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Prenatal Testosterone Increases Sensitivity to Prenatal Stressors in Males with Disruptive Behavior Disorders

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Abstract

Disruptive Behavior Disorders (DBD) exhibit a sex-biased prevalence rate favoring boys, and prenatal testosterone exposure appears to be part of the complex etiology of these disorders. The current study examines whether high prenatal testosterone exposure may heighten risk for DBD symptoms in males by increasing susceptibility to negative environmental conditions such as maternal nicotine and alcohol use during pregnancy. Participants were 109 three- to six-year-olds (64% male; 72% with DBD) and their 109 primary caregivers and 55 daycare providers/teachers who completed a multi-informant diagnostic procedure. A proxy of prenatal testosterone exposure, finger-length ratios, interacted with maternal report of prenatal nicotine use to predict teacher-rated hyperactivity-impulsivity during preschool, for boys, but not girls, although the three-way interaction was not significant. Prenatal testosterone interacted with prenatal alcohol exposure to predict teacher-rated hyperactivity-impulsivity and ODD symptoms differentially based on child sex (significant three-way interaction). Boys with higher levels of prenatal testosterone who were also exposed to higher levels of nicotine and alcohol during pregnancy exhibited increased hyperactivity-impulsivity during early childhood, but girls did not exhibit this same pattern. Thus, high prenatal testosterone exposure seems to increase risk for DBD symptoms particularly in males by increasing susceptibility to prenatal environmental stressors.

Keywords

Disruptive Behavior; hormones; prenatal; sex differences

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1. INTRODUCTION

Disruptive Behaviors Disorders (DBD), including Oppositional-Defiant Disorder (ODD) and arguably Attention-Deficit/Hyperactivity Disorder (ADHD), the latter of which also overlaps substantially with neurodevelopmental disorders, are common and impairing childhood behavior disorders that often begin as early as preschool (Keenan & Wakschlag, 2002; Pelham, Foster, & Robb, 2007; Sheeringa, 2003). DBD exhibit a sex-biased prevalence rate, occurring approximately three times as often in boys as girls (Costello, Foley & Angold, 2006). Based on this sex-biased prevalence rate, prenatal sex hormone exposure, such as prenatal testosterone exposure, may be one viable factor that increases risk for childhood DBD.

High levels of prenatal testosterone exposure, measured indirectly using masculinized finger-length ratios, have been associated with DBD and ADHD during childhood and adulthood, as well as associated behavioral traits including low conscientiousness/effortful control, high activity levels and sensation-seeking, and high aggression (Geschwind & Galaburda, 1985; Fink et al., 2006; Fink et al., 2007; Martel et al., 2008; McFadden et al., 2005). Yet, the effect size of associations between prenatal testosterone exposure and DBD-related behaviors is in the small to medium range, suggesting that it is only part of the complex etiology of these disorders. A key remaining question concerns how prenatal testosterone exerts downstream effects on behaviors related to DBD.

Theory suggests that high levels of prenatal testosterone slow down neural development in utero in males compared to females, perhaps lengthening the prenatal period during which males (vs. females) are particularly sensitive to environmental influences (Martel et al., 2009; Morris, Jordan, & Breedlove, 2004). Thus, negative prenatal environmental influences may exert particularly negative effects on male (vs. female) fetuses because they are vulnerable to them for longer periods of time during pregnancy (Martel, in press). High maternal use of nicotine and alcohol during pregnancy are two such important prenatal environmental stressors that have been associated with DBD (Kuhn et al., 2010; Langley et al., 2007; Neuman et al., 2007). These prenatal stressors seem to exert particularly potent effects on and through interactions with the dopaminergic neurotransmission system, particularly in the prefrontal cortex, which develops slowly during the prenatal period (Goldstein & Volkow, 2002; Morris et al., 2004). Such influences on developing neural circuitry may be particularly relevant to DBD-related behaviors including executive function and traits like sensation-seeking (Huizink & Mulder, 2006, Beauchaine et al., 2009; Noland, et al., 2003). Yet, little work has examined whether males (vs. females) are particularly susceptible to these negative prenatal environmental influences on DBD due to their higher prenatal testosterone levels, as one would expect based on this theory.

