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HORMONAL ASSOCIATIONS WITH CHILDHOOD ADHD AND ASSOCIATED TRAIT AND NEUROPSYCHOLOGICAL MECHANISMS

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ABSTRACT

HORMONAL ASSOCIATIONS WITH CHILDHOOD ADHD AND ASSOCIATED TRAIT AND NEUROPSYCHOLOGICAL MECHANISMS

By

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Attention-Deficit/Hyperactivity Disorder (ADHD) is a childhood disorder that has a sex-biased prevalence rate of between 2:1 and 9:1 (male:female). Gonadal hormones such as testosterone and estradiol are important, yet under-explored, candidates to help explain this male-biased prevalence rate. Testosterone and estradiol may act via psychological mechanisms related to ADHD. Here, these are conceived as neuropsychological executive function and two personality traits: conscientiousness and reactive control. Participants in this study were 312 children (168 with ADHD; 178 boys), who completed a multi-stage clinical diagnostic process, hand scans, venipuncture blood draws, and a neuropsychological assessment battery. Primary caregivers completed trait rating scales and teachers completed ratings of ADHD behaviors. Girls had higher levels of conscientiousness than boys within the control group, whereas girls and boys in the ADHD group had comparable, low levels of conscientiousness. Within the ADHD group, girls had higher levels of reactive control than boys. However, within the control group, girls and boys did not differ in reactive control. Finger-length ratio, serving as an index of prenatal testosterone exposure, was related to inattentive symptoms. The personality trait of lower conscientiousness, or thoughtful regulation, statistically mediated the relationship between finger-length ratios and inattentive ADHD symptoms. Contrary to hypotheses, circulating estradiol was not related to ADHD symptoms in girls. In contrast, high levels of circulating testosterone were related to fewer ADHD symptoms in girls. It

is concluded that prenatal testosterone increases risk for ADHD in boys, perhaps through organizational effects on dopamine brain systems. Higher levels of circulating testosterone may be protective for girls. Differences in gonadal hormone levels may help to explain the sex-biased prevalence rate and sex differences in correlates observed in childhood ADHD.

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The introduction for this dissertation is comprised of four sections. The first section provides background information on ADHD including sex differences in ADHD expression and a summary of the neural structures implicated in ADHD. The second section examines neuropsychological executive function and temperament traits as behavioral markers of developing neural structures relevant to ADHD. The third section provides background on hormonal influences on early development with a focus on the sex hormones, testosterone and estradiol. These two hormones are the focus because they are likely candidates for sex differences in hormonal levels across children's development. Moreover, there is substantial empirical support for their effects on cognitive functioning and behavior. In the fourth section of the introduction, hypothesized hormonal influences on ADHD and its mechanisms are considered. Hypotheses are then explicated.

Overall, this dissertation argues that ADHD symptoms, its key mechanisms (i.e., executive function and certain temperament traits), and the underpinning neural structures, may be influenced by gonadal hormones. That is, testosterone and estradiol may shape key neural structures, which in turn alter neuropsychological and affective (temperamental) functioning, leading to ADHD symptoms. If so, then these relations should be detectable via association of prenatal and/or circulating hormone levels to neuropsychological executive function, traits, and symptoms. In this way, gonadal hormones may make males more vulnerable to the development of ADHD than girls by

differentially impacting the behavior and neural mechanisms that give rise to this childhood disorder.

I. Background on ADHD

Overview

Attention-Deficit/Hyperactivity Disorder (ADHD), a childhood behavioral disorder characterized by extremes of inattention, hyperactivity, and impulsivity, arises early in childhood (DSM-IV; American Psychiatric Association [APA], 2000; Hart, Lahey, Loeber, Applegate, and Frick, 1995; Lahey et al., 2005; Nigg, 2006). One of the most-replicated ADHD research findings is the predominant male-to-female ratio, estimated to be between 2:1 and 9:1. The disorder cannot be fully understood without explaining males' increased vulnerability, yet the causal mechanisms of this male-biased prevalence remain a mystery. Gonadal hormones are one potential source of this sex-biased prevalence, yet little attention has been given to hormonal mechanisms. Gonadal hormones exert dramatic and long-lasting effects on neural circuitry, cognition, and behavior during the prenatal period and early childhood. As I outline, some of these effects appear to be quite relevant to inattentive and hyperactive-impulsive ADHD symptoms. They also appear related to the neuropsychological executive functions and temperament/personality[1] traits that may be involved in ADHD. Thus, it is surprising that gonadal hormones are seldom investigated in regard to ADHD.

[1] In children, traits could arguably be termed temperament or personality since they are likely to encompass some of each. For simplicity, temperament will be used to describe childhood character traits in this document, although it is acknowledged that these traits doubtless incorporate both temperament and personality components.

What is ADHD?

ADHD, as conceptualized in the *DSM-IV* (APA, 2000), is comprised of two basic symptom domains (inattention-disorganization [e.g., "does not seem to listen when spoken to directly"] and hyperactivity/impulsivity [e.g., "often fidgets or squirms" or "often interrupts"]). These emanate in three subtypes: primarily inattentive, primarily hyperactive-impulsive, and combined. Each subtype is defined in the *DSM-IV* as requiring the presence of at least six symptoms (or at least twelve symptoms for the combined subtype), lasting at least six months, beginning before seven years of age, and causing marked impairment. It is important to distinguish these two symptom domains because, as discussed later, they are hypothesized to have different neural substrates and correlates.

Symptoms appear to follow a developmental trajectory such that problems with impulse control arise early and problems with inattention emerge somewhat later. Hyperactivity/impulsivity often drops off later in childhood or during adolescence (Barkley, 2003; Olson, 1996). The mean age of onset is typically between ages three and four, although the symptoms of ADHD vary for each individual across the lifespan (Hart et al., 1995).

ADHD prevalence is estimated at between three and five percent for children in the United States (APA, 2000). It has a high co-occurrence with other disruptive behavior disorders, including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD; Barkley, 2003). ODD is a behavioral disorder characterized by patterns of defiant and hostile behavior (APA, 2000). CD is a behavioral disorder in which the basic rights of others and social norms are consistently violated (APA, 2000). Thus, it is of interest

whether effects of hormones on ADHD will be specific to ADHD or will also be related to disruptive behavior problems more generally.

The core behavioral symptom domains of inattention and hyperactivity-impulsivity are important to understand. They are associated with a variety of impairments, including deficits in cognition, language, adaptive functioning, motor development, emotion, school performance, task performance, neuropsychological executive functioning, peer status, psychological comorbidity, and medical and health risks (Barkley, 2003; Hinshaw, 2002; Olson, 1996). The severity of these impairments underscores the importance of understanding the etiology of this disorder.

With regard to causal mechanisms that lead to ADHD, recent theories postulate two pathways, one feeding into inattentive and the other into hyperactive-impulsive symptoms. The first path involves an executive function component, whereas the second path involves a motivational/affective component (Sonuga-Barke, 2005). According to this theory, mesocortical dopamine (DA) circuitry (i.e., the striatum and the caudate) is implicated in executive control problems, especially faulty effortful or strategic response inhibition. This, in turn, gives rise to the inattentive-disorganized symptoms of ADHD (Nigg & Casey, 2005; Sagvolden, Johansen, Aase, & Russell, 2004; Sonuga-Barke, 2005). More recent work clarifies that the right lateralized striatal-frontal circuit is likely involved in response suppression. In contrast, mesolimbic DA circuitry (i.e., nucleus accumbens) is implicated in temperamental incentive approach problems (Nigg, 2006). In turn, it is thought to shape hyperactive-impulsive symptoms of ADHD (Sagvolden et al., 2004; Sonuga-Barke, 2005). At the level of psychological mechanism, the pathway related to inattentive symptoms operates through cognitive control. The pathway related

to hyperactive-impulsive symptoms operates through affective dysregulation.

Returning to the level of the brain, a communality shared by both pathways is the involvement of DA dysregulation, specifically hypodopaminergic extracellular functioning (Volkow et al., 2004; Volkow, Wang, Fowler, & Ding, 2005). The present dissertation exploits this theory to highlight the influence gonadal hormones may have on the development of childhood ADHD via distinct pathways corresponding to these two routes. This argument is based on the likelihood that hormones affect the development of DA circuits in a variety of ways, discussed later.

Sex Differences in ADHD Expression

To date, most research on sex differences in relation to ADHD has focused on illustrating the potential for gender-biased ADHD referral rates. Comparatively little research has addressed sex differences in etiological correlates of the disorder (Biederman et al., 2002; Hartung et al., 2002; Rutter, Caspi, & Moffitt, 2003). This continuing relative shortage of studies is surprising since over a decade ago there was consensus that such knowledge was needed (Arnold, 1996).

As a result, the initial data on sex differences in ADHD are intriguing but inconclusive. Clinically, boys with ADHD are often believed to be more inattentive and hyperactive-impulsive than girls with the disorder (Gaub & Carlson, 1997; Gershon, 2002, Hartung et al., 2002). Girls with the disorder appear to be twice as likely as boys to evidence the inattentive type of ADHD (Biederman et al., 2002). Further, some research suggests that there are differences in the pattern of comorbidity between boys and girls. Specifically, girls with ADHD may experience relatively more comorbid internalizing psychopathology and less externalizing psychopathology than boys with ADHD (Arnold,

1996; Biederman et al., 1999; Gaub & Carlson, 1997). Girls with ADHD also appear to be at a higher risk for later substance abuse than boys (Biederman et al., 2002; Hinshaw, 2002). Sex differences in comorbidity may also be based on subtype, with boys with the combined subtype more likely to experience mood disorders and girls with the inattentive subtype more likely to experience anxiety disorders (Bauermeister et al., 2007). Further, girls with ADHD may have higher rates of speech and language disorders than boys (Hinshaw, 2002; James & Taylor, 1990).

Sex differences on cognitive tasks are worth noting, although their implications for ADHD remain unclear. Some data suggest that girls with ADHD may have more cognitive impairment than boys with the disorder (Biederman et al., 1999; Gaub & Carlson, 1997; Newcorn et al., 2001). However, other studies have found few to no sex differences on neuropsychological tasks (Rucklidge & Tannock, 2002; Seidman et al., 1997). Further, in one study, boys with the combined subtype of ADHD had deficits in motor response inhibition (an executive skill) whereas boys with the inattentive subtype did not (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). In this same study, girls with either the combined or the inattentive subtype exhibited these same deficits. Other data suggest that girls with ADHD are autonomically hypo-aroused and have more brain abnormalities than boys with ADHD (Ernst et al., 1994; Hermens et al., 2004).

Neural Structures Implicated in ADHD

Childhood ADHD is associated at the group level with several key structural and functional brain abnormalities that may be related to hormonal action. Two of the most well-replicated structural findings are reduced volume in (a) the right cortical hemisphere and (b) the dorsolateral, orbital, and anterior cingulate areas of the prefrontal cortex

(Casey et al., 1997a; Castellanos et al., 2001; Durston, 2003; Hill et al., 2003; Nigg, 2006; Seidman, Vlaera, & Makris, 2005). Other studies find that children with ADHD have reductions in the volume of the caudate in the basal ganglia, the corpus callosum, and the cerebellar vermis (Casey et al., 1997b; Castellanos et al., 2001; Durston, 2003; Hill et al., 2003; Seidman, Vlaera, & Makris, 2005; Willis & Weiler, 2005).

Altogether these findings suggest that there may be widespread cerebral volume reduction in children with ADHD, potentially most evidenced in the frontal-striatal and cerebellar regions of the brain. One commonality shared by these regions is that they have extensive dopaminergic projections that are characterized by reduced extracellular DA in children with ADHD (Nigg & Casey, 2005; Tucker & Williamson, 1984; Volkow et al., 2005).

Summary

ADHD is a childhood behavior disorder with a sex-biased prevalence rate favoring males. Yet sex differences in the expression of the disorder are speculative and under-researched. ADHD's neural underpinnings are better-established. The frontal-striatal and cerebellar regions of the brain, characterized by extensive dopaminergic circuitry, appear to be altered in children with ADHD. Specifically, there are reduced levels of extracellular DA in these neural regions. As outlined in the next sections, gonadal hormones appear to influence the development of these neural regions. Further, these regions are related to the causal mechanisms of ADHD at the psychological level, namely problems with executive functions and motivational/affective deficits (Castellanos & Tannock, 2002; Nigg, 2006; Sagvolden et al., 2004).

II. Executive Function (EF) and Temperament Traits as Mechanisms of ADHD

Overview

EF and temperament will be introduced and defined as hypothetical core mechanisms of ADHD. EF and temperament are constructs at the psychological level of analysis that are amenable to behavioral measurement. However, they also serve as indices of the neural dysfunction implicated in the disorder. If hormones alter the functioning of the dopaminergic circuits by making them less efficient, then this may be detectable on behavioral measures related to those same circuits. Next, a framework for integrating EF and temperament is explicated.

Neuropsychological Executive Function

Deficits in neuropsychological EF are one of the most commonly-studied correlates of ADHD (Barkley, 1997; 2003; Nigg et al., 2002), although little attention has been given to sex differences and hormonal influences. EF has most often been defined as the ability to regulate cognition and behavior in order to attain a goal (Nigg, 2000; Pennington & Ozonoff, 1996). Barkley (1997; 2003) developed a hybrid model of ADHD that postulates that several EFs interact with behavioral inhibition and motor control to lead to the development of ADHD. Others have suggested that set shifting, working memory, response inhibition, and planning are important components of EF (Pennington & Ozonoff, 1996). New research has also examined response variability, or intra-individual variability, as an important component of cognitive functioning in ADHD (Russell et al., 2006). EF relies heavily on prefrontal-striatal circuitry and dopaminergic function (Casey, 2005; Nigg, 2000, 2006; Pennington & Ozonoff, 1996), and intra-individual variability may reflect a catecholaminergic deficiency that influences the

ability to modulate oscillations in neuronal activity (Castellanos et al., 2005). The components of EF (i.e., motor inhibition, output speed, planning, working memory, and response inhibition), response variability, and their biological underpinnings are less efficient in children with ADHD as a group (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nigg et al., 2002; Seidman, Valera, & Makris, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

Within the broad domain of EF, deficits in cognitive control in the form of response inhibition have been emphasized in ADHD. Children with ADHD are impaired in their ability to withhold a dominant response in order to perform a subordinate one (Barkley, 1997; Schacher, Tannock, Marriott, & Logan, 1995). Primary among tests that assess this ability is the Logan (1994) Stop Task. It asks that a child withhold the well-learned response of pushing a key when a tone sounds. Many studies suggest that response inhibition is slower or less efficient in children with ADHD (for a review, see Willcutt et al., 2005). This problem is thought to stem from abnormalities in the frontodorsal striatal circuit, including the right anterior cingulate (Alexander, Crutcher, & DeLong, 1991). That circuit relies heavily on modulation by DA.

