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Prenatal Testosterone and Preschool Disruptive Behavior Disorders

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Abstract

Disruptive Behaviors Disorders (DBD), including Oppositional-Defiant Disorder (ODD) and Attention-Deficit/Hyperactivity Disorder (ADHD), are fairly common and highly impairing childhood behavior disorders that can be diagnosed as early as preschool. Prenatal exposure to testosterone may be particularly relevant to these early-emerging DBDs that exhibit a sex-biased prevalence rate favoring males. The current study examined associations between preschool DBD symptom domains and prenatal exposure to testosterone measured indirectly via right 2D:4D finger-length ratios. The study sample consisted of 109 preschool-age children between ages 3 and 6 (64% males; 72% with DBD) and their primary caregivers. Primary caregivers completed a semi-structured interview (i.e., Kiddie Disruptive Behavior Disorder Schedule), as well as symptom questionnaires (i.e., Disruptive Behavior Rating Scale, Peer Conflict Scale); teachers and/or daycare providers completed symptom questionnaires and children provided measures of prenatal testosterone exposure, measured indirectly via finger-length ratios (i.e., right 2D:4D). Study results indicated a significant association of high prenatal testosterone (i.e., smaller right 2D:4D) with high hyperactive-impulsive ADHD symptoms in girls but not boys, suggesting that the effect may be driven by, or might only exist in, girls. The present study suggests that prenatal exposure to testosterone may increase risk for early ADHD, particularly hyperactivity-impulsivity, in preschool girls.

Keywords

Preschool children; ADHD; Prenatal; Testosterone; Hyperactivity; Impulsivity

1. INTRODUCTION

Disruptive Behavior Disorders (DBD) is an overarching diagnostic category that includes several common childhood disorders, including Oppositional Defiant Disorder (ODD),

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Conduct Disorder (CD), and arguably Attention-Deficit/ Hyperactivity Disorder (ADHD), highly impairing and prevalent disorders (APA, 2000; Campbell et al., 2006). Recent advances in assessment techniques have allowed for reliable and valid diagnoses of DBD to be made in preschool-age children (Harvey, Youngwirth, Thakar, & Errazuriz, 2009; Keenan et al., 2007). Preliminary work examining external correlates and risk factors for preschool DBD find similar associations as those for childhood DBD (Lavigne, et al. 1998). However, preschool DBD is understudied relative to childhood DBD so more work is needed, particularly in the domain of biological risk factors since these factors have received limited attention in the preschool population. Sex hormones may be one particularly relevant risk factor for DBDs due to these disorders' sex-biased prevalence rate (APA, 2000) and work suggesting possible sex differences in etiology and mechanisms (Gaub & Carlson, 1997; Gershon, 2002; Zahn-Waxler, Shirtcliff, & Marceau, 2008).

Sex hormones play many roles in the development and function of the human body and brain. Organizational effects of hormones are believed to play an important role in the structural organization of the brain and body with subsequent effects on sex-typed behavior (Goy & McEwen, 1980). Specifically, work in animals suggests that this sexual differentiation (ie., masculinization/de-feminization) of behavior is primarily due to the effects of prenatal testosterone exposure which is higher in males than in females (Nelson, 2005; Phoenix, Goy, Gerall & Young, 1959). High levels of prenatal testosterone appear to masculinize parts of the brain, particularly the dopaminergic system, with downstream effects on sex-typed behavior relevant to DBD such as rough-and-tumble play (Hines & Kaufman, 1994; Sanchez-Martin et al., 2000).

More specifically, high levels of prenatal testosterone appear to lead to increased cell death within the brain, increased neural lateralization, slower development of the brain, and differential modulation of neurotransmission including dopamine (Etgen, 2002; Morris, Jordan, & Breedlove, 2004). In boys, the dopamine system may be especially sensitive to these hormonal effects because it is slower to develop prenatally. This slowed development may provide a longer period of time where hormone exposure can influence prenatal dopaminergic gene expression (Andersen & Teicher, 2000; Previc, 2007).

Importantly, these early prenatal hormone, or organizational, effects are touted as stable, irreversible, and early-emerging (Arnold & Breedlove, 1985). Thus, organizational theory of prenatal testosterone effects on behavior suggests that prenatal testosterone might influence early-emerging DBDs that are more common in males by altering the dopaminergic neurotransmission system that underlies these disorders, leading to masculinization of traits (e.g., disinhibition) and behaviors (e.g., aggression) that are associated with DBD (Hines & Kaufman, 1994; Sagvolden, Johansen, Aase, & Russell, 2005; Sanchez-Martin et al., 2000).