Thus, one possible theory of sex differences in the prevalence rate of DBD is that high prenatal testosterone exposure may increase susceptibility to negative environmental conditions such as maternal nicotine and alcohol use during pregnancy in males (vs. females) with particular effects on DBD-related behavior (Martel, in press). The current study is the first to examine this idea empirically by evaluating interactions between prenatal testosterone exposure, prenatal environmental conditions (i.e., maternal prenatal nicotine

and alcohol use), and child sex in relation to child DBD symptoms, albeit using a proxy measure of prenatal testosterone and retrospective maternal report of prenatal substance use as a preliminary first step. Hypotheses are that prenatal testosterone exposure, negative prenatal environmental circumstances (i.e., maternal prenatal nicotine and alcohol use), and child sex will interact in relation to DBD symptoms (Haslam et al., 2006). In particular, it is predicted that high prenatal testosterone exposure will be associated with increased DBD when exposure to prenatal maternal nicotine and alcohol use is high, and these effects will be specific to males (vs. females).

2. METHODS

2.1. Participants

2.1.1. Overview—Participants were 109 preschoolers between the ages of three and six (*M*=4.34 years, *SD*=1.08) and their primary caregivers (hereafter termed parents for simplicity; 67% mothers with the remaining 33% fathers+mothers together, fathers only, foster parents, or grandmothers with guardianship). As shown in Table 1, sixty four percent of the sample was male, and 36% of the sample represented an ethnic or racial minority (28% African American), coded dichotomously (0=non-Hispanic Caucasian; 1= any ethnic or racial minority). Family income ranged from below $20,000 to above $100,000 annually. Parental highest educational level ranged from grade school to doctorate, and family employment ranged from unemployed to full-time weekly.

Based on multistage and comprehensive diagnostic screening procedures (detailed below), preschoolers were recruited into two groups: those with Disruptive Behavior Disorders (DBD; *n*=79), subdivided into those with ADHD-only (*n*=18), Oppositional-Defiant Disorder (ODD)-only (*n*=18), and ADHD+ODD (*n*=43); and children without DBD (*n*=30). The non-DBD group included preschoolers with minimal and subthreshold symptoms to provide a more continuous measure of symptoms, consistent with research suggesting that DBD may be better captured by continuous dimensions than categorical diagnosis and to be sensitive to the young age of the sample (Leblanc et al., 2008; Levy et al., 1997; Marcus & Barry, 2011). No siblings were included.

2.1.2. Recruitment and Identification—Participants were recruited from an urban, Southern United States community primarily through direct mailings to families with children between the ages of three and six and internet postings, as well as through advertisements in newspapers and flyers posted at doctors' offices, community centers, daycares, and on campus bulletin boards. Two sets of advertisements were utilized; one set of advertisements targeted children between ages 3 and 6 with disruptive behavior problems and/or attention problems and a second set of advertisements targeted children between ages 3 and 6 without these types of problems. After recruitment, all families passed through a multi-gated screening process. An initial telephone screening was conducted to rule out children prescribed psychotropic medication or children with neurological impairments, mental retardation, psychosis, autism spectrum disorders, seizure history, head injury with loss of consciousness, or other major medical conditions. Only 10 families were screened out at this phase. All families screened into the study at this point completed written and verbal informed consent procedures prior to data collection and consistent with the

university Institutional Review Board, the National Institute of Mental Health, American Psychiatric Association guidelines, and in compliance with national and local legislation. All families were compensated $50 for their participation.

During the second stage, parents and preschoolers attended a campus laboratory visit. Before and during the laboratory visit, diagnostic information was collected via parent and teacher/caregiver ratings. Parents completed the Kiddie Disruptive Behavior Disorders Schedule (K-DBDS; Orvaschel & Puig-Antich, 1995), a semi-structured diagnostic interview modeled after the Schedule for Affective Disorders and Schizophrenia for School-Age Children administered by a trained graduate student clinician (Leblanc et al., 2008). The K-DBDS demonstrates high test-retest reliability and high inter-rater reliability in the preschool population (Leblanc et al., 2008). In the current study, fidelity to interview procedure was determined by calculation of reliability of blind interviewer ratings of DBD symptoms on a randomly-chosen 10% of families. Inter-rater clinician agreement was adequate for symptoms (ICC=.97).

Families were mailed teacher/caregiver questionnaires one week prior to the laboratory visit and instructed to provide the questionnaires to children's teacher, daycare provider, or babysitters who then mailed the completed questionnaires back to the university. When available (i.e., available on 50% of participating families), teacher/caregiver report on DBD symptoms was obtained via report on the Disruptive Behavior Rating Scale (DBRS; Barkley & Murphy, 2006). Response rate did not differ based on child DBD diagnostic group ($\chi^2[3]=.59$, $p=.9$), ethnic/racial minority status ($\chi^2[1]=1.73$, $p=.19$), or family income ($t[97]=1.82$, $p=.07$). Ultimately, clinical diagnoses and groupings were determined by the Principal Investigator, a licensed clinical psychologist, after a review of parent ratings on the K-DBDS and (when available) teacher/caregiver ratings on the DBRS, consistent with current best practice guidelines for current diagnosis (Pelham et al., 2005).