Temperament

Although various temperament traits have been linked to externalizing disorders and ADHD (Huey & Weisz, 1997; Martel & Nigg, 2006; Nigg et al., 2002; White, 1999), little research has examined the possibility that hormones may be related to sex differences in these relations. Girls with ADHD have similar personality characteristics and manifest similar interpersonal and emotional problems as boys with the disorder (Befera & Barkley, 1985; Greene et al., 2001). However, sex differences in the normal

development of child temperament are established. Girls have higher levels of self-regulation (McCabe, Cunnington, & Brooks-Gunn, 2004). Specifically, girls show more self-regulated compliance, higher effortful control and conscientiousness, lower impulsivity, and more competent social functioning than same age boys (Fabes et al., 1999; Kochanska, Tjebkes, & Forman, 1998; Zahn-Waxler, Schmitz, Fulker, Robinson, & Emde, 1996). A meta-analysis on sex differences in temperament in children suggests that girls exhibit higher effortful control than boys (Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006). If these traits give rise to ADHD, then girls and boys with ADHD might show sex differences in the expression of ADHD symptoms that are related to an outgrowth of normal sex differences in temperament traits. Alternatively, different traits may contribute to the disorder for girls and boys.

Many temperament/personality constructs relate to behavioral control and thus potentially to ADHD. Well-studied examples are effortful control, reactive control, ego control, behavioral/emotional regulation, and conscientiousness. These constructs have a great deal of overlap with one another. Thus, their patterns of relation to ADHD are similar (Eisenberg et al., 2000; Nigg, 2000). However, there is a distinction between effortful control and reactive control. Reactive control has theoretical overlap with motivational, or affective, deficits.

Incentive responding is widely viewed as important in ADHD. For example, the Dynamic Developmental Theory of ADHD (Sagvolden et al., 2004) suggests that altered reward/motivation is a core deficit. Altered reward/motivation in turn is believed to be due to dysfunction of DA system branches. These include frontoventral striatal reward circuits, frontoamygdala circuitry, and mesolimbic branches, including nucleus

accumbens (Casey, 2005; Nigg & Casey, 2005; Sonuga-Barke, 2005). This concept of altered reward/motivation is consistent with one of Sonuga-Barke's (2005) two pathways to ADHD: the motivational/affective pathway.

Reactive control is conceptually related to this reward/motivation argument because it has been defined as a form of control that is reactively modulated (Murray & Kochanska, 2002; Valiente et al., 2003). Reactive responding is directly dependent on immediate incentives (or cues that there is an immediate incentive available) rather than mentally represented future incentives. Traits like effortful control/conscientiousness, in contrast, are defined as flexibly managed control (Murray & Kochanska, 2002; Valiente et al., 2003). Effortful traits are related to behavioral patterns that facilitate the attainment of a later goal that may be held in working memory.

Following on that distinction, distinctions can be drawn between two kinds of control: top down effortful control (i.e., most related to executive control) and bottom up reactive control (i.e., most related to motivational processes). Effortful control (defined as the temperament trait of thoughtful or planful regulation) and conscientiousness (defined as the personality trait of planfulness) are very similar trait constructs. Although some specialists in personality see distinctions between them at the item level, for purposes of this study, they are treated as measuring virtually the same domain. Both have been equally linked to cognitive control. Further, they both appear, at least conceptually, to be underpinned by similar frontal-striatal neural circuitry (Rothbart & Posner, 2006). Finally, they both refer to the ability to suppress a dominant response in order to respond to contextual demands and are thought of as examples of "top-down" processing (Rothbart & Rueda, 2005). Reactive control, most related to incentive-based motivational

processes and their neural underpinnings, refers to reactive processes that are relatively automatic and therefore not under conscious control. They are more akin to "bottom up" responses to stimuli or incentives (Murray & Kochanska, 2002; Valiente et al., 2003).

Both of these major traits, top down control and bottom up control, have been related to children's adaptation, social functioning, and problem behaviors (Eisenberg et al., 2001; 2004). Valiente and colleagues (2003) found links between reactive control, effortful control, and externalizing problems. Further, as children got older, effortful control was a stronger predictor of future externalizing behavior than was prior externalizing behavior, even after statistically adjusting for reactive control. A review of the literature by White (1999) suggested associations between low levels of control, low levels of conscientiousness, and ADHD. This supposition was confirmed in a large multi-site study of personality traits and ADHD (Nigg et al., 2002). Thus, temperament and personality research has consistently found children and adults with ADHD to be characterized by low levels of conscientiousness (Nigg et al., 2002; Nigg, Goldsmith, & Sachek, 2004). A somewhat smaller literature suggests that children with ADHD have lower levels of temperamental effortful or reactive control (Huey & Weisz, 1997).

Integration of Executive and Temperamental Views of Regulation

The dopaminergic brain circuitry implicated in ADHD can be assessed by neuroimaging, but of central interest here are functional abilities at the psychological level of analysis. These can be indexed by laboratory behavioral measures (e.g., neuropsychological tests) and by behavioral trait measures (e.g., temperament), providing a convergent evidence approach. Based on the proceeding, EF and temperament trait control can be reformulated into an integrated model with (a) effortful (i.e., EF and

effortful control/conscientiousness) and (b) reactive (i.e., motivation/delay aversion and reactive control) components. These are then hypothesized to be underpinned by similar neural circuitry whether assessed via cognitive measures or behavioral ratings (Nigg, 2006; Nigg & Casey, 2005).

As schematized in Figure 1, executive control (a neuropsychological construct) and effortful control/conscientiousness (a temperament construct) are thought to involve "top-down" processing, or processing in the prefrontal regions that modulates activity in limbic, striatal, as well as posterior cortical areas (Nigg, 2006; Nigg & Casey, 2005). In contrast, reactive temperamental response involves a more "bottom-up" processing style, generated by activity in the limbic areas and then interrupting processing in the prefrontal regions (Nigg, 2006; Nigg & Casey, 2005). Thus, effortful control is associated with activity in the prefrontal cortex whether it is viewed as cognitive control and EFs or as the temperamental construct of effortful control and conscientiousness (Nigg, 2006; Nigg & Casey, 2005).

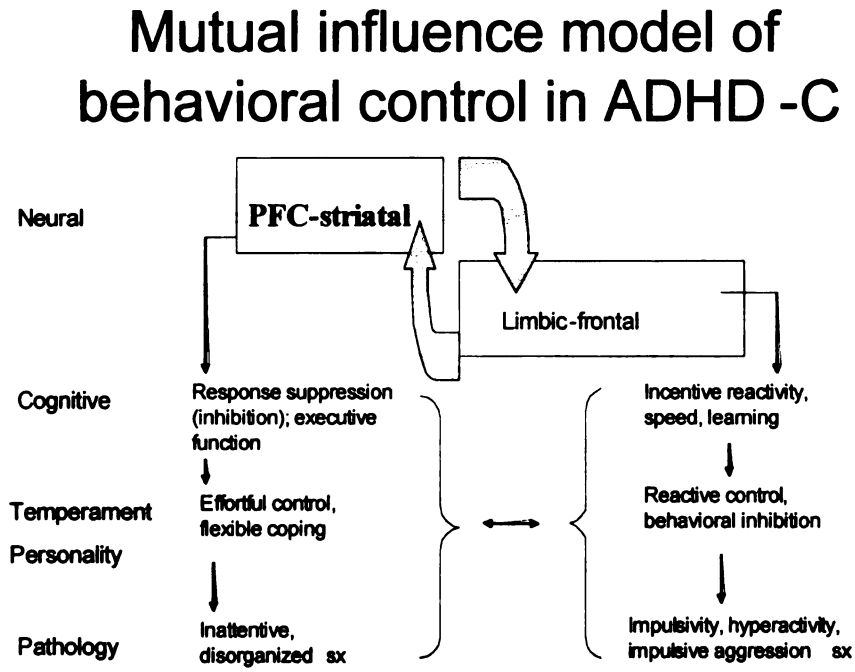

Figure 1. Mutual Influence Model of Behavioral Control in ADHD-C

In contrast, reactive response is seen as more dependent on subcortical areas such as the nucleus accumbens (related to approach processing) and potentially the amygdala (related to fear and withdrawal processing). Reactive control may be related to a general approach system. Since DA is involved in the neural circuitry that underpins executive control and temperamental control, then hormones that influence DA may influence these mechanisms, and this may be a route to their influence on ADHD symptoms (Nigg & Casey, 2005; Sonuga-Barke, 2005).

Summary

Deficits in neuropsychological EF and two key domains of temperament, effortful control and reactive control, are likely correlates of ADHD. The theoretical perspective adopted here, drawn from the work of several different theorists, suggests that the mesocortical DA circuit (including striatum) is implicated in (a) executive control

problems, such as response inhibition, (b) the temperament trait of effortful control/conscientiousness (Rothbart & Bates, 1998), and (c) the ADHD symptom domain of inattentive symptoms. In contrast, the nucleus accumbens and the mesolimbic DA circuit are implicated in (a) temperamental reactive response, especially approach, and (b) hyperactive-impulsive symptoms of ADHD (Nigg, 2006; Sagvolden et al., 2004; Sonuga-Barke, 2005). Both circuitries are influenced by prenatal and circulating levels of gonadal hormones, as discussed in the following sections.

III. Hormonal Influences on Development and on DA circuitry

Overview

Alterations in hormones seem like appealing candidates for explaining sex differences in the prevalence and expression of certain childhood disorders, including ADHD, although such relations are seldom examined and remain unclear. The reasons for this apparent connection are many, deriving from the many ways in which hormones influence the neural circuitry implicated in ADHD. Gonadal hormones exert organizational effects and the activational effects. Although these mechanisms are discussed as separate for our purposes, it is acknowledged that they are likely interactive and dynamic in nature. I discuss each of these mechanisms in turn.

Organizational Effects of Sex Hormones

Since ADHD emerges in childhood, gonadal hormones might exert their effects on ADHD through organizational effects on brain development. Organizational effects on the brain usually occur during a critical period of development. During this period, hormones permanently affect the developing brain, thus indirectly altering behavior even into adulthood (Breedlove & Hampson, 2002). In animals, organizational effects occur in

part through the aromatization of androgens (i.e., a large class of hormones that includes testosterone) into estradiol. However, in humans, most of these effects appear to occur directly through the effects of androgens, especially testosterone (Morris, Jordan, & Breedlove, 2004). This difference in organizational effects between animals and humans highlights the need for human studies of hormonal influences on behavior in childhood.

Sexual differentiation, a term used to describe how organisms develop into males and females, is a process that is integrally tied with organizational effects that occur during prenatal development. Thus, it is important to understand relevant theories of this developmental process. There are three theories of sexual differentiation: classical, active feminization, and gradient. These three models are not necessarily mutually exclusive, and thus all three can potentially be considered to address phenomenon such as ADHD.

The classical theory of sexual differentiation states that androgens cause masculine development, while the absence of androgen is linked to feminine development (Hines, 2002). This model of sexual differentiation has been well-studied in relation to prenatal animal development. This line of research suggests that testosterone, acting through the modulation of cell death rate, is the most likely source of organizational effects during the prenatal period (Morris, Jordan, & Breedlove, 2004). Testosterone, by differentially modulating the rate of cell death in various regions of the brain, may lead to the development of relatively larger or smaller size brain regions in males as compared to females. It can be hypothesized that hormonal effects of prenatal testosterone may make boys more vulnerable to the development of ADHD in early childhood though the modulation of cell death rate.

The second, gradient model of sexual differentiation states that hormones

influence not just behavioral differences (e.g., in cognition, childhood play, and aggression) between sexes, but also behavioral differences within sex (Collaer & Hines, 1995; Hines, 2002). Thus, levels of prenatal and childhood testosterone and estrogen may jointly influence the development of DA neural circuitry in boys and girls, and thus indirectly affect cognitive profiles and behavioral symptoms.

The third model of sexual differentiation, the active feminization model, states that ovarian hormones may play an active role in the feminization of neural circuitry and behavior (Collaer & Hines, 1995; Hines, 2002). Estrogen (i.e., a large class of hormone that includes estradiol) may influence and provide some neuroprotection for the development of DA circuitry in particular. Thus, it can be hypothesized that estrogen protects girls from the development of ADHD by protecting DA circuitry from insult.

Prenatal Testosterone and Classical, Organizational Effects

Animal, particularly rat, research on prenatal development often emphasizes the classical model of sexual differentiation and the role of androgens (especially testosterone). As already noted, such research suggests that high levels of testosterone early in gestation may lead to increased cell death, particularly within the right hemisphere of the brain (Morris, Jordan, & Breedlove, 2004), as well as increasing neural lateralization and slowing development of the brain (Goodman, 1991; Lyon & Gadisseux, 1991). The brain may be more vulnerable to insult while cell death is going on than after it has consolidated. Therefore, increased cell proliferation and cell death, increased lateralization, and slower development may make males more vulnerable to environmental insult by prolonging the course of their neural development (Lyon & Gadisseux, 1991; Morris, Jordan, & Breedlove, 2004).

In rats, a masculine pattern of neural development has been linked to an extended period of overproduction and subsequent pruning of DA receptors, a pattern that is speculated to parallel the childhood rise and fall of hyperactive ADHD symptoms (Andersen & Teicher, 2000). This idea is echoed in a theory of human disorder--Geschwind's (1987) theory of cerebral lateralization. He suggested that males are at increased risk for learning disorder and hyperactivity because fetal testosterone slows development in the left hemisphere of the brain, modifying cerebral lateralization (McManus & Bryden, 1991). If males are more vulnerable to prenatal insult and to the development of structural abnormalities in the left hemisphere due to their slower rate of prenatal development, they may also be more likely to develop behavioral problems in early childhood. Testosterone also appears to modulate neurotransmitter excitability prenatally. When pregnant rats were exposed to restraint stress, their male pups had reduced testosterone levels, as well as increased DA levels in the striatum (Gerardin et al., 2005).

Overall, testosterone appears to exert prenatal, organizational effects through its modulation of cell death in the brain. Additionally, there is some evidence that testosterone may influence dopaminergic neurotransmission and excitability, especially after exposure to prenatal stress.