Recent work has examined prenatal testosterone (measured indirectly using finger-length ratios) associations with the common DBD of ODD and ADHD. Although there are limitations to using an indirect measure of prenatal testosterone like finger-length ratios (e.g., see Berenbaum, Bryk, Nowak, Quigley, & Moffat, 2009; Honk et al., 2011), finger-length ratios are easy to obtain, exhibit fairly consistent sex differences, and show moderate-size associations with prenatal testosterone levels (Brown et al., 2002; Manning et al., 1998;

McIntyre, 2006). In particular, most prior work suggest that the right 2D:4D (i.e., the ratio between the right index finger and right ring finger) is a particularly well-replicated indirect index of prenatal testosterone with smaller ratios indicating increased masculinization, or increased exposure to testosterone (Brown et al., 2002; Manning et al., 1998; McIntyre, 2006). Studies support associations between smaller, or more masculinized, right 2D:4D and DBD, particularly ADHD, but have focused on school-age (or older) populations (Martel et al., 2008; McFadden et al., 2005). Higher prenatal testosterone exposure, measured indirectly using finger-length ratios, further appear to be related to general DBD-related behaviors including aggression, conduct problems, and hyperactivity in school-age children and adults (Bailey & Hurd, 2005; Cohen-Bendahan et al., 2005; Fink, Manning, Williams, & Podmore-Nappin, 2007). In addition, indirect indicators of exposure to high levels of prenatal testosterone have been associated with conduct problems and hyperactivity in preschool females (Williams, Greenhalgh, & Manning, 2003); it is notable that this is one of the few studies conducted in preschool-age children. Thus, high exposure to prenatal testosterone, even measured indirectly, appears to have important effects on preschool and childhood behaviors relevant to DBD and ADHD, including inattention, hyperactivity, conduct problems and aggression with some sex specificity of associations. A notable limitation of work to date is attention to younger, preschool-age children.

The current study makes an innovative contribution to the literature by examining associations between an indirect measure of prenatal testosterone, finger-length ratios, and common DBD during preschool. Study hypotheses were that prenatal testosterone would increase risk for common preschool DBDs, including ADHD. More particularly, it is predicted that finger-length ratios indicating prenatal testosterone exposure would be smaller, or more masculinized (indicating higher prenatal testosterone exposure), among preschoolers with ODD and ADHD compared to preschoolers without ODD or ADHD. Further, smaller finger-length ratios were expected to be associated with increased preschool ODD and ADHD symptoms. Finally, sex differences in hormonal associations with DBD behaviors were explored.

2. METHOD

2.1 Participants

Participants in this study were 109 preschool children between the ages of 3 and 6 ($M = 4.82$ years, $SD = 1.10$) and their primary caregivers (67.1% mothers, 20.7% fathers and mothers, 9.8% fathers only or grandmothers with guardianship). Approximately 61% of the sample was male, and approximately 33% was ethnic minority (26% African American; 2% Latino, 4% Mixed ethnicity). The 109 child participants were over recruited for DBD-related problems. To this end, the sample consisted of 64 children with some form of common preschool DBD (i.e., 18 children with ADHD, 18 children with ODD, 43 children with ADHD+ODD) and 30 children without diagnosable DBD, including subthreshold cases.

2.2 Procedure

Study procedures were multi-stage. Participants were first recruited through direct mailings across five parishes to families with children between the ages of 3 and 6, as well as through

newspaper advertisements in local newspapers, internet postings, and flyers placed around the campus, pediatrician offices, schools, and child care centers. Next, an initial phone screening was completed with the caregiver prior to admission to the study. During this screening, questions were asked about demographic characteristics (e.g., regarding socioeconomic status, ethnicity, etc.), child DBD symptoms, and study exclusionary criteria. Study exclusionary criteria included child diagnosis of a physical handicap, pervasive developmental disorder, neurological disorder, psychosis, or mental retardation/intellectual disability. All families screened into the study at this point completed written and verbal informed consent procedures consistent with the Institutional Review Board, the National Institute of Mental Health, and APA guidelines.

Next, caregivers and children attended an on-campus laboratory visit. Before and during this laboratory visit, diagnostic information was collected via parent and teacher/caregiver ratings. 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). In the current study, approximately 67% of completed teacher/caregiver report was provided by teachers, with most of the remaining questionnaires completed by daycare providers or babysitters. Some families did not have teacher/caregiver report available because they could not identify a second reporter; however, in most cases of missing data, teachers/caregivers did not return the questionnaire measures. Response rate did not differ based on child DBD diagnostic group ($\chi^2[3]=.59, p=.9$).