2.2. Measures

2.2.1. Symptom Counts—Parent and teacher/caregiver reports on symptoms were available via the Disruptive Behavior Rating Scale (DBRS; Barkley & Murphy, 2006), which assesses symptoms using a 0 to 3 scale for a more continuous dimension. Symptom domain scores were calculated as sums of scores within each diagnostic subdomain (ODD symptoms, inattentive ADHD symptoms, hyperactive-impulsive ADHD symptoms). The DBRS has high internal consistency ranging from .78 to .96 in the preschool age range (Pelletier et al., 2006). All scales for parent and teacher/caregiver report on the DBRS had high internal reliability (all alphas > .92) in the current sample. Teacher ratings were returned for approximately half of the sample ($N=55$). Primary analyses were conducted using teacher report on the DBRS to minimize shared source variance and to constrain the number of analyses conducted (and hence decrease Type I error).

2.2.2. Prenatal Testosterone Exposure—Prenatal hormone levels were measured indirectly via finger length ratios. Although these ratios exhibit well-established associations with prenatal hormone levels, the mechanisms of these effects remain unexplained, making it a somewhat controversial measure of such influences (Brown et al., 2002; Cohen-

Bendahan et al., 2005; Lutchmaya et al. 2004; McIntyre, 2006; Zheng & Cohn, 2011). Levels of prenatal testosterone measured via routine amniocentesis have been found to be significantly correlated with finger length ratios (McIntyre, 2006), and women with Congenital Adrenal Hyperplasia, or women exposed to high levels of adrenal androgens in utero, have more masculine finger length ratios (Manning et al., 1998; Phelps, 1952). However, it should be noted that geographic, racial, and ethnic differences in finger-length ratios have been found (Loehlin et al., 2006; Manning et al., 2000; 2004; Phelps, 1952; Terrance et al., 2000), and the mechanisms of these effects remain poorly understood.

In the current study, finger length ratio measurements were obtained using an electronic caliper. All fingers (i.e., 2D [index finger], 3D [middle finger], 4D [ring finger], 5D [little finger]) are measured on the palm side of the hand, from the connection to the palm to the tip of the finger. Interrater reliability was satisfactory, computed via correlations between independent measurements of finger-lengths on approximately ten percent of the sample (ICC=.83–.99). As recommended, ratios were computed for each pair of fingers (e.g., 2D/4D; Brown et al., 2002; Cohen-Bendahan et al., 2005). Right 2D:4D was emphasized in the current study since it is the most well-established and best-replicated in regard to human behavioral sex differences (Cohen-Bendahan et al., 2005). Smaller finger-length ratios (i.e., 4D slightly longer than 2D) are considered indicative of higher exposure to prenatal testosterone, and this continuous measure was utilized in study analyses.

2.2.3. Prenatal Environmental Factors—A thorough and confidential background questionnaire was administered to participants by trained study staff that asked structured questions about alcohol, nicotine, and other recreational drug use during pregnancy, including if use occurred and, if so, during which months of pregnancy use occurred, the frequency with which average use occurred, and the prenatal month during which heaviest use occurred. It should be noted that there was no external validation of the veracity of these reports, consistent with other work done in this area (see D'Onofrio et al., 2007; Knopik et al., 2006; Neuman et al., 2007). Analyses emphasized the frequency with which use occurred for both alcohol and nicotine. This variable ranged from 0 (never used) to 5 (used daily).

2.3. Statistical Analysis

Analyses were conducted using Mplus (Muthen & Muthen, 2012) which allows for the statistical control of non-normality and outliers through the use of robust maximum likelihood estimation and utilizes full information likelihood estimation (i.e., FIML or direct fitting), a method of directly fitting models to raw data without imputing values to address any missingness (Burchinal & Neebe, 2006; Curran, West, & Finch, 1996). Hierarchical regressions were conducted with main effects entered at step 1, two-way interactions entered at step 2, and the three-way interactions entered at step 3, per recommendations (Baron & Kenny, 1986; Dearing & Hamilton, 2006; Ellis et al., 2011; Kraemer et al., 2001). Power was adequate (.76) to detect a medium to large effect size (r = .4) in a sample of 55 participants; power was adequate (.8) to detect a medium effect size (r = .3), but not a small effect size, in 109 participants.

