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Prenatal testosterone and preschool Disruptive Behavior Disorders

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ABSTRACT

Disruptive Behavior 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.

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1. Introduction

Disruptive Behavior Disorders (DBD) is an overarching diagnostic category that includes several common childhood disorders, including Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), and arguably Attention-Deficit/Hyperactivity Disorder (ADHD), highly impairing and prevalent disorders (American Psychiatric Association, 2000; Campbell, Spieker, Burchinal, Poe, & The NICHD Early Child Care Research Network, 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 (American Psychiatric Association, 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 (i.e., 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

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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, Hines, Fane, & Breedlove, 2002; Manning, Scutt, Wilson, & Lewis-Jones, 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, Gobrogge, Breedlove, & Nigg, 2008; McFadden, Westhafer, Pasanen, Carlson, & Tucker, 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, Buitelaar, van Goozen, Orlebeke, & Cohen-Kettenis, 2005a; Cohen-Bendahan, van de Beek, et al., 2005b; 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 socio-economic 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

2.3.1. 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

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