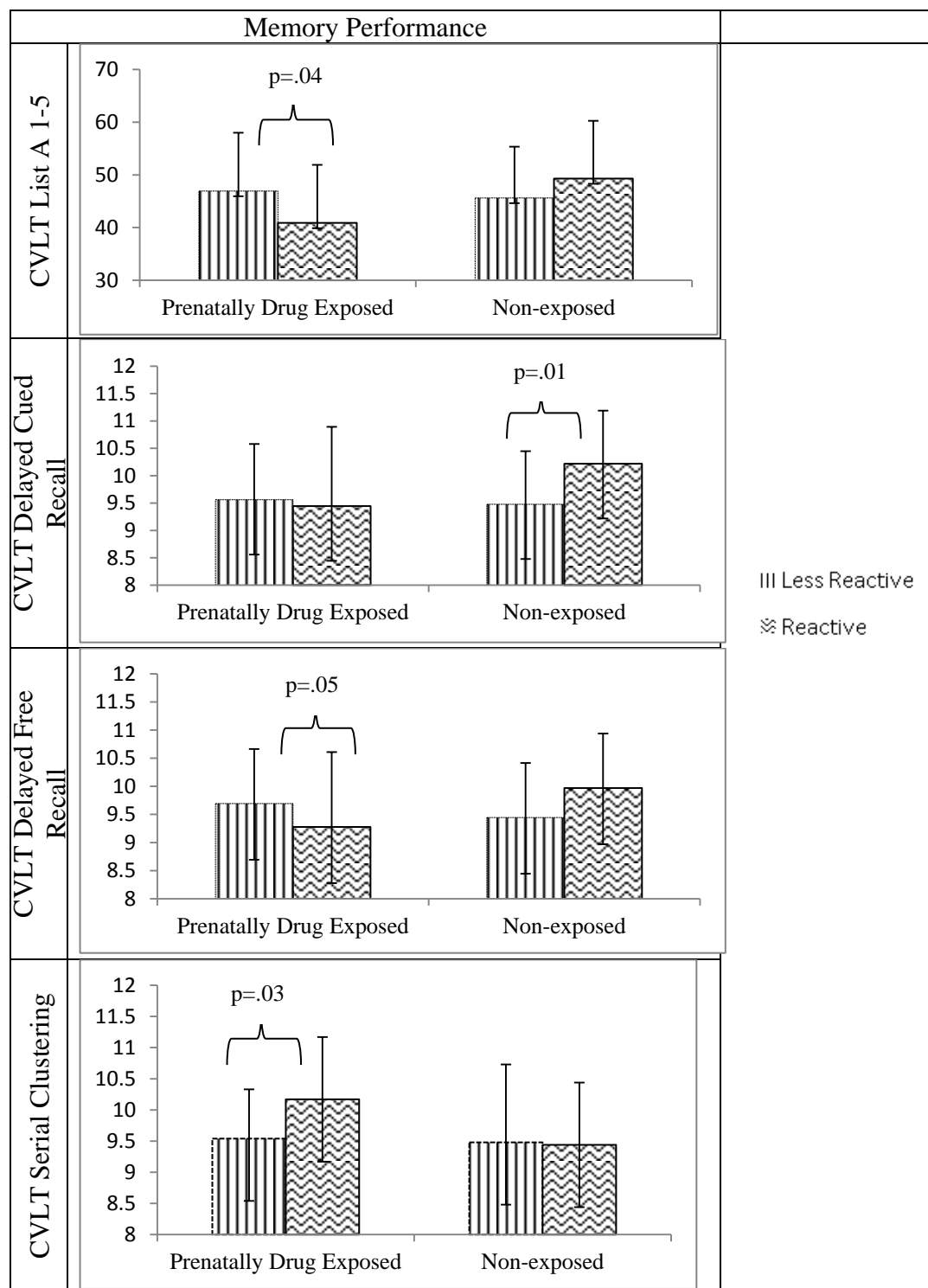
335 Figure 2. Prenatal Drug Exposure Moderates the Association between Stress Reactivity and  
 336 Memory Performance on the Children's Memory Scales





337 Note. CMS = Children's Memory Scales

338 Figure 3. *Prenatal Drug Exposure Moderates the Association between Cortisol Change and*  
 339 *CVLT Scores*



340 Note: CVLT = California Verbal Learning Test; A higher score is optimal for Lists 1-5, cued and delayed  
 341 recall while a lower score is optimal for serial clustering; A constant of 10 was added to the cued recall,  
 342 delayed recall and serial clustering scores for graphing purposes to enhance clarity.

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