3. RESULTS

As shown in Table 1, child age and sex did not significantly differ between diagnostic groups (all $p>.1$). However, child race/ethnicity and family income significantly differed between the four diagnostic groups ($p<.05$). Specifically, there were more racial/ethnic minorities within the ADHD and ADHD+ODD diagnostic groups compared to the ODD and non-DBD groups, and family income was lower in the ADHD and ODD+ADHD groups compared to the ODD and non-DBD groups. Therefore, child race/ethnicity and family income was covaried in all main study analyses. Bivariate correlations between parent and teacher DBD symptom ratings within domain were all significant and at least in the moderate range (r range from .52 to .59, all $p<.01$).

3.1. Associations Among Prenatal Testosterone Exposure, Prenatal Nicotine Exposure, Prenatal Alcohol Exposure, and Child DBD Symptoms

Based on bivariate correlations (shown in Table 2), there were no significant associations between prenatal testosterone, nicotine, or alcohol exposure and teacher-rated child DBD symptoms (all $p>.4$). A lack of main effects suggests the possibility of interactive effects because if children differ in their sensitivity to prenatal stressors based on prenatal testosterone exposure, these contrasting effects in different groups of children might result in a lack of significant main effects. Non-Hispanic white children were exposed to more prenatal alcohol and exhibited fewer inattentive symptoms; lower family income was associated with ethnic/racial minority status and higher prenatal nicotine use.

3.2. Interactions Among Prenatal Testosterone Exposure, Child Sex, and Prenatal Environmental Influences

Based on multivariate regression analyses, shown in Table 3, covarying child race/ethnicity and family income, prenatal testosterone exposure interacted with prenatal nicotine use to predict teacher-rated hyperactivity-impulsivity during preschool, for boys ($t=-2.06$, $p=.05$), but not girls ($t=-1.35$, $p=.2$), although the three-way interaction was not significant ($t=-.52$, $p=.61$). This sex effect was also present for ADHD inattentive symptoms ($t=-2.16$, $p=.05$ for males; $t=-1.61$, $p=.13$ for females), for not for ODD symptoms ($p\geq.4$ for males and females). As shown in Figure 1, boys exposed to higher prenatal testosterone and increased nicotine use during the prenatal period exhibited higher hyperactivity-impulsivity during preschool. This effect was largely absent for girls.

Using the same analytic strategy, prenatal testosterone interacted with prenatal alcohol exposure to predict teacher-rated hyperactivity-impulsivity differentially based on child sex (three-way interaction $t=-2.49$, $p=.02$). The three-way interaction was also significant for ODD symptoms ($t=2.25$, $p=.03$), but not inattention ($p=.25$). As shown in Figures 2a and 2b, boys who were exposed to higher levels of prenatal testosterone and alcohol during pregnancy exhibited increased hyperactivity-impulsivity during early childhood, but girls did not exhibit this same pattern.

None of the three-way interactions were significant in predicting parent-rated ADHD or ODD symptoms (p range .53–.98). However, there were significant sex by prenatal alcohol

exposure interactions predicting parent-rated ADHD symptoms (i.e., hyperactivity-impulsivity and inattention; $p<.05$).

4. DISCUSSION

The current study examined one possible mechanism by which prenatal testosterone exposure might increase risk for DBD differentially in boys, namely by increasing male susceptibility to environmental stressors such as prenatal nicotine and alcohol use during pregnancy. Results of the current study were consistent with this idea; a proxy measure of prenatal testosterone exposure seemed to interact with maternal retrospective report of prenatal stressors differentially based on child sex to increase risk for early teacher-rated childhood hyperactivity-impulsivity. Study results suggest that males who were exposed to higher levels of prenatal testosterone and higher maternal alcohol (and, to a lesser extent, nicotine) use during pregnancy exhibited increased hyperactivity-impulsivity during early childhood, but females did not exhibit this pattern. Further, while effects of prenatal nicotine use appeared relatively specific to hyperactivity-impulsivity, effects of prenatal alcohol use generalized across child hyperactivity-impulsivity and ODD symptoms.