2.3 Measures

DBD Diagnosis and Symptom Counts—During the laboratory visit, the Kiddie Disruptive Behavior Disorders Schedule was administered to the parent (maternal report in 61% of cases; parents together, father only, or grandparent in 39% of cases) by a trained graduate-level clinician to determine symptom counts and diagnosis of ODD, CD, and ADHD. This semi-structured interview is modeled after the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Orvaschel & Puig-Antich, 1995) and contains developmentally-sensitive diagnostic criteria that are highly consistent with the DSM-IV (Keenan et al., 2007). This semi-structured interview has been well validated for use with preschoolers (Leblanc et al., 2008). In the current study, fidelity to the interview procedure was determined via stringent check-out procedures before interview administration. Interrater reliability was assessed in the current sample via a comparison of interviewer ratings on approximately ten percent of families interviewed. Inter-rater reliability for total DBD symptoms was adequate (ICC=.974), as well as inter-rater reliability for total ADHD subtype symptoms (ICC=.969-.993) and ODD symptoms totals (ICC=.821) on the KDBDS.

The Disruptive Behavior Rating Scale (DBRS; Barkley & Murphy, 2006) was used to assess DSM-IV diagnostic symptoms from the child's teacher or other caregiver (if available; available on approximately 50% of participants). The DBRS utilizes a 0 to 3 rating scale with 0 indicating the behavior occurs "never or rarely" and 3 indicating the behavior occurs "very often." This symptom checklist has high face validity and is reliable (Pelletier et al., 2006). It has been shown to have internal consistency of between .78 and .96 when used

with preschoolers (Pelletier et al., 2006). For the current sample internal consistency of teacher/caregiver reports on the DBRS was high (all alphas $> .92$). Final diagnosis was determined by the study principal investigator, a licensed clinical psychologist, following consideration of both parent and teacher ratings of symptoms on the KDBDS and DBRS respectively, based on current best practices guidelines of diagnosis of ADHD and ODD in children (APA, 2000; Pelham et al., 2005). A second blind diagnostician also independently reviewed parent and teacher ratings of child symptoms to reach a diagnosis on a random ten percent of cases with a 100% agreement rate ($\kappa=1$).

In the current study, main analyses on DBD symptoms utilize final parent-report symptom counts for ADHD inattention, ADHD hyperactivity-impulsivity, oppositional-defiance, and total DBD, generated by summing symptom counts within each domain from the KDBDS. Based on the sample size, power was adequate (.76) to detect a small to moderate effect size (Martel et al., 2008; McFadden et al., 2005). Due to the relatively large amount of missing teacher report data, power was judged to be too low (.40) to detect small to moderate effects using teacher-reported symptoms; therefore, teacher-reported symptoms were not considered further in the present report.

2.4 Prenatal Testosterone Exposure

Prenatal testosterone exposure was measured indirectly via finger-length ratios. Although somewhat controversial (Berenbaum, Bryk, Nowak, Quigley, & Moffat, 2009; Honk et al., 2011), these ratios are often utilized as a proximal measurement of prenatal hormone levels (Cohen-Bendahan et al., 2005; Manning et al., 1998). In the current study, finger-length measurements were obtained using an electronic caliper. All fingers were measured on the palm-side of the hand, from the connection to the palm to the tip of the finger. Inter-rater reliability was adequate, computed via intra-class correlations (.83–.99) between independent measurements of finger-lengths on approximately ten percent of the sample. As recommended, ratios were computed for each pair of fingers (e.g., 2D/4D; Manning et al., 1998; Phelps, 1952). Right 2D:4D (i.e., the ratio of the right index finger to the right ring finger) 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 longer than 2D) are considered indicative of higher exposure to prenatal testosterone.

3. RESULTS

The DBD and non-DBD group differed significantly in age ($p=.003$), but not ethnicity, socioeconomic status, or sex (all $p>.1$; shown in Table 1). Further, the boys and girls in this sample did not significantly differ in the number of ADHD or total DBD symptoms reported by parents ($t[103]=.174, p=.862$; $t(103)=-.195, p=.846$). However, the DBD group was significantly older than the non-DBD group ($t[107]=-3.01, p=.003$). Therefore, age was covaried in all subsequent analyses involving DBD diagnosis or symptoms. The right 2D:4D finger-length ratios did not significantly differ by age ($F[43, 57]=.787, p=.793$), sex ($t[99]=-1.82, p=.071$), or ethnic group ($F[4, 96]=1.17, p=.330$).