Effects of Circulating Levels of Hormones

Circulating Testosterone and Gradient Effects

Testosterone also appears to modulate neurotransmitter excitability postnatally. After exposure to a novel environment, gonadectomized male rats treated with androgen exhibited inhibition of DA turnover in the medial prefrontal cortex and decreased activity

in the open field (Handa, Hejna, & Lorens, 1997). Estrogen-treated male rats showed the opposite pattern. Postnatally, testosterone plays a role in sexual motivation and behavior by acting on the three dopaminergic systems: the nigrostriatal, mesolimbic, and medial preoptic area systems (Hull, Muschamp, & Sato, 2004). According to a review of human and animal studies (Dominquez & Hull, 2005), testosterone influences the release of DA in at least one of these areas—the medial preoptic area. However, this is the area least relevant to ADHD.

Circulating Estradiol and Active Feminization Effects

In accordance with an active feminization model of sexual differentiation, estradiol may also influence the development of the dopaminergic system. Estrogen regulation of DA neurotransmission has been examined in rodent hypothalamus, striatum, nucleus accumbens, and frontal cortex—all regions important in human ADHD—with potential estradiol moderation effects (elucidated below) on both the nigrostriatal (motor system) and mesolimbic (higher order cognition and motivation) dopaminergic systems (Etgen, 2002). Further, levels of DA in the brain change over the course of the estrous cycle and following estrogen injections in rats (Etgen, 2002).

Research reviewing the effects of hormones on the development of disorders related to DA dysfunction like ADHD and Parkinson's disease suggests that estradiol may have a neuroprotective effect in midbrain dopaminergic neurons postnatally by regulating gene transcription, acting as an antioxidant, or though crosstalk with neurotrophic factors (Sawada & Shimohama, 2000). For example, treatment of gonadectomized female mice with estradiol decreased DA evocation and depletion of striatal DA in response to methamphetamine neurotoxicity (Dluzen & McDermott, 2002;

Myers, Anderson, & Dluzen, 2003). When ovarectomized monkeys were deprived of estrogen for 30 days, there was permanent loss of over 30% of DA cells in the substantia nigra (Leranth et al., 2000). Estrogen replacement restores these cells after ten days, but not 30 days, of deprivation. This neuroprotection has also been seen specifically in the nigrostriatal dopaminergic system, potentially by promoting the survival of some neurons at the expense of others (Dluzen & Mickley, 2005; Dohanich, 2002). Estrogen can also protect dopaminergic neurons following exposure to toxins (Etgen, 2002).

In a series of studies (Becker 1999; Becker & Rudick, 1999; Hu, Crombag, Robinson, & Becker, 2004; Zhou, Cunningham, & Thomas, 2003), Becker and colleagues found normal sex differences in dopaminergic function in the striatum and nucleus accumbens in male and female rats that may be due to hormonal mechanisms. Specifically, acute injections of estradiol early in development led to increased DA release in the striatum and nucleus accumbens and an enhanced response to amphetamine injection in the form of hyperactivity and stereotyped behaviors. Estrogen may also influence performance on learning and memory tasks that are dependent on the striatum. When ovariectomized rats were injected with estradiol, they became more sensitive to the effects of a D_2 DA receptor antagonist and made more errors on a learned, elevated plus maze with a food reward (Daniel, Sulzer, & Hulst, 2005).

Several studies have shown that injections of DA into the nucleus accumbens of ovariectomized/estrogen-primed rats (vs. ovariectomized rats) resulted in a reduction in DA uptake and an increase in DA clearance time at the synapse (Pandaranandaka, Poonyachoti, & Kalandakanond-Thongsong, 2006; Thompson, 1999). Several mechanisms of estrogenic action on DA neurotransmission in the striatum and nucleus

accumbens have been suggested. Treatment of ovariectomized and estrogen-primed rats with an agent of the D_2 DA receptor suggests that steroid modulation of dopaminergic transport in the striatum and nucleus accumbens is due to steroid-mediated action at the DA autoreceptor/DA transporter coupling and independent action of estrogen on the DA transporter (Thompson, Bridges, & Weirs, 2001). Estrogen administration in ovariectomized rats selectively reduced the expression of the regulators of G-protein signaling proteins (RGS) in the nucleus accumbens shell, suggesting that estrogen may facilitate DA signaling by affecting RGS mRNA expression (Sharifi, Brady, & Koenig, 2004).

Summary

Overall, prenatal testosterone and circulating levels of testosterone and estradiol may influence the development of ADHD and its corresponding mechanisms via their influence on relevant DA circuitry. Prenatal levels of testosterone may exert organizational effects on the DA circuits implicated in ADHD, for example, through modulation of cell death in the brain. Testosterone may be a prenatal risk factor for ADHD by making males more vulnerable to the development of abnormalities in DA circuitry. As to the nature of these abnormalities, one possibility is decreased levels of extracellular DA, resulting in less efficient DA modulation of responding. Additionally, there is some evidence that testosterone may influence postnatal dopaminergic neurotransmission and excitability, particularly in response to prenatal stress. Circulating levels of estradiol may have a neuroprotective impact on the DA system during childhood, in contrast to the effects of testosterone. Estradiol may also have protective, postnatal effects through its modulation of DA neurotransmission, perhaps by preventing

over-transmission. Further, in correspondence with a gradient model of sexual differentiation, relative levels or ratios between testosterone and estradiol may be related to ADHD symptoms. Of course, it may be that not all of these effects are linear. For example, hormones may interact with genetic vulnerability in order to influence ADHD. However, such gene by hormone effects are beyond the scope of this dissertation.

IV. Hormonal Influences on ADHD Symptoms, Mechanisms, and Correlates

Organizational Effects of Hormones on ADHD Symptoms, Mechanisms, and Correlates

Circulating levels of testosterone and estradiol are potentially able to alter functioning and development in cognitive control and motivational/affective DA circuitry, two of the key circuits implicated in ADHD. Recent research addresses the influence of prenatal hormones on psychological processes relevant to this discussion, such as ADHD symptoms and their related mechanisms of postnatal EF and approach/affective systems. Other research has focused on other correlates of ADHD such as sensation-seeking, attention, motor movement, and arousal. The literature includes several human studies and suggestive animal studies.

In the six studies examining the relationship between prenatal hormones and childhood ADHD symptoms in human clinical samples, finger-length ratios served as an indirect measure of prenatal androgen exposure. These ratios show reliable sex differences (Manning, 2002). They serve as a promising index of prenatal exposure to androgens since finger-length ratios are thought to be diminished by exposure to high levels of androgens early in development (Lutchmaya et al., 2004; Malas, Dogan, Evcil, & Desdicioglu, 2006; Okten, Kalyoncu, & Taris, 2002). Girls with congenital adrenal hyperplasia (CAH; exposed to high prental levels of adrenal androgens) show more

masculinized ratios (Brown, Hines, Fane, & Breedlove, 2002). Further, although finger-length ratios show some change across development, the rank order, or serial stability, of finger-length ratios remained largely the same over the course of childhood (McIntyre, Cohn, & Ellison, 2006; Trivers, Manning, & Jacobson, 2006).[2]

In three prior studies with well-characterized clinical samples, children with ADHD-PI were characterized by smaller (i.e., more masculinized) finger-length ratios measured by photocopies or scanner (McFadden, Westhafer, Pasanen, Carlson, & Tucker, 2005). Boys with autism/Asperger and ADHD/ODD had more masculinized ratios, measured by calipers, than boys with anxiety disorders (De Bruin, Verheij, Wiegman, & Ferdinand, 2006). A recent study by the author (Martel, Gobrogge, Breedlove, & Nigg, in press) examined associations between finger-length ratios (right index finger to ring finger ratio [right 2D:4D]) and ADHD in a larger sample of children and adolescents with ADHD than utilized in the current study (which is more limited in sample size due to its focus on executive and trait measures that were not available in as many children). Right hand finger-length ratios showed significant mean differences by sex, as well as associations with ADHD diagnosis. Boys with ADHD had more masculinized finger-length ratios. More masculine right 2D:4D and 3D:4D ratios were correlated with parent and teacher-rated inattentive and hyperactive-impulsive ADHD symptoms in boys, but not in girls. Masculinized finger lengths appeared to be a general risk factor for the development of inattentive, hyperactive-impulsive, and oppositional-defiant symptoms with most risk for inattention.

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[2] One important caveat here is that there may be differences in finger length measurements based the method of measurement. For example, photocopies yield lower finger-length ratios than direct finger measurements (Manning, Fink, Neave, & Caswell, 2005). For this reason, in the current study, photocopies were obtained on all children. A subset of children was also measured using calipers in order to examine what differences exist due to measurement method.

In another study (Williams, Greenhalgh, & Manning, 2003), using a non-clinical sample, high hyperactivity in childhood was related to lower right 2D:4D ratios, measured by scanner and calipers-- indicative of high levels of prenatal androgen exposure. In two samples of school-age children from the UK and Austria (Fink, Manning, Williams, & Podmore-Nappin, 2007), more masculine right and left 2D:4D, measured by photocopies and calipers, were associated with total difficulties and poor conduct in boys and girls. Specific to the UK sample, more masculine 2D:4D was related to more hyperactivity and more conduct problems, in boys but not in girls (Fink, Manning, Williams, & Podmore-Nappin, 2007). In a college sample mostly comprised of females (Stevenson et al., 2007), more masculinized 2D:4D on the left hand, measured by calipers, was related to more inattentive and hyperactive-impulsive symptoms, but only in the females.

Overall, in clinical samples, more masculine finger-length ratios were linked with increased ADHD symptoms and, in particular, with increased inattentive ADHD symptoms (De Bruin et al., 2006; Martel et al., in press; McFadden et al., 2005). In population samples, more masculine finger-length ratios were related to increased hyperactivity, although these relations were occasionally only found in girls or only found in boys (Fink et al., 2007; Stevenson et al., 2007; Williams et al., 2003).

With regard to studies of related behavior problems, graduate and undergraduate students with higher sensation-seeking evidenced more masculine finger-length ratios, measured by photocopies and calipers (Austin, Manning, McInroy, & Mathews, 2002; Fink, Neave, Laughton, & Manning, 2006). With regard to cognitive abilities, a review concluded that moderate to high levels of prenatal and early postnatal levels of androgens

facilitated the development of spatial ability by adulthood (evident both in normal human adults and in human adults who had lifelong hormonal abnormalities; Berenbaum, Korman, & Leveroni, 1995).

I now turn to animal studies. King and colleagues (2000) suggested that early androgen treatment decreased spatial memory in spontaneously hypertensive rats (SHR)—a strain commonly used as an animal model of ADHD. Thus, androgen levels appeared to facilitate spatial ability, but hinder spatial memory. Androgen levels also decreased DA innervation in the same animals (King, Kelly, & Delville, 2000). Androgen treatment during the early postnatal period in the male SHR was also associated with increased path lengths in the open field, a behavior viewed as an animal analogue of activity level (Li & Huang, 2006). One intriguing but unreplicated animal study is of interest as well. In that study, both male and female SHRs were hyperactive and exhibited discrimination problems, but their behavior differed markedly and was attributed to different mechanisms (Berger & Sagvolden, 1998). Females were postulated to have a deficit in attentional mechanisms, whereas males' behavior was attributed to a shorter delay-of-reinforcement gradient.

Effects of Circulating Levels of Hormones on ADHD Symptoms, Mechanisms, and Correlates

There is no research to date on the relationship of circulating hormones and ADHD symptoms in childhood; the present study is the first. Addressing the influence of estrogen levels on concurrent cognition and attention, a review of the organization of estrogen receptors (ER) in the human brain suggests that ERβ may play a role in general cognition, memory, and motor speed, all functions that are at least subtly implicated in

ADHD (Ostlund, Keller, & Hurd, 2003). Research examining postmenopausal women taking estrogen has found contradictory results such that higher levels of estradiol have been concurrently associated with better oral reading and verbal working memory and also with a higher risk of cognitive decline (Kang, Weuve, & Grodstein, 2004; Shaywitz et al., 2003).

Janowsky and colleagues (1998) found that circulating hormone levels in normal human adults were related to performance on motor speed tasks that showed sex differences. In addition, higher levels of estradiol were related to better performance on measures of spatial cognition in women, while higher levels of testosterone were related to better performance on verbal recall for men (Janowsky et al., 1998). Jennings and colleagues (1998) reported that levels of circulating estradiol were positively associated with women's performance on a sequential motor task, believed by those authors to involve the basal ganglia. fMRI research further suggested that orbitofrontal reactivity to emotional stimuli varied across the menstrual cycle in humans (Protopopescu et al., 2005). Estrogen may weaken limbic arousal by increasing cortical control over the amygdala (Goldstein et al., 2005), which would serve to dampen affective and more general cognitive reactivity.

Thus, circulating estradiol appears to be related to some neuropsychological functions, in particular to spatial ability and to motor movement, although it is unclear whether these results would generalize to children. It also appears related to activity in the limbic-frontal circuit, at least in adult women, which suggests it may be relevant to ADHD's hyperactive-impulsive symptoms and reactive/affective processes.

Several animal studies have also been conducted examining circulating levels of

estrogen and its effect on relevant animal analogues. Shansky and colleagues (2004) found that female rats appeared to have worse prefrontal cortical dysfunction (as indicated by their worsened performance on a spatial working memory task, delayed alternation) during times of their cycle that were characterized by higher levels of estradiol. Thus, optimal, but not high, levels of estrogen may be linked to lower levels of hyperactive-impulsive ADHD symptoms.

However, animal research also suggests that gonadal hormones can make stimuli more or less salient, affecting perception (Maney, 2006) and potentially attention. Research in primates indicates that levels of estradiol are positively related to visuospatial attention in females (Shively & Bethea, 2004). Jentsch and Taylor (2003) found that circulating hormone levels influence attention and impulsivity in normal and gonadectomized male and female Sprague-Dawley rats (i.e., rats often used as controls in comparison to the SHR animal model of ADHD). Intact male rats were more impulsive (i.e., made more premature errors) than intact female rats. However, ovariectomies worsened motor impulsiveness and orchidectomies worsened attentional performance. Thus, estrogen and testosterone may be related to distinct aspects of ADHD, with optimal levels of estradiol relevant to the hyperactive-impulsive aspects of ADHD and optimal levels of testosterone to the inattentive aspects. However, few other data like this are available with which to evaluate that idea.

Overall, little research has examined EF and reactive/affective processes. Existing studies shed some light on attention, general intellectual ability, motor movement, and arousal. Direct evaluation of hormonal effects on relevant mechanisms or correlates drawn from theories of ADHD is entirely lacking. Initial data on the relations among

hormones, cognition (i.e., reading, etc.), attention, motor movement, and arousal is intriguing, yet far from definitive in regard to ADHD. As it currently stands, sex hormones may be related to some forms of cognition, prefrontal arousal, impulsive behaviors, inattention, neuropsychological performance, and motor movement. Interesting yet preliminary sex differences have been noted in these domains in some animal and human studies (e.g., King, Kelly, & Delville, 2000; Shively & Bethea, 2004).