These results are in line with the idea that high prenatal testosterone exposure may make males more sensitive to prenatal environmental stressors, compared to females, potentially by slowing down fetal growth (Martel et al., 2009; Morris, Jordan, & Breedlove, 2004). Higher prenatal testosterone levels may function to increase sensitivity to early environmental conditions in males in order to calibrate a phenotype so that it will be well-suited for coping with these early childhood environmental conditions (Ellis et al., 2012; Geary, 2010; Martel, in press). Thus, males with high prenatal testosterone levels may be particularly sensitive to prenatal cues suggesting a harsh and/or unpredictable childhood environment with resulting neurobiological effects on dopaminergic neurotransmission and prefrontal cortex function, developing late during the prenatal period (Martel, in press; Morris et al., 2004; Goldstein & Volkow, 2002). These neurobiological effects, in turn, instantiate DBD behaviors and associated traits, including executive dysfunction, sensation-seeking, and aggression (Beauchaine et al., 2009; Huizink et al., 2006; Noland et al, 2003).

These ideas are consistent with evolutionary developmental theory, particularly sexual selection (Geary, 2010) and differential susceptibility (Ellis et al., 2012). Rather than exerting direct effects on the developing fetus, prenatal environmental stressors may provide clues that are particularly important for male fetuses that the environment is unpredictable and/or harsh, thus suggesting that DBD-related behaviors and associated traits (e.g., sensation-seeking) are going to be the most adaptive strategies for successful mating and reproduction in this environment since these behaviors facilitate male-male competition for mates (Geary, 2010; Martel, in press). Testosterone may instantiate this effect particularly in males (vs. females) by operating above a particular cutoff that may be most evident in males. Future work should examine this idea empirically and evaluate whether males are differentially susceptible to positive environmental conditions (e.g., proper nutrition) during pregnancy in such a way as to decrease DBD risk. This type of work has important implications for the development of prevention strategies, suggesting that pregnant women,

particularly those expecting boys, may especially benefit from refraining from use of alcohol and nicotine during pregnancy (Becker et al., 2008; Bennett, Bendersky, & Lewis, 2007).

Notably, results were significant using measures that did not contain shared source variance (i.e., when utilizing teacher report of symptoms and parent report of prenatal stressor exposure), although, interestingly, results did not hold using parent-report of symptoms. This might be because ADHD symptoms can manifest differently based on the situational context (APA, 2013; De Los Reyes & Kazdin, 2005; Dirks et al., 2012). It is possible that parents who used higher levels of alcohol and nicotine use during pregnancy may be less objective raters of their children's inattention and hyperactivity-impulsivity compared to teachers (Bennett et al., 2007; Knopik et al., 2006). However, it is important to note that we cannot rule out the possibility that teacher findings may be due to a Type I error; therefore, it will be important to replicate these effects. Interestingly, interactive effects of prenatal nicotine and alcohol use differed somewhat. While effects of maternal prenatal nicotine use were specific to hyperactivity-impulsivity, effects of maternal prenatal alcohol use generalized across hyperactivity-impulsivity and oppositionality. These results might be due to the somewhat different neurobiological effects of nicotine and alcohol (Koob, 2000; Lavliolette & van der Kooy, 2004; Markou, 2008).

However, it should be noted that these effects could be due to a third variable such as later environmental influences or common genetic influences (D'Onofrio et al., 2007). Parental psychopathology particularly merits attention in future work as it might influence later child behavioral outcomes through genetic transmission, prenatal smoking and alcohol use, postnatal parenting behaviors, and evocative effects of child temperament on parenting (Harold et al., 2013; Johnston et al., 2012; Knopik et al., 2006; Massey & Compton, 2013; Mills-Koonce et al., 2007). Further, race/ethnicity and family income and socioeconomic status, as well as other sociodemographic factors influencing child outcomes, merit attention in future work (Martel, 2013; Miller et al., 2009; Samuel et al., 1997). That is, low family income, race/ethnicity, low maternal education, or maternal psychopathology may account for prenatal smoking and testosterone effects on child disruptive behavior (Martel, 2013). We did not find ethnic or racial differences in finger-length ratios as is common (Loehlin et al., 2006; Manning et al., 2000; 2004; Phelps, 1952; Terrance et al., 2000); this might be because our sample was very diverse and that, in combination with the small sample size, may have limited power to detect effects. Prenatal substance use was measured retrospectively which might have made reporting biases more likely; a study limitation is that there was no independent validation of this retrospective report. Current study findings suggest the utility of investment in approaches that allow for prospective measurement of substance use during pregnancy and longitudinal follow-up of offspring. The current study relied on an indirect proxy measure of prenatal testosterone levels, finger-length ratios, which – although well-validated—is controversial and has limitations including substantial ethnic/racial differences, as well as unclear mechanisms (Brown et al., 2002; Cohen-Bendahan et al., 2005; Lutchmaya et al. 2004; Zheng & Cohn, 2011). Finally, the small sample size and limited statistical power was a salient limitation. Based on the current study's preliminary findings using such a measure, future work could invest in attempts to measure prenatal testosterone levels directly, perhaps via amniocentesis (van de Beek, 2004).