3.1 Are there group differences in prenatal testosterone based on DBD diagnosis?

In order to examine group differences in right 2D:4D between the DBD and non-DBD diagnostic groups, an analysis of covariance ANCOVA, covarying child age, was conducted. The ANCOVA was non-significant ($F[1, 98]=.312, p=.578$), indicating that the DBD and non-DBD groups did not significantly differ in right 2D:4D. When ethnicity was also covaried (in line with previous literature suggesting ethnic differences in finger-length ratios) the ANCOVA remained non-significant ($F[1, 97]=.644, p=.424$). In order to explore group differences in right 2D:4D between children with and without ADHD and ODD, two ANCOVAs were conducted. These analyses suggested likewise that there were no significant ADHD or ODD diagnostic group differences in right 2D:4D ($F[1, 98]=.404, p=.526$ for ADHD; $F[1, 98]=.479, p=.490$, for ODD).

3.2 Are there associations between prenatal testosterone and DBD symptoms?

Partial correlations, covarying child age, were conducted to examine associations between right 2D:4D and DBD symptoms. As shown in Table 2, smaller right 2D:4D (which is indicative of higher prenatal testosterone exposure) was significantly associated with increased hyperactive-impulsive ADHD symptoms ($r[98]=-0.213, p=.033, d=.487$). However, there were no significant associations between right 2D:4D and any of the other DBD symptom domains, including inattentive ADHD, ODD, or total DBD symptoms.

3.3 Is prenatal testosterone more strongly/only associated with DBD in females (vs. males)?

Partial correlations between prenatal testosterone and DBD symptoms, covarying child age, were conducted separately within sex in order to examine whether the association between right 2D:4D and DBD symptoms was stronger for males or females. As shown in Table 2, most correlations between prenatal testosterone and DBD symptoms were non-significant in both sexes (range of $r=-.164-.181$; range of $p=.087-.922$; $d=.333-.368$), although there was a significant correlation between prenatal testosterone and hyperactive-impulsive symptoms for females ($r[38]=-0.339, p=.032, d=.721$), that was not significant for males ($r[57]=-0.070, p=.600, d=.140$).

3.4 Secondary Checks

Although right 2D:4D did not differ significantly by ethnic group in the present sample, previous work has demonstrated that 2D:4D often exhibits significant ethnic differences (e.g., McIntyre, 2006). Therefore, analyses involving right 2D:4D were rerun covarying ethnicity in addition to child age. Results were essentially unchanged.

4. DISCUSSION

This study evaluated the association between prenatal testosterone exposure, measured indirectly via finger-length ratios, and common DBD symptoms in preschoolers. Overall, the current study suggests that high prenatal testosterone exposure may preferentially increase risk for hyperactivity-impulsivity, but not other common DBD symptoms domains, in young preschool-age girls.

In the current study, prenatal testosterone exposure, measured indirectly using right 2D:4D, was significantly associated with hyperactive/impulsive ADHD symptoms, in line with research conducted in school-age children linking more masculinized right 2D:4D with ADHD symptoms (Martel et al., 2008; McFadden et al., 2005). However, the current study suggested that prenatal testosterone was more specifically linked to hyperactive-impulsive ADHD symptoms in preschool-age children and specifically girls, which is somewhat different than prior work in older children suggesting particularly salient associations with inattention (Martel et al., 2008; McFadden et al., 2005). This difference could be due to the fact that hyperactivity-impulsivity is a particularly prominent manifestation of ADHD in preschoolers, exhibiting normative developmental decreases over time (Lahey et al., 2004; Sanson & Prior, 1999). Importantly, hyperactivity-impulsivity and activity level exhibit striking sex differences as early as infancy (Campbell & Eaton, 1999; Garstein & Rothbart, 2003). Thus, preschool hyperactivity-impulsivity may be particularly sensitive to organizational hormonal effects.

The organizational-activational theory of hormonal effects suggests that high prenatal testosterone may masculinize the early development of the nervous system with downstream effects on traits and behaviors such as hyperactivity-impulsivity (Nelson, 2005). Although the mechanisms of such effects remain unclear, high prenatal testosterone exposure may influence early-emerging DBDs and associated traits by influencing the development of the dopaminergic neurotransmission system that underlies these disorders (Andersen & Teicher, 2000; Sagvolden, Johansen, Aase, & Russell, 2005). The early manifestation of hyperactivity-impulsivity may – in turn—increase risk for other later-emerging DBD behaviors such as ODD, aggression, and inattention (Martel et al., 2009; Nagin & Trembley, 2001).