The absence of research on the ADHD mechanisms of EF and reactive/affective temperamental processes remains a huge gap. Irrespective of the general scarcity and limitations of the current research on hormonal influence on human development, several hypotheses might be generated regarding potential hormonal influence on the development of neural circuitry and processes implicated in ADHD. I turn to these next.

Summary and Hypothesized Models of Hormonal Influence on ADHD

Overall, the research reviewed herein on humans and animals suggests that hormones may have organizational effects on two key DA neural circuits associated with ADHD: the frontal-striatal circuit (via the striatum) and the frontal-limbic circuit (via the nucleus accumbens). Yet, links between hormones and ADHD, as well as with the cognitive and behavioral profile associated with ADHD, have hardly begun to be examined in human children. If hormones influence the neural structures implicated in ADHD, then association should be able to be detected via alterations in neuropsychological and/or temperamental measures that are associated with ADHD and are also correlated with integrity of these same neural circuits.

I next explain in more detail two main routes: a prenatal route involving testosterone and a childhood route involving circulating levels of testosterone or

estradiol.

1. Prenatal route. First, I argue that prenatal testosterone may influence the relationship between the development of the striatum and DA function in those regions, as evidenced by EF. The striatum is potentially central to the development of inattentive symptoms of ADHD. High levels of testosterone may influence the pattern of development of striatal DA receptors, leading to overproduction of these receptors in childhood (Andersen & Teicher, 2000). An overproduction of DA receptors may lead to increased uptake of neurotransmitters from the synaptic cleft and lower levels of extracellular DA. High levels of testosterone may also decrease the production and availability of DA within the frontal-striatum and/or modulate circulating levels of DA within the brain (Gerardin et al., 2005) through neurosteriod by DA interactions.[3]

Alterations in dopaminergic function and frontal-striatal neural circuitry appear to underpin top down control by decreasing the efficiency of arousal and other regulatory processes needed to sustain attention. In turn, breakdowns in such control are theorized to lead to inattentive ADHD symptoms. In fact, previous work indicates that children with ADHD are characterized by alterations in or decreased levels of dopaminergic activity (e.g., Volkow et al., 2005). In addition, abnormalities in dopaminergic structure and function in the frontal-striatal region of the brain has been implicated in the deficits in top down control exhibited by children with ADHD (e.g., Nigg & Casey, 2005).

High levels of prenatal testosterone may also be more subtly related to reactive

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[3] This description is not exhaustive. Prenatal levels of testosterone may have additional effects on neurobiology that are not examined in the current study. For example, testosterone may moderate the relationship between genes and the development of neurotransmission/neurobiology by interacting with genetic risk for the disorder. It may also moderate the relationship between prenatal risk factors (e.g., exposure to environmental contaminants such as PCBs and DDT) and dopaminergic neurotransmission (Miller, Gainetdinov, & Caron, 2000; Nigg, 2006). Those are potential topics for subsequent studies.

control via alterations in mesolimbic circuitry, particularly via influences on the nucleus accumbens. Since the alterations in the nucleus accumbens and the limbic system are implicated in reactive processes (Whittle, Allen, Lubman, & Yucal, 2006), hormonal influences on this neural circuitry may impact both reactive processes and corresponding hyperactive-impulsive ADHD symptoms.

One key hypothesis therefore was that high levels of prenatal testosterone, measured via finger-length ratios, are related to more impaired top down control, evidenced by weaker EF and lower effortful control/conscientiousness, and more inattentive ADHD symptoms in boys. If so, EF and effortful traits should mediate the relationship between finger-length ratios and inattentive ADHD symptoms in childhood, as shown in Figure 2.

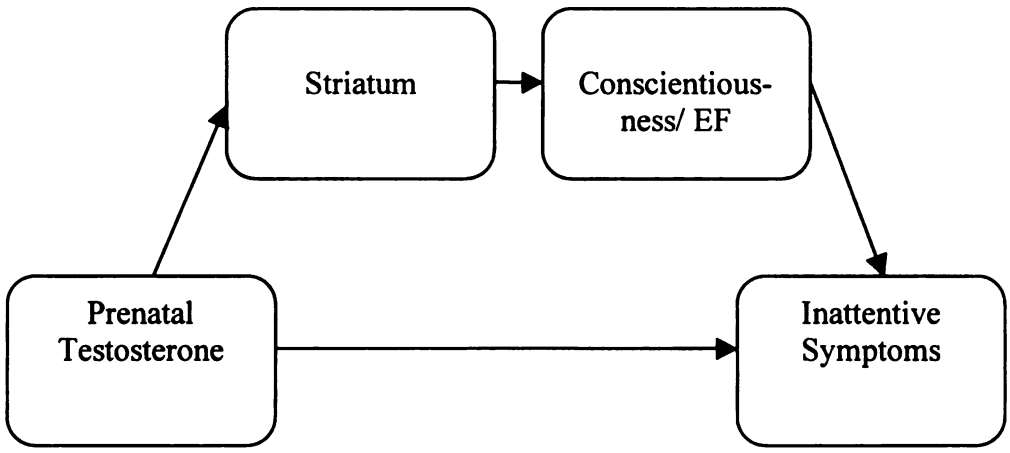


Figure 2. Mediator Model for Prenatal Testosterone Effects on ADHD

2. Childhood effect. Second, circulating testosterone or estradiol levels may

influence motor symptoms and hyperactivity during childhood. Circulating estradiol may modulate DA activity in both the striatum and nucleus accumbens (i.e., both of the ADHD-relevant pathways). One way it can do so is by providing neuroprotection against oxidative stress in the nigrostriatal dopaminergic system (Becker, 1999; Dluzen & Mickley, 2005; Sawada & Shimohama, 2000). Thus, circulating levels of estradiol may be protective against ADHD in childhood by mitigating neural responses to illness and injury.

Secondly, recent research on animals and humans suggests that sensory perception, cognition, arousal, attention, and affective processes can be influenced by circulating sex hormones through their effect on the amygdala (Goldstein et al., 2005; Maney, 2006; Protopopescu et al., 2005; Shively & Bethea, 2004), a part of the reactive control circuitry. Thus, circulating levels of estradiol may be positively related to reactive control and negatively related to ADHD symptoms of hyperactivity/impulsivity, providing some protection against the development of ADHD. As shown in Figure 3, circulating levels of estradiol may mediate the relationship between reactive temperamental control and current hyperactive-impulsive ADHD symptoms in girls. The relationship between circulating levels of testosterone and childhood ADHD symptoms is less clear and is examined in this study in exploratory fashion.

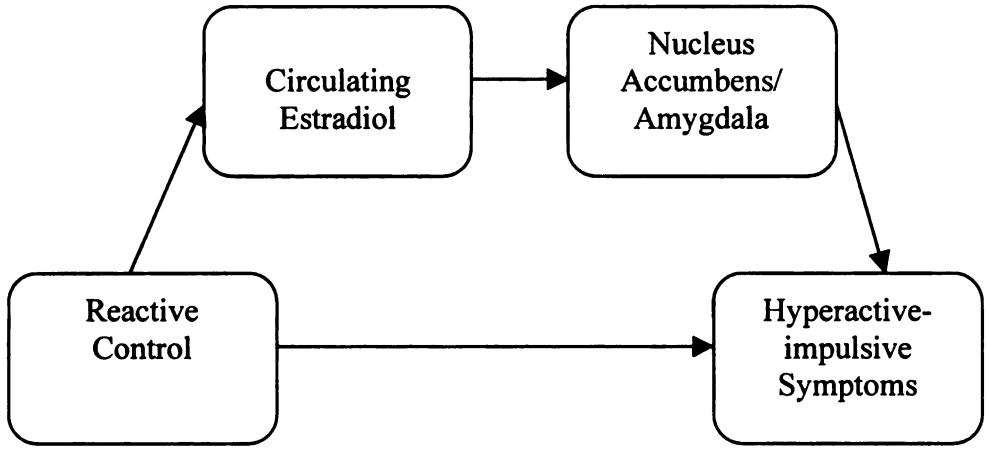


Figure 3. Mediator Model for Circulating Estradiol Effects on ADHD

As a third route, circulating gonadal hormones may influence ADHD symptoms through a balance between circulating levels of testosterone and estradiol or an optimal level of gonadal hormones. That is, a higher ratio of testosterone to estradiol may be more characteristic of ADHD and moderate, but not high, levels of estradiol may facilitate adaptive affective regulation and fewer ADHD symptoms.

Conclusion

Sex hormones apparently influence the development of some of the same neural circuitry that is implicated in ADHD. In particular, testosterone and estradiol appear to influence the pre- and postnatal development of the prefrontal cortex, striatum, and nucleus accumbens, as well as influencing dopaminergic neurotransmission in these regions. Prenatal testosterone seems to reduce DA transmission and so would likely result in less efficient operation of effortful control systems. Circulating estradiol appears to protect the integrity of dopaminergic function and so would lead to more efficient

reactive control operations. Consistent with this picture, the following was hypothesized. (1) Prenatal testosterone is related to inattentive ADHD symptoms (in boys), mediated by impaired EF and weak effortful control/conscientiousness. (2) Circulating levels of estradiol mediate the relationship between reactive temperamental traits and current hyperactive-impulsive ADHD symptoms (in girls). Alternatively, in both boys and girls, an optimal balance of circulating testosterone to estradiol or an optimal level of estradiol may lower risk. If so, it would emerge that a larger testosterone to estradiol ratio predicts more inattentive ADHD symptoms and more impaired executive and effortful control/conscientiousness. At the same time, if this is true, then estradiol will exhibit a curvilinear relationship with hyperactive-impulsive ADHD symptoms and reactive control.

METHOD

Participants

The current study reports on 312 participants who were drawn from an adolescent sample (ages 14-17) and a new child sample (ages 8-13). The only difference in project protocol entails slight variation in the neuropsychological battery administered. The 312 children came from 274 families. Thus, 38 siblings are included in these analyses. 22 sibling pairs were disconcordant for ADHD (i.e., one was diagnosed with ADHD and the other was a non-ADHD control). Five sibling pairs were both diagnosed with ADHD, and 8 siblings pairs were non-ADHD controls.

Through the use of a multistage screening process, these participants were recruited into two groups, ADHD and control, with 168 children with ADHD (89 combined subtype, 78 inattentive subtype, and 1 hyperactive-impulsive subtype) and 144 controls. Within the whole group, there were 178 boys and 134 girls, with 106 boys and 62 girls in the ADHD group and 72 boys and 72 girls in the control group. Most adolescents and children had ADHD, cognitive, and temperament measures available. However, not all adolescents and children had circulating hormone measures available, as explained later.

Demographic statistics on the sample, broken into ADHD, control, and total groups, can be seen in Table 1. There were significantly more boys in the ADHD group than in the control group, and children in the ADHD group were significantly younger than children in the control group ($p<.05$). In addition, and as expected, children with ADHD had more ADHD symptoms, higher Conners' *t*-scores, and more ODD and CD symptoms than children in the non-ADHD control group ($p<.01$).

Table 1

Sample Demographics

	ADHD *n*=168	Controls *n*=144	Total *N*=312
Males	106 (63.1%)	72 (50%)	178 (57.1%)*
Ethnic Minority	40 (23.81%)	38 (26.39%)	78 (25%)
Age	12.71(3.01)	14.01(2.76)	13.31(2.96)**
Family Income	71173.91(83045.01)	77306.52(55531.69)	74051.52(71400.45)
Full Scale IQ	103.09(12.66)	111.55(14.34)	106.98(14.08)
Inattention Symptoms[1]	8.54(.72)	1.86(1.91)	5.42(3.62)**
Hyperactive Symptoms[1]	6.19(2.90)	1.17(1.44)	3.85(3.43)**
ODD Symptoms	2.41(2.48)	.51(1.21)	1.59(2.23)**
CD Symptoms	.35(.73)	.05(.22)	.23(.58)**
Conners' Cognitive Problems (P)	71.08(10.64)	47.66(6.97)	60.37(14.83)**
Conners' Hyperactivity (P)	67.42(15.80)	49.17(7.57)	58.93(15.58)**
Connors' ADHD T-score (P)	72.27(9.33)	48.11(7.05)	61.18(14.67)**
Conners' Cognitive Problems (T)	60.15(11.47)	48.63(7.39)	54.58(11.28)**
Conners' Hyperactivity (T)	61.84(14.80)	50.60(10.53)	56.37(14.05)**
Connors' ADHD T-score (T)	66.43(12.78)	50.03(9.58)	58.42(13.98)**

Note. *p<.05. **p<.01. (P)=parent-report. (T)=teacher-report. [1] = parent+teacher OR algorithm ADHD symptoms based on K-SADS. Significant group differences tested by t-tests or chi-square statistics.

Multistage recruitment and diagnostic assignment process

All participants were recruited from mid-Michigan schools, clinics, and community through public advertisements and announcements, mass mailings, and outreach to schools and clinics in order to recruit as broad and representative of a sample as possible. The first stage was a screen that precluded any children who took slow-acting psychotropic medication (i.e., prednisone, antidepressant, anti-psychotic, anticonvulsant medications), had major medical or neurological conditions, including genetic, gonadal, or hormonal abnormalities as reported by the parent, and who did not speak English as their first language.

At the second stage, parents and teachers completed normative behavior rating scales: School and Home versions of the ADHD Rating Scales (DuPaul, Power, Anastopolous, & Reid, 1998), the Parent and Teacher Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1992), and the Conners (1997) Parent and Teacher Rating Scales-Revised-Short Forms. These scales were chosen based on their empirically-validated cut-offs, thorough coverage of symptoms, and adequate reliability and validity. Further, these scales are among the most widely-accepted rating scales currently used and were judged to have the best cut score data for screening (Ostrander, Weinfurt, Yarnold, & August, 1998; Power et al., 1998). Test-retest reliability for these scales range from .62 to .95. Internal reliability in this study ranged from .84 to .96, and validity coefficients range from .78 to .98 (Conners, 1997; DuPaul et al., 1998; Reynolds & Kamphaus, 1992).

For the third stage, participants completed an individual, semi-structured, clinical interview (i.e., KSADS-E; Puig-Antich and Ryan, 1986). The KSADS-E was chosen

because its structure is clinically sensitive, and it provides a thorough coverage of childhood disorders (Biederman et al., 1990; Biederman et al., 1992). For the child sample, girls were asked if they had started menstruation and, in the case of the affirmative, given a premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) symptom checklist (i.e., Daily Record of Severity of Problems; Yonkers et al., 1997) to complete as part of their questionnaire packets. This information was not available on the archival adolescent sample, however.