4.1. Conclusions

Overall, study results suggest the possibility that prenatal testosterone exposure may interact with prenatal stressors differentially based on child sex to increase risk for early childhood DBD symptoms, particularly hyperactivity-impulsivity. Prospective work beginning during pregnancy is needed to critically evaluate the idea that prenatal testosterone exposure operates on DBD-related behaviors by increasing male susceptibility to negative prenatal environmental influences.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Disruptive Behavior Disorders (DBD) have a sex-biased prevalence rate.
- Mechanisms of these sex differences remain unknown.
- Analyses suggest that finger-length ratios interact with prenatal stressors in boys.
- Prenatal testosterone may increase sensitivity to prenatal stressors in boys with DBD.

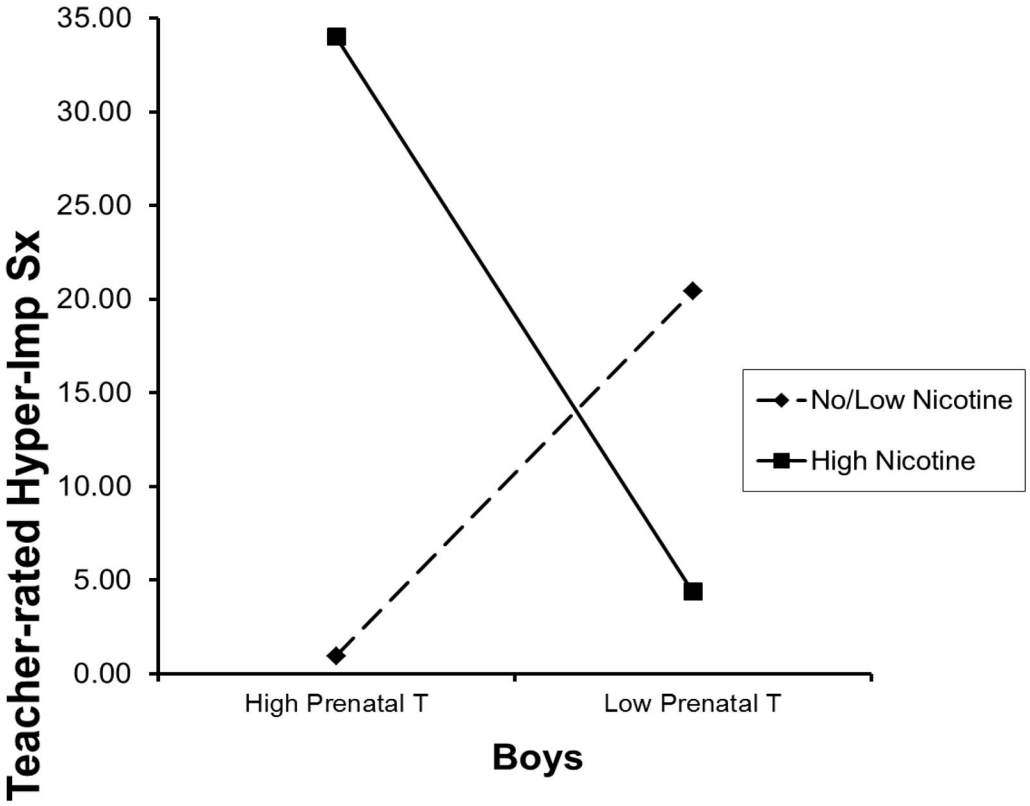

Figure 1.

Prenatal Testosterone by Prenatal Nicotine Use Interaction in Relation to Teacher-rated Preschool Hyperactivity-Impulsivity in Boys

Note. Hyper-Imp Sx=Hyperactivity-impulsivity symptoms. T=testosterone.

