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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 the 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.

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 and Wakschlag, 2002; Pelham et al., 2007; Sheeringa, 2003). DBD exhibit a sex-biased prevalence rate, occurring approximately three times as often in boys as girls (Costello et al., 2006). Based on this sex-biased prevalence rate, prenatal sex hormone exposure, such as prenatal testosterone exposure, may be one viable factor that increases the 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 and 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 et al., 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, 2014). 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 and 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 and 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

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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, 2014). 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, 64% 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 and 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 the ages 3 and 6 with disruptive behavior problems and/or attention problems and a second set of advertisements targeted children between the 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.

Table 1
Demographic and descriptive information on sample by clinical group.

	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)	
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[a]	0,3[a]	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. 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 associate degree, 6 for bachelor's degree, 7 for master's or equivalent degree, and 8 for doctorate. Parental employment modes: 0 for unemployed, 1 for 1–19 h part-time weekly, 2 for 20–39 h 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.

* $p < .05$.

** $p < .01$.

[a] Multiple modes.