The data from the interviews and parent and teacher rating scales were then presented to a clinical diagnostic team consisting of a social worker, board certified child psychiatrist, and licensed clinical child psychologist. A "best estimate" diagnostic process was implemented, in which the psychiatrist and psychologist independently arrived at a clinical decision regarding ADHD diagnosis, subtype, and presence of comorbid disorders. Their agreement rates were acceptable for ADHD, its subtypes, and current Oppositional Defiant Disorder and Conduct Disorder (all kappas $\geq .89$). In the event of a disagreement, they conferred and easily arrived at consensus; if they could not, the case was omitted.

Comorbid psychiatric and learning problems

For both samples, comorbid symptoms and diagnoses (i.e., anxiety disorders, mood disorders, Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, Tic disorders, ODD, and CD) were assessed via modules of the relevant parent semi-structured or structured interview and behavioral rating scales. IQ and learning disability were assessed with a reliable and valid three-subtest form of the Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003a) and the Wechsler Individual Achievement

Test (WIAT; PsychCorp, 2005) Basic Reading and Mathematical Reasoning subtests.

Exclusionary Criteria

Autistic Disorder, Mental Retardation, Schizophrenia, Bipolar Disorder, Fetal Alcohol syndrome, known neurological disorder, Cerebral Palsy, Tourette's disorder, genetic, gonadal, and hormonal abnormalities, PMS (when data available), and PMDD (when data available) were exclusionary criteria.

Medication rule out and wash out

Children and adolescents with ADHD attended neurocognitive assessment visits after an appropriate washout from psychostimulant and other ADHD medication (for short-acting stimulants, 24 hours; for slow release formulas, 48 hours). Individuals taking long-lasting psychotrophic medications were necessarily excluded when possible for purposes of the neuropsychological testing and blood draw. Although taking of hormones such as prednisone or birth control pills was not formally screened out in the initial years of data collection, information on medications was obtained. In the current study, 115 participants had a prescription for stimulant medication, and four participants had a prescription for birth control pills.

Measures

Executive Function (EF)

The neuropsychological EF measures examined components of EF derived from the model suggested by Pennington (1996). These tests were administered in a fixed order so as to minimize children's fatigue.

Response Inhibition

The tracking version of the Stop Task is a well-validated computer task (Band,

van der Molen, & Logan, 2003; Logan, 1994) during which the participant is instructed to press the "X" key when s/he sees the letter X on the computer screen and the "O" key when s/he sees the letter O on the screen. When the child hears a tone before the letter flashes, s/he tries to refrain from responding. The Stop Task, with alpha reliability higher than .8, measures the ability to suppress a motor response on cue. A measure of inhibitory control, stop signal reaction time, was computed by subtracting mean stop signal latency from mean go response time.

Response Variability

A response variability measure was obtained from the Stop Task, defined as the within-child variability of the reaction time on the "go" trials. This measure served as an index of response variability, conceptualized as reflecting degree of interference between "hot" and "cool" EF processes, energetic deficits, and temporal instability of responding (Russell et al., 2006).

Set-Shifting

The Trailmaking Task, a subtest of the Halstead-Reitan Neuropsychological Battery, requires the participant to trace a path between numbers and letters as quickly as possible without errors. Widely used in neuropsychological research measuring frontal lobe function, the outcome measure of the task was set-shifting, measured as the time taken to complete the more difficult Form B minus the time to complete Form A (Reitan & Wolfson, 1985; Spreen & Strauss, 1991).

IQ and Academic Achievement

Child IQ was assessed with the widely-used and extensively-researched Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) or the Wechsler Intelligence

Scale for Children-Third Edition (WISC-III). A reliable and valid 3-subtest short form was used to estimate the Full Scale Intelligence Quotient (Wechsler, 2003a; 2003b). While the WISC-III was used for the adolescent sample, the WISC-IV was used for the new sample. In instances where this variable is used as a covariate in the analyses, standardized scores were used.

Temperament Traits

The current study examined two key traits: conscientiousness and reactive control. They were hypothesized to be relevant to the development of ADHD via distinct pathways (see Figure 1). To measure these traits, the mother (or primary caregiver) completed the common language version of the California Child Q-Sort (CCQ; Caspi et al., 1992).

The CCQ is a typical Q-Sort consisting of 100 cards which must be placed in a forced-choice, 9-category, rectangular distribution. The rater describes the child by placing descriptive cards in one of the categories, ranging from 1 (least descriptive) to 9 (most descriptive). Items in the middle are thus uninformative, and those on the two ends are most informative. The items for the reactive control scale examined in the current dissertation were selected to follow the suggestions of Eisenberg and colleagues (1996), consisting of 14 items with internal reliability of .74. To measure conscientiousness, a scale developed by John and colleagues (1994) was used, consisting of nine items with internal reliability of .87.

Sex Hormones

Circulating Levels of Estradiol and Testosterone

Venipuncture blood draws were performed at the MSU Clinical Center at 5:00 in

the evening, for half of the adolescent sample (i.e., those obtained in the latter half of that data collection period after funding for blood draws had been obtained; thus, this was expected to be a random sample from that group) and the entirety of the child sample. Immediately after the blood draw, the child had another rest period along with snack and drink, and then-- at 5:30--- neuropsychological testing in the laboratory began. The blood draws were preceded by informed parent consent and child assent. For girls who had begun menstruation, data regarding the first date of their menstrual cycle, the end date of their last two menstrual cycles, and a history of missed periods was collected by a female staff member in private after the establishment of the confidentiality policy and rapport. These data were checked against the relative levels of hormones in their blood in order to validate their self-report to the extent possible, although such validation was limited in girls of low gynecological age (i.e., with low hormone levels).

Samples were stored in a -20 freezer in the Psychology Building, although they were shortly moved to a -80 freezer, and storage duration was minimized. Estradiol was analyzed in Dr. Fisher's laboratory using standard serum/plasma radioimmunoassay kits. Because the manufacturer failed to supply enough kits, estradiol data were missing for 18 cases. These cases were considered missing at random.

The clinical laboratory at Michigan State University is certified by both the College of American Pathology and Clinical Lab Improvement Act. Duplicate analyses of the same samples were run in the laboratory using separate kits in order to assure the reliability of the results. The coefficient of variation used in the laboratory within runs was less than ten percent variation, meaning that duplicate samples that differed by more than ten percent were deemed unacceptable. Reliability between runs was also checked

by obtaining the average mean and standard deviation of each run for between six to eight runs. Then, values from other runs were rejected if they fell more than one or two standard deviations outside of these average values. In addition, the sensitivity of the estradiol assay in measuring low levels of estradiol in prepubertal girls was a critical issue that was monitored in an ongoing fashion. Less than 5% of samples fell outside the reliably-detectable range.

All samples were assayed for salivary testosterone in duplicate using a highly-sensitive enzyme immunoassay (Cat. No. 1-2402/1-2412, Salimetrics LLC, State College PA). Although Salimetrics' EIA kits were designed for use with salivary samples, they were successfully validated on low levels of serum testosterone before use with the current sample using test samples with known concentrations of testosterone. 25 uL of a 1:10 serum dilution was used per test. The test used 25 ul of saliva per determination, has a lower limit of sensitivity of 1.0 pg/mL, standard curve range from 6.1 pg/mL to 600 pg/mL, an average intra-assay coefficient of variation of 4.6%, and an average inter-assay coefficient of variation of 8.25%. Method accuracy determined by spike recovery averaged 104.4%, and linearity determined by serial dilution averaged 99.9%. The correlations between serum and saliva was highly significant with r (14) = 0.91, p<0.001 for males and r (12) = 0.61, p<0.001 for females. Testosterone, originally measured in nanograms per milliliter, was converted to picograms per milliliter so that it would be comparable to estradiol measurements when discussing or graphing absolute levels. Then, a ratio was computed between testosterone and estradiol (i.e., testosterone/estradiol).

Self-ratings of pubertal morphological changes for the children and adolescents

was assessed with the Pubertal Development Scale (Angold et al., 1999; Petersen, Richards, & Boxer, 1988), using a self-report rating scale completed by the child and by the parent about the child. A categorical and continuous pubertal status variable was generated from this rating scale. Although this report obviously is not as valid as a physical exam, the correlation between self-report and physician rating of pubertal development is .70 (Petersen et al., 1988), suggesting that this approach had some validity for the present study.

One hundred eight-one children in the current study had Pubertal Development Scale data. In these 181 participants, maternal and child report on the Pubertal Development Scale correlated at .80 ($p<.01$) for categorical stage and .81 ($p<.01$) for continuous pubertal stage. Thus, these indices were averaged to form a composite categorical and continuous measure of pubertal stage. Of the 60 girls who had circulating estradiol data available, 28 had not started menstruating and 32 had started menstruating. Fifteen girls reported the dates of their previous two cycles and had hormone data available. The combination of both forms of data suggested that nine girls were in the follicular phase, 1 was in the ovulatory phase, and 5 were in the luteal phase. The remaining girls who had started menstruation either did not report their cycle information, their phase was unable to be determined because they had irregular cycles, or their reported cycle information did not agree with their hormone levels, as compared to tables with normative levels per menstrual cycle phase for their age.

Prenatal Levels of Testosterone via Finger length Ratios

Finger length ratio was used to index prenatal testosterone (for discussion of validity of this procedure, see McFadden et al., 2005). This approach is a relatively

established procedure for measuring prenatal androgen exposure; however, it remains debated (Cohen-Bendahan, van de Beek, & Berenbaum, 2005). Child finger-length images were obtained using a photocopier,[4] and measurements were taken using a ruler. For the photocopier measurements, children were asked to remove any jewelry and place their two hands side-by-side, fingers closed, onto a clear template marked like a ruler. A one-pound bag of rice was then placed over their hands to provide a contrast, and their hands were photocopied. The examiner then asked the parent for information regarding the number of older and younger siblings of the child, the birth order of the child, and the presence of any miscarriages (and gender if known) before the birth of the child. Two raters then independently recorded measurements of the finger-length of index, middle, ring, and little fingers. The measurements between raters were reliable (n=20; all r above .91; all p<.01) with an average correlation between the two raters' measurement of finger-lengths of .97. Ratios were then computed between each of the pairs of fingers on both hands. The ratios exhibiting large sex differences and most often used in prior research were the right 2D:4D and the right 2D:5D (Fink et al., 2007; Martel et al., in press; Stevenson et al., 2007). It should be noted that finger-length ratios show ethnic, as well as sex, differences (Cohen-Bendahan et al., 2005).

Data Analysis

[4] Photocopies of finger length may introduce some distortion into the calculation of finger-length ratios (Manning, Fink, Neave, & Caswell, 2005). Such effects were not a major focus because they presumably would not be able to explain ADHD-specific effects. However, as a precaution, calipers were also used in addition to photocopies and rulers for a subset of children to enable comparison between these two different measures of finger length. For the subset of the sample (n=57) who had photocopied image and caliper measurements available, correlations between raw finger lengths were large and significant (average r=.84, p<.01). However, correlations between finger-length ratios, computed from photocopied images and caliper measurements, were relatively low and marginally significant (average r=.26, average p=.13) consistent with the literature on lower reliability of ratio scores than raw scores (Manning et al., 2005). For main study analyses, photocopies of finger-length ratios were analyzed, and this potential unreliability is noted as a limitation in the discussion.

Initial descriptive data analysis, such as t-tests, correlations, and MANOVAs, were handled using SPSS. Subsequent data analyses, such as regressions and mediation analyses, were handled using Mplus.

Handling of Outliers and Skewed, Nonnormal Data

For variables with outliers, trimmed means were used (Wilcox, 2002). That is, outliers that were greater than 3 standard scores from the mean were trimmed to be within three standard scores of the mean. An exception to this rule was made for clinical (i.e., hormonal) data. In this case, severe outliers were deleted since they appeared to be inaccurate measurements, and the deleted data points were handled with the FIML procedure described below. This was true for less than 5% of data points. For variables that were significantly skewed or nonnormal (as indicated by the Kolmogorov-Smirnov and Shapiro-Wilk tests), data transformations were attempted. However, data transformations were not successful in correcting the nonnormality of the data. Thus, subsequent univariate and multivariate regressions were conducted using the Mplus software package (Muthen & Muthen, 2007) which allows for the statistical control of non-normality and outliers through the use of robust maximum likelihood estimation (Curran, West, & Finch, 1996).

Handling of Missing Data

The current sample was comprised of all adolescents and children who had diagnostic, trait, EF, and finger length data available (N=312). Of these, approximately, 200 participants had circulating hormone data available. Missingness for the hormone data (and for all other variables) was handled using Mplus since MPlus provides full information maximum likelihood estimation under MCAR (missing completely at

random) and MAR (missing at random; Muthen & Muthen, 2007). Full information likelihood estimation (i.e., FIML or direct fitting) is a method of directly fitting models to raw data without imputing values (McCartney, Burchinal, & Bub, 2006). A state-of-the-art missing data technique, FIML is seen as having all the strengths of single and multiple data imputation, while also being easy to interpret since only one parameter (rather than multiple parameters) is produced by the analysis. In addition, FIML can be used when the amount of missing data is moderate or large (i.e., up to thirty percent missingness; McCartney, Burchinal, & Bub, 2006).

Handling of Non-independence of Data

The presence of siblings and the resulting non-independence of data points were handled using the clustering feature of MPlus. This clustering feature takes into account the non-independence of the data when computing test statistics and significance tests.

Choice of Covariates

Covariates varied for each type of analysis, but the choice of covariates followed pre-set rules. For any analyses utilizing all children (i.e., both boys and girls), sex was covaried in order to control for the greater number of boys in the ADHD group, as compared to the control group. For analyses examining finger-length ratio, ethnicity was also covaried due to the fact that finger-length ratios show ethnic differences. For analyses examining circulating hormone levels, age was covaried in order to control for age differences between the ADHD and control groups.

Correction for Type I Error

Due to the number of statistical tests conducted in the current study, a correction for Type I error was implemented. A Bonferroni correction for all tests was viewed as

excessively stringent as it would result in unacceptably low power, particularly due to the fact that several tests were run as "control tests" (i.e., not expected to result in positive findings). Therefore, results in the current study were considered significant if they had a p-value at or below .01. Results with a p-value at or below .05 were considered marginally significant or at trend-level.

RESULTS

Descriptive Statistics and Preliminary Data Checks

Descriptive statistics. Descriptive statistics on the sample, broken into ADHD, control, and total groups, are shown in Table 2. As shown in Table 2, the right 2D:4D and 3D:4D were marginally more masculine (i.e., smaller) in the ADHD group as compared to the control group ($p<.05$). In addition, children with ADHD, as compared to controls, exhibited significantly more impaired response inhibition ($p<.01$), increased response variability ($p<.01$), less conscientiousness ($p<.01$), and less reactive control ($p<.01$). Children with ADHD also had marginally decreased set-shifting ability ($p<.05$). These results were as expected.