Figure 2a

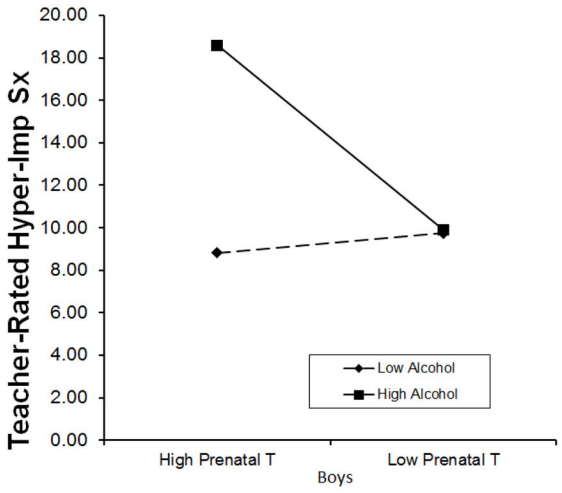

Figure 2b

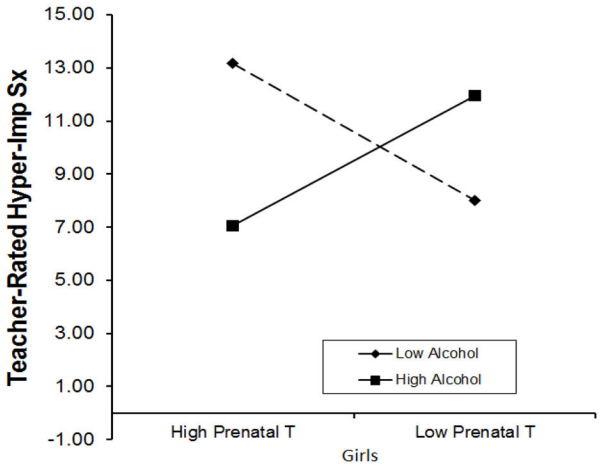

Figure 2.

Figure 2a. Sex by Prenatal Testosterone by Prenatal Alcohol Use Interaction in Relation to Teacher-rated Preschool Hyperactivity-Impulsivity: Boys

Figure 2b. Sex by Prenatal Testosterone by Prenatal Alcohol Use Interaction in Relation to Teacher-rated Preschool Hyperactivity-Impulsivity: Girls

Note. Hyper-Imp Sx=Hyperactivity-impulsivity symptoms. T=testosterone.

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Table 1

Demographic and Descriptive Information on Sample by Clinical Group

M (*SD*)	Non-DBD (c) *n*=30	ODD (o) *n*=18	ADHD (a) *n*=18	ODD+ADHD (oa) *n*=43	
Age	3.9(1.03)	4.56(1.25)	4.56(.92)	4.47(1.05)	
Sex (*N*[% male])	14(46.7)	10(55.6)	13(72.2)	27(62.8)	
Race/Ethnicity (*N*[% minority])	7(23.3)	2(11.2)	10(55.6)	17(39.6)*	
Caucasian	23(76.7)	16(88.9)	8(44.4)	26(60.5)	
African American	7(23.3)	0(0)	9(50)	12(27.9)	
Latino	0(0)	0(0)	1(5.6)	2(4.7)	
American Indian	0(0)	1(5.6)	0(0)	0(0)	
Mixed	0(0)	1(5.6)	0(0)	3(7)	
Family Income (mode)	3	5	1	0*	
Maternal Education	4	6	4	4	
Maternal Employment	0,3†	0,3†	0	3	
Paternal Education	4	4	4	4	
Paternal Employment	3	3	3	3	
Prenatal Testosterone	.97(.07)	.97(.09)	.95(.06)	.97(.06)	
Prenatal Nicotine Use	.38(.1.02)	.20(.41)	.83(1.58)	.37(1.08)	
Prenatal Alcohol Use	1.24(1.98)	.60(1.6)	.28(1.18)	1.2(1.95)	
ODD symptoms (P)	2.97(3.08)[1,2]	10(6.02)[1,3]	5.83(3.28)[3,4]	11.6(7.24)[2,4]**	c<a<o<oa
ADHD symptoms (P)	8.6(6.86)[1,2,3]	19.73(12.98)[1,4]	26.72(9.09)[2,5]	35.26(13.54)[3,4,5]**	c<o<a<oa
Inattention	3.77(3.87)[1,2,3]	8.93(6.77)[1,4]	11.39(5.88)[2,5]	16(7.29)[3,4,5]**	c<o<a<oa
Hyper-Imp	4.83(3.76)[1,2,3]	10.8(6.62)[1,4,5]	15.33(5.43)[2,4,6]	19.26(7.04)[3,5,6]**	c<o<a<oa
ODD symptoms (T)	2.77(3.75)[1]	4(3.84)[2]	4.6(4.16)[3]	11.84(6.68)[1,2,3]**	others<oa
ADHD symptoms (T)	10.08(9.11)[1,2]	7.78(7.97)[3,4]	37.6(10.16)[1,3]	36.32(8.51)[2,4]**	c,o<a,oa
Inattention	4.15(4.26)[1,2]	3.89(3.95)[3,4]	23.2(2.95)[1,3,4]	17.95(5.75)[2,4]**	c,o<a, oa
Hyper-Imp	5.92(5.59)[1,2]	3.89(4.17)[3,4]	14.4(8.91)[1,3]	18.39(5.41)[2,4]**	c,o<a,oa