Interestingly, the association between prenatal testosterone and increased hyperactivity-impulsivity was only significant in girls (vs. boys). This finding is in line with previous work showing that higher prenatal testosterone exposure is associated with preschool hyperactivity in girls, as well as peer and social difficulties (Gaub & Carlson, 1997; Williams, Greenhalgh, & Manning, 2003). Higher levels of prenatal testosterone may increase risk for early-emerging behavior traits that exhibit sex differences like hyperactivity-impulsivity (Campbell & Eaton, 1999; Garstein & Rothbart, 2003), and these effects may be most easily detected in girls because they exhibit more variable levels of prenatal testosterone exposure, compared to boys who, generally speaking, exhibit more uniformly high levels of prenatal testosterone exposure (Baron-Cohen, 1999; Nelson, 2005). Testosterone may be particularly potent in its effects in females compared to males during this period (Bateup et al., 2002; van Honk et al., 2004; Wirth & Schultheiss, 2007).

Although the present study utilized a community-recruited clinical sample, well-validated, comprehensive, and stringent clinical assessment strategies, there are limitations. The present study was cross-sectional and used finger-length as a proxy of prenatal testosterone exposure. Future work should consider using a longitudinal design that combines direct measurement of prenatal testosterone levels in utero with later evaluation of DBD symptoms during preschool and later childhood to more critically evaluate associations between prenatal hormone exposure and development of DBD symptoms over time. The relatively

small sample utilized in the present study is also a limitation. This sample size might have limited power to detect effects, particularly in regard to sex specificity of effects, although power analyses suggested that power was adequate for primary analyses. Finally, although the use of a community-recruited sample enriched for clinical symptoms is considered a strength of the study, future work should assess generalizability of the current results via examination of these associations in clinical and general population samples. The clinical nature of the sample may account for the lack of a significant sex difference in right 2D:4D (due to girls with DBD having more masculinized finger-length ratios).

5. CONCLUSION

Study findings suggested that prenatal testosterone exposure was significantly associated with increased hyperactivity-impulsivity in girls, but not with inattention or oppositional-defiance. Thus, high prenatal testosterone exposure, measured indirectly via finger-length ratios, may increase risk for ADHD in girls as early as preschool via effects on hyperactivity-impulsivity.

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HIGHLIGHTS

We examined the relationship between prenatal testosterone and DBD among preschool children.

Finger length ratios were measured as an indicator of prenatal testosterone levels.

Smaller ratios were associated with greater hyperactive/impulsive symptoms in girls.

Results suggest that high prenatal testosterone may be a risk factor for childhood ADHD.

Table 1

Descriptive Information on the Sample

	Non-DBD (c)	ODD (o)	ADHD (a)	ODD+ADHD (oa)
M (SD)	n=30	n=18	n=18	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)
Ethnicity (N[% minority])	7(23.3)	2(11.2)	10(55.6)	17(39.6)*
Family Income (mode)	3	5	1	0 *
Maternal Employment (mode)	3	0,3,4	2	4
Right 2D:4D Ratio	.974(.07)	.973(.09)	.950(.06)	.974(.06)
ODD symptoms (P)	1.50(1.22) ¹	4.67(.907) ¹	2.28(.826) ¹	5.49(1.45) ^{1*}
ADHD symptoms (P)	3.27(2.56) ^{1,2,3,4}	7.11(5.60) ^{1,2,3,4}	11.28(3.16) ^{1,2,3}	12.44(3.71) ^{1,2,4*}
Inattention	1.03(1.35) ^{1,2,3,4}	3.00(3.01) ^{1,2,4}	4.28(2.59) ^{1,3}	5.02(2.69) ^{1,2,4**}
Hyper-Imp	2.23(1.65) ^{1,2,3,4}	4.11(2.78) ^{1,2,3,4}	7.00(1.68) ^{1,2,3}	7.42(1.91) ^{1,2,4**}
ODD symptoms (T)	2.77(3.75) ¹	4(3.84) ²	4.6(4.16) ³	11.84(6.68) ^{1,2,3**}
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,
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 (P)=Parent report on KDBDS. (T)=Teacher report on DBRS.

Table 2

Partial Correlations of Prenatal Testosterone and DBD Symptoms

DBD Symptoms	Right 2D:4D		
	Full Sample	Females Only	Males Only
	<i>n</i> =109	<i>n</i> =41	<i>n</i> =68
ODD Sx	.099	.016	.181
Conduct Disorder Sx	-.003	.054	-.015
Inattentive Sx	-.042	-.164	.017
Hyperactive Sx	-.213*	-.339*	-.070
Total ADHD Sx	-.142	-.274	-.030
Total DBD Sx	-.070	-.167	.026

*Note:**
p < .05 Age covaried.

Sx=Symptoms as measured by parent report on the K-DBDS.