Table 2

Descriptive Statistics by Diagnostic Group

	ADHD *n*=168	Control *n*=144	Total *N*=312
R 2D:4D	.94(.06)	.96(07)	.95(.06)*
(*z*-score)	-.14(.92)	.18(1.07)	0(1)
R 2D:5D	1.50(.19)	1.54(.21)	1.52(.20)
(trimmed *z*-score)	-.08(.94)	.09(1)	-.01(.97)
R 3D:4D	1.12(.04)	1.14(.05)	1.13(.05)
(trimmed *z*-score)	-.15(.91)	.19(1.02)	-.00(.97)*
Pubertal Stage (cat.)[1]	2.84(1.08)	3.31(1.45)	3.03(1.13)*
Pubertal Stage (cont.)[1]	10.27(4.45)	12.06(4.50)	10.98(4.54)*
Testosterone (ng/mL)	.95(1.13)	1.15(1.11)	1.02(1.12)
Estradiol (pg/mL)	35.43(39.35)	31.66(26.99)	34.00(35.13)
Response Inhibition	284.10(125.00)	233.72(78.50)	259.64(107.81)**
(trimmed *z*-score)	.20(1.08)	-.24(.73)	-.01(.95)
Variability	153.22(47.14)	130.21(39.62)	142.10(45.07)**
(trimmed *z*-score)	.21(.91)	-.25(.85)	-.02(.91)
Set-shifting	55.90(24.80)	50.60(26.81)	53.45(25.84)*
(trimmed *z*-score)	.08(.90)	-.15(.82)	-.02(.87)
Conscientiousness	4.05(1.25)	6.40(1.19)	5.13(1.69)**
Reactive Control	4.29(1.12)	5.25(.99)	4.73(1.17)**

Note. *p<.05. **p<.01. Significant group differences tested by t-tests. [1] = categorical and continuous measures of pubertal stage are assessed via an average of child and maternal ratings on the Pubertal Development Scale.

Preliminary Data Check I: Subtype differences in finger-length ratios, neuropsychological EF, or temperament traits in children with ADHD and controls

A MANCOVA, covarying sex and ethnicity, was conducted to examine subtype differences in three finger-length ratios (i.e., right 2D:4D, 2D:5D, and 3D:4D). There were no significant differences between subtypes in finger-length ratios (F[3, 119]=1.71, η^2=.04, p>.05). A MANCOVA, covarying sex, examined subtype differences in cognitive control (i.e., response inhibition, variability, and set-shifting) and was also nonsignificant (F[3, 119]=.95, η^2=.02, p>.05). A MANCOVA, covarying sex, was conducted to examine subtype differences in traits. The combined subtype had lower conscientiousness and reactive control than did the inattentive subtype (F[2,163]=14.17, η^2=.15, p<.01). Since no subtype differences were noted in hormone measures and in order to maximize statistical power, the two subtypes were pooled in subsequent analyses.

Preliminary Data Check II: Sex and diagnostic differences in finger-length ratios, neuropsychological EF, or temperament traits in children with ADHD and controls

Descriptive statistics, broken into four groups by sex and diagnostic group, are shown in Table 3. Three MANCOVAs were conducted to examine sex and diagnostic differences in 1) finger finger-length ratios, 2) EF, and 3) temperament traits.

Table 3

Descriptive Statistics by Sex within Diagnostic Group

	ADHD(n=168)		**Control** (n=144)	
	Boys n=106	Girls n=62	Boys n=72	Girls n=72
R 2D:4D	.93(.06)	.97(.05)**	.95(.07)	.98(.06)+
(z-scores)	-.38(.89)	.26(.84)	-.00(1.09)	.38(1.02)
R 2D:5D	1.46(.18)	1.57(.17)	1.51(.20)	1.57(.22)
(trimmed z-scores)	-.30(.92)	.27(.87)**	-.06(.94)	.26(1.04)
R 3D:4D	1.11(.05)	1.14(.03)	1.14(.05)	1.14(.04)
(trimmed z-scores)	-.38(.94)	.21(.73)**	.10(1.10)	.29(.93)
Pubertal Stage (cat.)[1]	2.72(.96)	3.05(1.23)	3.23(.99)	3.43(1.32)
Pubertal Stage (cont.)[1]	8.83(3.27)	12.83(5.11)**	10.57(3.52)	13.85(4.93)**
Testosterone (ng/mL)	1.27(1.34)	.43(.17)**	1.66(1.31)	.63(.48)**
Estradiol (pg/mL)	20.77(12.29)	59.29(54.3)**	23.04(8.65)	43.16(37.42)*
Response Inhibition	293.20(137.87)	266.34(94.01)	243.90(78.44)	222.63(77.74)
(trimmed z-scores)	.27(1.17)	.06(.87)	-.15(.73)	-.34(.72)
Variability	154.78(46.14)	150.14(49.47)	127.27(39.33)	133.40(40.04)
(trimmed z-scores)	.24(.86)	.15(1.00)	-.33(.87)	-.17(.83)
Set-shifting	58.14(26.61)	52.06(21.00)	54.32(32.00)	46.88(19.89)
(trimmed z-scores)	.16(.94)	-.05(.81)	-.04(.86)	-.25(.77)
Conscientiousness	4.02(1.13)	4.11(1.44)	6.12(1.26)	6.68(1.04)**
Reactive Control	4.13(1.09)	4.55(1.14)*	5.29(1.06)	5.22(.93)

Note. +p<.10. *p<.05. **p<.01. Significant group differences for boys vs. girls within diagnosis were tested by t-tests. [1] = categorical and continuous measures of pubertal stage are assessed via an average of child and maternal ratings on the Pubertal Development Scale.

The first MANCOVA examined sex and diagnostic differences, controlling for ethnicity, in right 2D:4D, 2D:5D, and 3D:4D entered together in the MANCOVA. There was a significant multivariate main effect for sex (F[3, 214]=4.99, λ=.94, η^2=.07, p<.01) in the expected direction (i.e., boys had more masculine finger-length ratios), but not for diagnostic status (F[3, 214]=1.80, λ=.98, η^2=.03, p>.05). The interaction between sex and diagnostic status was not significant (F[3, 214]=.74, η^2=.01, p>.05).

ANCOVA was conducted to examine sex and diagnostic differences in right 2D:4D (i.e., the most widely validated finger-length ratio), controlling for ethnicity. Sex and ADHD main effects were significant in the expected direction: boys and children with ADHD had more masculine finger-length ratios (F=13.96, η^2=.06, p<.01 for sex; F=4.13, η^2=.02, p<.05 for ADHD). The interaction between sex and diagnostic status was not significant (p=.34). The ADHD effect held in a single-factor ANCOVA with sex and ethnicity covaried (F=4.79, η^2=.02, p<.05).

The second MANOVA examined sex and diagnostic differences in EF. There was a significant multivariate main effect of ADHD diagnostic status (F[3, 235]=6.26, λ=.93, η^2=.07, p<.01), but no significant sex differences (F[3, 235]=2.08, λ=.97, η^2=.03, p>.05) or interactions (F[3, 235]=.32, λ=1.00, η^2=.004, p>.05). Diagnostic differences in EF have been well-validated (e.g., Nigg et al., 2002). Sex differences in EF are more controversial. However, the current study's results are in line with some work on sex differences in EF which have failed to find sex effects (Seidman et al., 2005).

The third MANOVA examined sex and diagnostic differences in the two personality traits, conscientiousness and reactive control, that had been selected as behavioral probes of top down and bottom up control respectively. The interaction

between sex and ADHD diagnosis was significant (F[2, 307]=4.76, λ=.97, η^2=.03, p<.01). Girls had higher levels of conscientiousness than boys in the non-ADHD group. Girls had higher levels of reactive control than boys within the ADHD group (Table 3).

Bivariate correlations were conducted between hormone measures and symptoms, cognitive control, and traits in the full sample. These correlations, conducted for descriptive purposes, are shown in Table 4. As can be seen, right 2D:4D was significantly related to inattention, hyperactivity-impulsivity, and conscientiousness, in the expected direction (i.e., more masculine finger-length ratios related to more symptoms and less conscientiousness). In addition, circulating estradiol was significantly and positively related to reactive control, but only marginally, inversely related to hyperactivity-impulsivity.

Table 4

Correlations among Hormone Measures, Clinical Symptoms, and Trait and Cognitive Control

	R 2D:4D	2D:5D	3D:4D	Estradiol	Testosterone
Inatt Sx	-.21**	-.11	-.19**	-.02	-.07
Hyper Sx	-.20**	-.09	-.19**	-.16+	-.16*
Cog Probs (T)	-.08	.03	-.09	.14	-.02
Hyper (T)	-.09	-.01	-.06	.16+	-.17+
Cog Probs (P)	-.11	-.05	-.12	.13	-.12
Hyper (P)	-.16*	-.11	-.14*	-.01	.08
ODD sx	-.14	-.08	-.08	.01	.03
CD sx	.03	.03	-.04	.11	-.06
Consc	.22**	.07	.17*	-.01	.05
Rx Cont	.15*	.03	.23**	.26**	.14+
SSRT	-.02	-.13	-.13	.09	.13
SD	-.10	-.01	-.10	.07	-.09
Trails B	-.02	.01	-.08	.07	.05

Note. +$p<.10$. *$p<.05$. **$p<.01$. Inatt Sx= Inattentive symptoms. Hyper Sx=Hyperactive-impulsive symptoms. Cog Probs (T)=teacher-rated Cognitive Problems. Hyper (T)=teacher-rated Hyperactivity. Cog Probs (P)=parent-rated cognitive problems. Hyper (P)=parent-rated hyperactivity. ODD Sx=Oppositional-Defiant symptoms. CD Sx=Conduct Disorder symptoms. Consc=Conscientiousness. Rx Cont=Reactive Control. SSRT=Response Inhibition. SD=Response Variability. Trails B=Set-Shifting.

Overall, finger-length ratios showed expected sex differences, supporting the validity of the supposition that the ratios are indexing prenatal testosterone exposure and providing a minimal necessary condition for proceeding to the main analyses. Significant

sex differences were apparent for trait, but not EF, measures, also consistent with the literature. In addition, correlational analyses in the combined group of boys and girls provide preliminary support and justification for formally testing the hypothesized mediation analyses, which now follow.

Question 1: Do levels of prenatal testosterone as inferred from right 2D:4D predict (a) more inattentive symptoms and (b) more impaired EF or conscientiousness in boys?

In boys, lower (i.e., more masculine) right 2D:4D predicted more inattentive symptoms (β=-.23, z=-2.70, R^2=.05, p<.01), controlling for ethnicity (covaried in all subsequent analyses involving finger-length ratios). Lower right 2D:4D also significantly predicted less conscientiousness (β=.25, z=3.20, R^2=.08, p<.01). Right 2D:4D was not significantly related to response inhibition (β=-.06, z=-.44, R^2=.004, p>.05). Low conscientiousness significantly predicted inattentive symptoms (β=-.70, z=-11.74, R^2=.48, p<.01), while poor response inhibition only marginally predicted inattentive symptoms (β=.23, z=3.64, R^2=.05, p<.05).

Right 2D:4D was marginally related to reactive control (β=.19, z=-2.46, R^2=.06, p<.05) and hyperactive-impulsive ADHD symptoms (β=-.20, z=-2.29, R^2=.06, p<.05). Right 2D:4D was not significantly related to ODD or CD symptoms (β=-.16, z=-1.66, R^2=.04 for ODD symptoms; β=.04, z=.64, R^2=.01; both p>.05).

For completeness, results were checked in the full sample (boys and girls combined; without covarying sex), with the same results, as follows. Lower right 2D:4D again predicted more inattentive symptoms (β=-.21, z=-3.26, R^2=.05, p<.01) and less

conscientiousness (β=.22, z=3.76, R^2=.05, p<.01).[5] Right 2D:4D was again not significantly related to response inhibition (β=-.04, z=-.43, R^2=.002, p>.05). Low conscientiousness significantly predicted inattentive symptoms (β=-.74, z=-19.73, R^2=.55, p<.01), while poor response inhibition was a marginal predictor of inattentive symptoms (β=.25, z=4.43, R^2=.06, p<.05).

In the full group, lower right 2D:4D was marginally related to less reactive control (β=.16, z=2.46, R^2=.02, p<.05) and significantly related to more hyperactive-impulsive symptoms (β=-.19, z=-2.82, R^2=.04, p<.01). Right 2D:4D was not significantly related to ODD (β=-.15, z=-1.79, R^2=.03, p>.05) or CD symptoms (β=.02, z=.29, R^2=.01, p>.05).

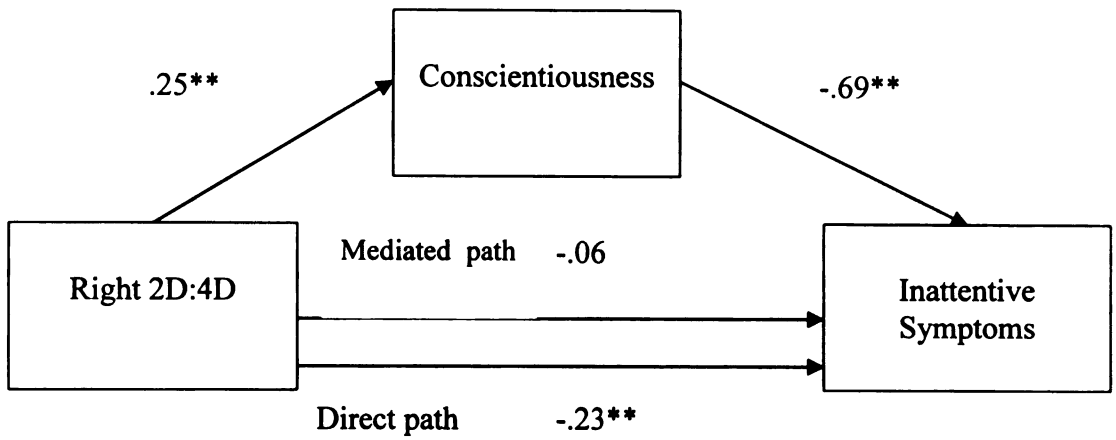
In summary, conscientiousness, but not EF, emerged as a possible mediator of prenatal testosterone effects on inattentive ADHD symptoms, because it was related to both ADHD symptom and right 2D:4D. This was next tested formally.