Note.

*p<.05.

** $p<.01$.

† multiple modes. Subgroup differences based on chi-square or ANOVA with follow-up LSD post hoc tests indicated with like superscripts. Family income modes: 0=annual income less than $20,000, 1=between $20,000 and $40,000, 2=between $40,000 and $60,000, 3=between $60,000 and $80,000, 4=between $80,000 and $100,000, and 5=over $100,000 annually. Parental education modes: 0 for grade school, 1 for some high school, 2 for high school equivalent, 3 for high school degree, 4 for some college, 5 for associates degree, 6 for bachelors degree, 7 for masters or equivalent degree, and 8 for doctorate. Parental employment modes: 0 for unemployed, 1 for 1–19 hours part-time weekly, 2 for 20–39 hours part-time weekly, and 3 for full-time weekly; sample mode=3. Nicotine and Alcohol Use scale=0 (never used) to 5 (used daily). (P)=Parent report. (T)=Teacher report.

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Table 2

Correlation Table

	1	2	3	4	5	6	7	8
1 Prenatal Testosterone	1							
2 Prenatal Nicotine	−.13	1						
3 Prenatal Alcohol	−.02	.12	1					
4 Child Inattention	−.1	−.01	−.13	1				
5 Child Hyperactivity	−.05	.09	.02	.73**	1			
6 Child ODD	−.13	.01	.08	.48**	.74**	1		
7 Racial/Ethnic minority status	.004	−.15	−.25*	.38*	.22	.19	1	
8 Family Income	.09	−.30**	.04	−.12	−.11	−.11	−.33**	1

Note.

*$p<.05$.

**$p<.01$. Child symptoms are teacher-rated. Racial/ethnic minority status: 0=non-Hispanic Caucasian; 1=any ethnic or racial minority.

Table 3

Regression Table of Interactions between Child Sex, Prenatal Testosterone, and Prenatal Substance Exposure in Relation to Teacher- and Parent-Rated Child Symptoms

DV:	Hyper-Imp Teacher/parent *n*=55/*N*=109	Inattention Teacher/parent	ODD Teacher/parent-report
IV (B: unstandardized beta coefficients):			
Step 1			
Sex	−1.11/−.20	−1.39/2.94	−1.99/.39
Prenatal T	1.01/−14.89	−7.30/−14.09	−2.49/2.13
Nicotine	.73/.23	.52/.79	−.85/.38
Step 2			
Sex x Prenatal T	−5.50/−8.98	12.27/4.93	24.18/4.04
Sex x Nicotine	1.12/1.16	4.71/4.77	1.38/4.04
Nicotine x Prenatal T	−155.31*/10.89	−135.88*/8.58	−57.72/4.01
Step 3			
Sex x Prenatal T x Nicotine	−96.57/71.18	−230.10/−13.65	−5.29/56.90
Step 1			
Sex	−1.11/−.20	−1.39/2.94	−1.99/.39
Prenatal T	1.01/−14.89	−7.30/−14.09	−2.49/2.13
Alcohol	.41/.02	.31/.61	−1.10/.39
Step 2			
Sex x Prenatal T	31.36/−17.14	42.68/−2.07	39.33/6.15
Sex x Alcohol	−2.50/−2.57**	−3.53*/−2.19*	−.89/−1.11
Alcohol x Prenatal T	2.12/1.19	2.32/.94	.38/.43
Step 3			
Sex x Prenatal T x Alcohol	17.52*/6.81	11.34/9.65	12.64*/.37

Note.

*$p<.05$.

**$p<.01$. Covariates of family income and racial/ethnic minority status not shown. Prenatal T=Prenatal testosterone. Hyper-imp=Hyperactivity-impulsivity.