Question 2: Does low conscientiousness mediate the relationship between prenatal levels of testosterone and inattentive ADHD symptoms in boys?

Since response inhibition was not significantly related to right 2D:4D it could not be a mediator based on the traditional Baron and Kenny (1986) prerequisites. Therefore, only conscientiousness was examined as a mediator between right 2D:4D and ADHD. Within boys, when right 2D:4D and conscientiousness were both entered as predictors of inattentive symptoms, right 2D:4D no longer significantly predicted inattentive symptoms (β=-.06, z=-.84, p>.05), but conscientiousness remained a significant predictor

[5] Finger-length ratios, measured by calipers, were not significantly related to inattentive ADHD symptoms (β=-.26, p>.05) or conscientiousness (β=.16, p>.05) in boys and girls, although the direction of effects was the same as for hand scan measurements.

(β=-.69, z=-10.86, R^2 for full model=.49, p<.01). The mediation model was significant (z=2.67, p<.01), according to the Sobel test developed by Preacher and Hayes (2004) and the bootstrapping confidence interval did not contain zero (95% c.i.: -15.35 to -3.01), supporting the mediation model in that the indirect path was significant. Thus, low conscientiousness mediated the relationship between right 2D:4D and inattentive ADHD symptoms in boys (Figure 4).



Note. All paths are identified using standardized coefficients. Conscientiousness was measured by maternal report. Inattentive symptoms were measured using a parent+teacher OR algorithm using DSM-IV symptom criteria. 95% c.i. of mediation effect: -15.35 to -3.01.

Figure 4. Conscientiousness Mediates the Relationship between Prenatal Testosterone and Inattentive ADHD Symptoms in Boys

Again for completeness, the same effects were tested in boys and girls combined. Once again, the same result held: When right 2D:4D and conscientiousness were both entered as predictors of inattentive symptoms, right 2D:4D no longer significantly predicted inattentive symptoms (β=-.05, z=-1.13, p>.05), but conscientiousness remained a significant predictor (β=-.74, z=-19.73, R^2 for full model=.55, p<.01). The mediation

model was significant (z=3.21, p<.01), according to the Sobel test developed by Preacher and Hayes (2004) and the bootstrapping confidence interval did not contain zero (95% c.i.: -13.56 to -3.83), supporting the mediation model shown in Figure 4.

Question 3: Does (a) more adaptive reactive control predict higher or more optimal levels of circulating estradiol and (b) do higher levels of circulating estradiol predict less hyperactive-impulsive ADHD symptoms in girls?

Within girls, higher reactive control did not significantly predict higher circulating levels of estradiol (β=.09, z=.80, R^2=.28, p>.05), and circulating estradiol did not significantly predict hyperactive-impulsive ADHD symptoms (β=.17, z=1.23, R^2=.08, p>.05), after controlling for ADHD versus control group differences in age. Lower reactive control significantly predicted more hyperactive-impulsive symptoms (β=-.36, z=-4.20, R^2=.18, p<.01).

In order to explore a possible curvilinear effect between estradiol levels and outcome, a quartile approach was utilized to examine mean differences in hyperactive-impulsive symptoms based on level of circulating estradiol. The first (25%) quartile was comprised of girls with estradiol levels of less than or equal to 16.60 pc/mL. The second (50%) quartile was comprised of girls with between 16.60 and 31.99 pc/mL of circulating estradiol. The third (75%) quartile was comprised of girls with between 31.99 and 78.00 pc/mL of circulating estradiol. The fourth quartile was comprised of girls with over 78.00 pc/mL of circulating estradiol. These four groups were compared via MANCOVA with a quadratic polynomial contrast. Age was covaried, and hyperactive-impulsive symptoms and reactive control were the dependent variables. The MANCOVA was not significant (F[6, 104]=1.36, η^2=.07, p>.05).

Question 4: Does circulating estradiol mediate the relationship between reactive control and hyperactive-impulsive ADHD symptoms in girls?

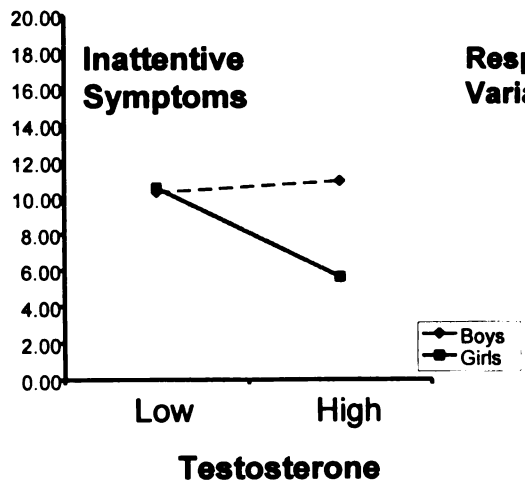
Reactive control did not significantly predict circulating estradiol, and circulating estradiol did not significantly predict hyperactivity-impulsivity. Thus, mediation did not occur as evidenced by these patterns of relations.

Question 5: Do lower ratios of testosterone to estradiol predict (a) less inattentive or hyperactive-impulsive ADHD symptoms and (b) better EF/conscientiousness or reactive control in boys and girls?

In the full group, testosterone and estradiol were correlated weakly and marginally at -.06 ($p<.05$). However, within sex, the correlation was substantial. In boys, testosterone and estradiol were significantly correlated at .51 ($p<.01$). In girls, testosterone and estradiol were significantly correlated at .35 ($p<.01$). Unsurprisingly, testosterone level was substantially correlated with testosterone:estradiol ratio ($r=.88$, $p<.01$). As expected, boys had higher levels of circulating levels of testosterone than girls ($t[163]=6.12$, $p<.01$) and higher ratios of testosterone to estradiol ($t[130]=8.48$, $p<.01$).

Because of the sex differences in circulating testosterone, interactions between sex and testosterone and between sex and the ratio of testosterone to estradiol were examined in regression analyses. Both testosterone and ratios of testosterone to estradiol were examined in order to examine any potential testosterone effects that might be independent of estradiol levels. In these regression analyses, ADHD symptoms, EF, and the two personality traits were each separately regressed on sex, hormones, and the interaction term, controlling for age. A significant interaction between sex and

testosterone was found in predicting inattentive symptoms (β=-.80, p<.01), and a marginal interaction between sex and testosterone was found in predicting response variability (β=-1.89, p<.05). There was a stronger relationship between higher circulating testosterone and fewer inattentive ADHD symptoms in girls (β=-.22, z=-2.80, R^2=.16, p<.01) than in boys (where the relationship was essentially zero; β=.02, z=.13, R^2=.03, p>.05 [shown in Figure 5]). There was also a stronger relationship between higher circulating testosterone and decreased response variability in girls (β=-.53, z=-1.95, R^2=.27, p<.10) than in boys (where the relationship was nearly zero, β=-.08, z=-.42, R^2=.04, p>.05 [shown in Figure 6]). Other interactions were not significant (p>.05).



Note. Inattentive symptoms=teacher+parent rated symptoms defined using OR algorithm.

Figure 5. Higher Levels of Testosterone are Related to Fewer Inattentive ADHD Symptoms in Girls

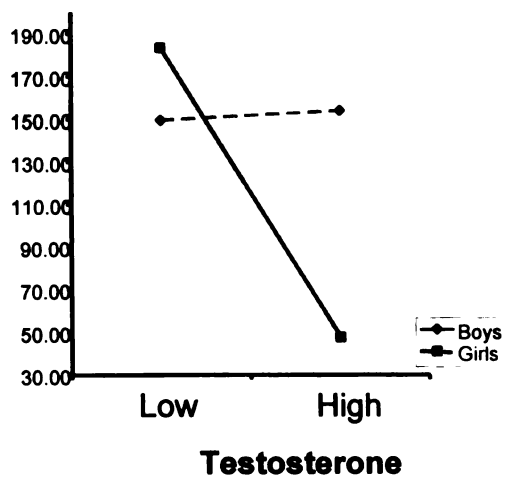
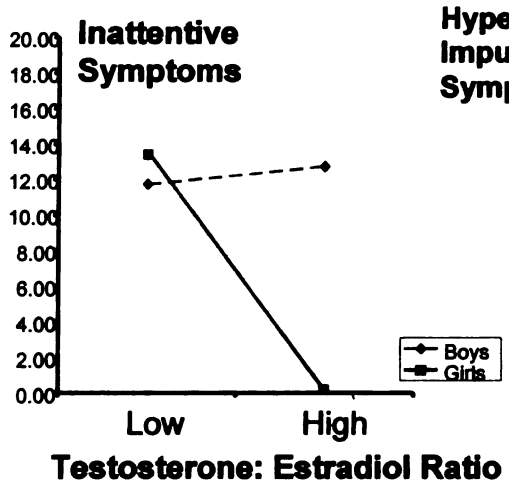


Figure 6. Higher Levels of Testosterone are Related to Less Response Variability in Girls.

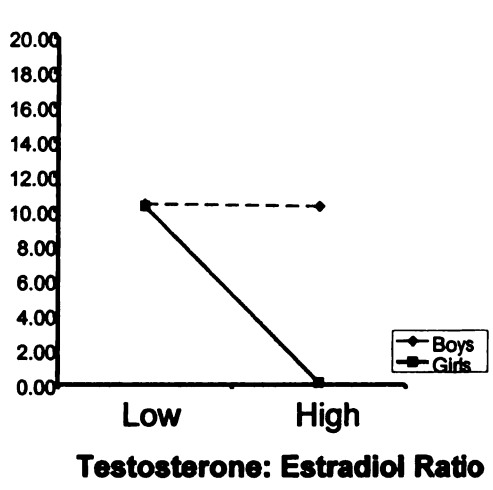
With regard to the ratio of testosterone to estradiol, marginal interactions by sex

were found for inattentive symptoms, hyperactive-impulsive symptoms, and conscientiousness (all $p<.05$). For girls, there was a significant relationship between testosterone:estradiol (T:E) ratios and inattentive symptoms ($\beta=-.43$, $z=-4.36$, $R^2=.28$, $p<.01$) such that more testosterone relative to estradiol (i.e., larger ratios) predicted fewer symptoms (shown in Figure 7); for boys, this relationship was slightly negative, but not nearly significant ($\beta=-.05$, $z=-.37$, $R^2=.03$, $p>.05$). Girls also exhibited a stronger relationship between T:E ratios and hyperactive-impulsive symptoms ($\beta=-.40$, $z=-4.22$, $R^2=.20$, $p<.01$) than did boys (where the relation was slightly negative but not significant; $\beta=-.13$, $z=-.93$, $R^2=.12$, $p>.05$) such that more testosterone relative to estradiol (i.e., larger ratios) was related to decreased hyperactive-impulsive symptoms (shown in Figure 8).



Note. Inattentive symptoms=teacher+parent rated symptoms defined using OR algorithm. Low ratios=more estradiol relative to testosterone. High ratios=more testosterone relative to estradiol.

Figure 7. High Testosterone:Estradiol Ratios are Related to Fewer Inattentive ADHD Symptoms in Girls

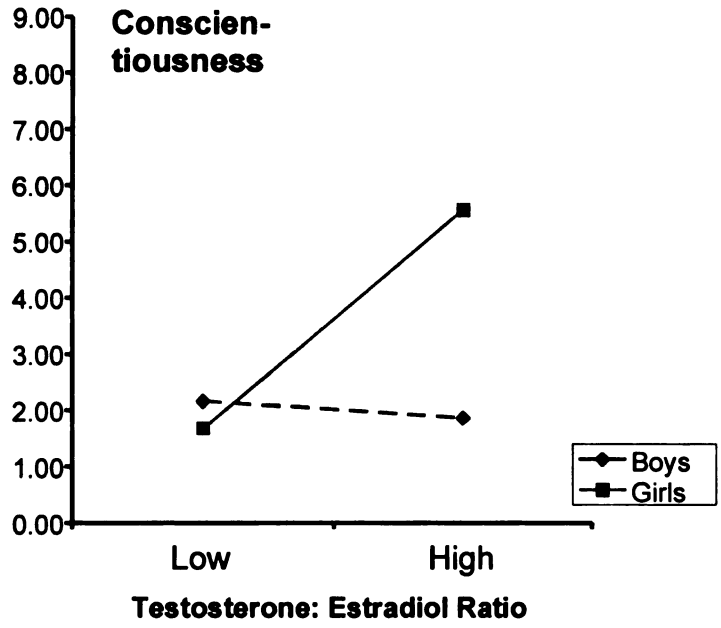


Note. Hyperactive-impulsive symptoms=teacher+parent rated symptoms defined using OR algorithm. Low ratios=more estradiol relative to testosterone. High ratios=more testosterone relative to estradiol.

Figure 8. High Testosterone:Estradiol Ratios are Related to Fewer Hyperactive-Impulsive ADHD Symptoms in Girls

Likewise, girls exhibited a stronger relationship between high T:E ratios and conscientiousness (which is inversely related to inattention; β=.26, z=2.22, R^2=.15, p<.05) than did boys (β=.01, z=.07, R^2=.04, p>.05) such that more testosterone relative to estradiol (i.e., larger ratios) was related to increased conscientiousness (shown in Figure 9). No other interactions (in regard to ADHD symptom domains, ODD symptoms, CD symptoms, or other traits or EF) were significant (all p>.05). Overall, it appeared that high levels of testosterone and high levels of testosterone relative to estradiol were protective for girls in regard to ADHD symptoms, response variability, and conscientiousness.

conscientiousness.



Note. Low ratios=more estradiol relative to testosterone. High ratios=more testosterone relative to estradiol.

Figure 9. High Testosterone:Estradiol Ratios are Related to Increased Conscientiousness in Girls

Therefore, three moderated mediation models were tested. Response variability was examined as a mediator of the relationship between circulating testosterone levels and inattentive symptoms in girls. Conscientiousness was examined as a mediator of the relationship between T:E ratios and inattentive symptoms in girls, and conscientiousness was examined as a mediator of the relationship between T:E ratios and hyperactive-impulsive symptoms in girls. Age was covaried in all moderated mediation analyses. In none of the three models did all paths reach significance. Moderated mediation effects were not significant for the relations among circulating testosterone, response variability, and inattentive symptoms (95% c.i.: -4.98 to .002; p=.13). Moderated mediation effects

were also not significant for the relations among T:E ratios, conscientiousness, and inattentive symptoms (95% c.i.: -.17 to .07; p=.25) or for the relations among T:E ratios, conscientiousness, and hyperactive-impulsive symptoms (95% c.i.: -.10 to .02; p=.35). Thus, in none of the models was moderated mediation supported. However, it should be noted that power was low to detect these effects, particularly because they occurred in girls.

DISCUSSION

Hormonal effects are often-touted, but seldom empirically examined, as key factors in childhood psychopathology and in ADHD specifically. The current study examined sex differences in ADHD in relation to mechanisms of top down (i.e., conscientiousness and EF) and bottom up (i.e., reactive) control. It also examined whether these behavioral probes might mediate relations between prenatal as well as circulating hormones and current childhood ADHD symptoms.

Summary of findings

The main four findings were as follows. First, normative sex differences in conscientiousness found in the control group were not evident in children with ADHD, and sex differences in reactive control seen in the ADHD group were not evident in the control group. Second, more masculine finger-length ratios, which are indicative of higher exposure to prenatal testosterone, were related to lower levels of conscientiousness and more inattentive ADHD symptoms in boys. Third, lower conscientiousness mediated the relationship between right 2D:4D and inattentive ADHD symptoms. Fourth, levels of circulating estradiol were not related to reactive control or hyperactivity, after controlling for age. However, increased circulating testosterone was related to less inattentive and hyperactive-impulsive ADHD symptoms in girls.

Overall, results are consistent with study hypotheses that high levels of prenatal testosterone lead to decreased conscientiousness, which in turn increases risk for inattentive symptoms of ADHD. Study hypotheses about circulating estradiol in girls were not supported. Instead, results were consistent with the idea that increased circulating levels of testosterone may provide some protection against ADHD symptoms

in girls. That effect was not hypothesized and so must be replicated. Key findings are now discussed in turn.

Sex Differences in Traits and EF

This was the first study to examine sex differences in traits (i.e., conscientiousness and reactive control) and EF, comparing across control and ADHD groups. Trait sex differences varied between the ADHD and control groups, manifested in significant interactions. While girls had higher levels of conscientiousness than boys within the control group, girls and boys in the ADHD group had comparable, low levels of conscientiousness. The sex difference in conscientiousness found in the control group is in keeping with past research. In childhood, girls typically exhibit higher levels of conscientiousness (i.e., are more planful) than boys (e.g., Else-Quest et al., 2006). These kinds of sex differences may not be due entirely to sex, but rather may be due to prenatal hormonal exposure that occurs in sex-specific patterns.

Sex and diagnostic differences were also noted for reactive control (i.e., reflexive, rather than effortful, regulation). Girls with ADHD had higher levels of reactive control than boys with the disorder, whereas girls and boys within the control group had comparable levels of reactive control. One potential interpretation of this finding is that reactive control serves as a sex-specific phenotype for childhood ADHD. As noted in longitudinal research by the author, boys and girls may arrive at ADHD through different routes (Martel, Lucia, Nigg, & Breslau, 2007). Boys may be at increased risk for ADHD symptoms due to poor motor coordination and increased motor restlessness (Martel et al., 2007). However, higher levels of reactive control may increase risk for ADHD symptoms in girls, potentially interacting with other types of reactive control such as negative

emotionality (Martel & Nigg, 2006). This interpretation would be consistent with the constitutional variability model of ADHD, which states that different causal factors are important for girls and boys (Rhee, Waldman, Hay, & Levy, 2001). Higher levels of reactive control may predispose girls, but not boys, to ADHD.

Although sex differences in traits were apparent, there were no sex differences in EF (i.e., response inhibition, response variability, or set-shifting) across the sample, or within the ADHD or control groups. Furthermore, hormones were not related to EF. This finding raises challenges for the theory of hormonal associations with ADHD mechanisms that was proposed in the current dissertation. One possible revision of the theory might be to acknowledge that EF may not be functioning as a true endophenotype for biological risk factors of ADHD in childhood. A second revision of the theory might propose that hormones may be related to more broad-based alterations of neural function rather than to alterations in the more localized neural circuitry implicated in EF.

EF may be more heavily influenced by socialization and experience than some recent theories have suggested. For example, some aspects of EF, such as response inhibition, may be more sensitive to the influence of parenting and classroom influences than others (e.g., set-shifting). EFs are, in fact, influenced by context characteristics such as time of day and structure of the environment (Antrop, Roeyers, & De Baecke, 2005). Recent research suggests that EF relations with genes, another biological marker, are relatively weak for individual EF measures, but stronger for the shared variance between EF measures (Friedman et al., in press). Another consideration is that EF may be heavily reliant upon frontal-striatal neural circuitry early in development (e.g., between the ages of three and six), but become more routinized and experiential-based during mid-to-late

childhood (e.g., between the ages of six and twelve). Thus, studies examining older children and adolescents may fail to find associations between EF and biological risk factors due to increased environmental influences on EF at later ages.

Hormones may be influencing general indices of brain development, such as rate of fetal growth, cerebral lateralization, and effects on the prefrontal cortex. In this way, they may have an impact on broader measures of behavior such as psychopathology and traits which capture a range of behaviors across numerous settings over a period of time, rather than specific measures of EF which capture a single behavior in a single setting at a single point in time. EF measures may be limited in their ability to tap into more broad-based brain alterations since they measure more localized neural activity. In this way, there may be components of conscientiousness (e.g., broad-based effortful control), unrelated to response inhibition, that are related both to hormones and ADHD. Alternatively, EF may be protected from hormonal influences on the striatum via its interaction with other neural systems that are not as DA-dependent, such as the cerebellum.

Traits and ADHD may be more related than EF and ADHD since measurement of behavioral traits and symptoms are more similar than the measurement of EF and symptoms. Traits may fall on a continuum with psychopathology, as suggested by a spectrum model of trait-psychopathology relations (Watson, Kotov, & Gamez, 2006). If extreme levels of maladaptive trait control predispose individuals to behavioral symptoms of ADHD or entirely overlap with ADHD symptoms, this phenomenon may account for the sex differences found in both domains. Temperament traits and ADHD symptoms may also be related because low levels of trait control predispose individuals

to the development of ADHD. This idea is consistent with a vulnerability model of trait-psychopathology relations (Watson et al., 2006). If traits do, in fact, predispose individuals to the development of psychopathology, traits may be a more proximal index of prenatal hormones than EF. Similarity of measurement of traits and symptoms may also conflate their mutual associations with sex and hormones.

Prenatal Testosterone Effects and ADHD

Lower (i.e., more masculine) finger-length ratios, particularly the right 2D:4D, were related to more inattentive ADHD symptoms. This finding replicates other research studies that have found that more masculine finger-length ratios are related to more externalizing problems and more ADHD symptoms (de Bruin et al., 2006; Fink et al., 2007; McFadden et al., 2005; Stevenson et al., 2007; Williams et al., 2003). Increased prenatal testosterone was related to trait dysregulation more generally, in that it was associated with lower levels of conscientiousness and increased ADHD symptoms. If ADHD is seen as emanating from a trait, rather than influencing the development of a trait, then the data were consistent with the idea that high levels of prenatal testosterone increase risk for low conscientiousness and the subsequent development of inattentive ADHD symptoms. In the current study, more masculine finger-length ratios were related to lower conscientiousness, which mediated the relationship between those ratios and inattentive ADHD symptoms in boys.

Exposure to prenatal testosterone, rather than male sex per se, was associated with ADHD and some forms of trait dysregulation. Current results are consistent with the idea that higher prenatal testosterone exposure increases inattention and does so via its association with conscientiousness in childhood. Children (i.e., both boys and girls) with

ADHD had more masculine finger-length ratios and lower levels of conscientiousness than children in the control group. In contrast, girls in the control group were characterized by higher levels of conscientiousness than boys in the control group and also had higher (i.e., more feminine) finger-length ratios.

Circulating Hormonal Effects and ADHD

Circulating estradiol did not appear to be related to fewer ADHD symptoms in girls via an association with reactive control, contrary to study hypotheses. Contrary to the theory proposed in this dissertation, circulating estradiol does not appear to be related to inattentive ADHD symptoms, hyperactive-impulsive ADHD symptoms or reactive control. Estradiol does not appear to have an effect on the nucleus accumbens or on the forms of reactive control that rely on this region of the brain. However, future research might examine effects of circulating estradiol on ADHD symptoms without controlling for age. It is likely that important variance in estradiol due to age and pubertal status was eliminated when controlling for age differences between the ADHD and control groups. Future research might examine estradiol-ADHD relations in a sample of children matched on age so as to assess whether hyperactive-impulsive ADHD symptoms improve over time due to age-related increases in estradiol.

Results indicated that ratios between testosterone and estradiol and/or circulating levels of testosterone were associated with ADHD in girls. Higher levels of testosterone were associated with fewer ADHD symptoms of inattention and hyperactivity-impulsivity in girls. This finding was unexpected and needs replication. However, if this finding was replicated, one possible explanation is that circulating testosterone levels counterbalance circulating estradiol levels.

However, an alternative explanation is that circulating testosterone levels are related to fewer symptoms in girls through another, currently unknown, protective mechanism. For example, protective effects of circulating testosterone may be seen in girls but not boys due to the fact that an optimal level of testosterone is related to decreased ADHD symptoms. Since girls have lower levels of testosterone than boys, an optimal effect may be more detectable in girls than in boys. A future study might address this point by examining curvilinear effects between testosterone and ADHD symptoms in a larger sample of girls across a wide range of ages.

Alternatively, the organizational effects of prenatal testosterone exposure in boys may make them less sensitive to circulating testosterone levels than girls. Circulating levels of testosterone in girls may have activational effects on the expression of ADHD symptoms in childhood, potentially via neurosteriod interactions with dopaminergic neurotransmission. The examination of circulating testosterone-ADHD relations in girls with congenital adrenal hyperplasia (CAH), a condition in which girls are exposed to high levels of prenatal androgens, would allow for the examination of organizational effects of testosterone in girls. If boys' insensitivity to circulating testosterone is due to the organizational effects of androgens, circulating levels of testosterone would not be protective for ADHD in girls with CAH. It should be noted that the relationship between testosterone and ADHD found in girls in this study was not hypothesized and requires replication.

Implications for Neural Development and Pathways to Developmental Psychopathology

Although these data are cross-sectional (and one could argue that ADHD influences conscientiousness rather than the other way around), the developmental

implications are still interesting. Prenatal testosterone exposure may influence the development of dopaminergic neural circuitry both during the prenatal period and throughout childhood. Differences in such neural circuitry and decreased extracellular DA may then predispose an individual toward certain behavioral tendencies that are first manifest in characteristic traits, beginning around 18 months of life and consolidating around age three or four (Aksan & Kochanska, 2004; Zuckerman, 2005). The characteristic trait of low control may begin to seem developmentally inappropriate and dysfunctional around six or seven years of age, since at this age children begin school and are expected to use trait and behavioral control to remain seated and listen to their teachers. At this stage of development, low levels of trait control may be manifest in behavioral syndromes like ADHD. This idea could be in line with a vulnerability (i.e., certain traits increase the likelihood of psychopathology), common cause (i.e, traits and psychopathology have a common cause), or spectrum (i.e., traits and psychopathology fall on a continuum) model of personality/temperament trait to psychopathology relations (Caspi & Shiner, in press; Watson et al., 2006).

However, as recent dual-pathway (Sonuga-Barke, 2005) or multi-pathway (Nigg, Goldsmith, & Sachek, 2004; Nigg, 2006) models suggest, there are likely multiple routes to the development of ADHD. In the instance of ADHD, prenatal androgen may influence the development of dopaminergic circuitry underpinning trait control, resulting in the precursors of low conscientiousness (e.g., low effortful control), occurring more often in boys. Low effortful control/conscientiousness may then emerge around the age of three or four years (Aksan & Kochanska, 2004) and eventually lead to behavioral symptoms of inattention. These symptoms may become most evident when the child

(most often, a boy) becomes old enough to begin attending school, although it should be noted that recent research indicates that ADHD can be reliably diagnosed as young as four years old (Lahey et al., 2005). Optimal levels of circulating testosterone and T:E ratios, rather than estradiol, may provide some protection against the further development of symptoms later in childhood in girls, potentially via neurosteriod interactions with DA neurotransmission in the frontal-striatal region of the brain.

More generally, hormones have implications for risk and protective factors for many disorders, including male-biased, childhood-onset, externalizing disorders and female-biased, adolescent-onset, internalizing disorders. However the present research suggests these effects will not be easy to find. There was no effect on EF, which weakens our ability to use hormones to explain ADHD-related phenomena. However, there were effects on traits, which is encouraging as a preliminary step to mapping these associations to the development of childhood ADHD. Prenatal and circulating hormonal mechanisms have the potential to illuminate the complex biological risk pathways that predispose individuals to developing ADHD in early childhood. Hormonal associations with childhood psychopathology also have the potential to illuminate mechanisms of sex differences in trait and cognitive correlates of psychopathology, as well as sex-biased prevalence rates favoring boys in childhood.

Limitations

The current study had several limitations. Because the design was cross-sectional and non-experimental, causality cannot be addressed (and, in fact, as was noted in passing, ADHD may be leading to lower conscientiousness rather than the other way around). The study had a relatively small sample of girls with available measures of

circulating estradiol and testosterone. If a larger sample had been available, mediation analyses might have been more conclusive. Additionally, it would have been informative to examine hormone-psychopathology relations in pre and post-menses girls separately, as well as to examine relations across the phases of the menstrual cycle. Sample size was too small to allow this kind of analysis in the current study.

The current study did not correct for item or conceptual overlap between traits and ADHD symptom counts since the integrity of trait and ADHD symptom scales were judged to be essential to the current work. Further, the prior work of the author indicated that the effects of item overlap are often modest (Martel & Nigg, 2006). In addition, multiple measures of temperament traits were not available. Future work might examine observational measures of traits in addition to parental report on rating forms. Finally, finger lengths and ratios were measured using photocopies and rulers. Questions about the reliability and validity of this measure remain. Analyses conducted on finger-length ratios measured via calipers utilized a sample that was too small to yield reliable findings. However, the effects of the caliper analyses were in the same direction as those conducted using hand scan measurements, providing some support for the validity of the hand scan approach to finger-length measurement. Future work might examine correlations between finger-length ratios, measured via photocopies/rulers and calipers, and actual prenatal testosterone exposure.

Summary

Overall, sex differences in key traits relevant to ADHD are apparent. Prenatal testosterone was related to inattentive symptoms of ADHD in boys, and this relationship was mediated statistically by low levels of conscientiousness. Circulating estradiol was

not related to reactive control or hyperactive-impulsive symptoms of ADHD. Higher levels of testosterone may protect against ADHD symptoms in girls, but this unexpected finding needs replication. Gonadal hormones appear to be related to ADHD, but the nature of these effects will require the continuing revision of theory. Broadly, gonadal hormones appear to increase general risk and protective factors for ADHD, potentially acting through trait mechanisms.

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