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Comparison of Children With and Without ADHD on Measures of Neurocognitive Ability and Androgen Exposure.

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Comparison of Children With and Without ADHD on Measures of Neurocognitive Ability and Androgen Exposure.

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Dedication

This work is dedicated to my family, friends, and teachers who have touched my life and made it a joy.

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Boys with Attention-Deficit/Hyperactivity Disorder (ADHD) were recruited from a local neuropsychology office with controls recruited from the community to assess the relationship between prenatal androgen exposure and ADHD, as well as the possible cognitive correlates of this exposure. Putative physiological markers of prenatal androgen exposure that were measured for each child included several types of otoacoustic emissions (OAEs) as well as finger-length ratios (FLRs). Neurocognitive measures included tasks which assessed components of attention, general intelligence, reading ability, and visuospatial skills. Several other variables which may also be

related to androgen exposure were included (e.g., sleep disturbance, handedness, number of older brothers) in the analyses. Children ranged in age from 7 to 12 years old with 13 controls, 19 children with ADHD/Combined Type (ADHD/C), 10 with ADHD/Inattentive Type (ADHD/IA), and an additional 11 children with ADHD/IA who were rated by their parents as having relatively high levels of an experimental construct (sluggish cognitive tempo; SCT). Because more boys than girls are diagnosed with ADHD, it was hypothesized that ADHD may be associated with prenatal masculinizing hormones (i.e., androgens), and that children with ADHD would appear more masculine on markers of androgen exposure (OAEs and FLRs) than controls. However, in our current study children with ADHD did not differ from controls on these measures. There was some evidence that children with SCT may represent a more homogenous group of children within the ADHD/IA diagnostic group, and that they may share a deficit in alerting attention. Consistent with theories suggesting subtype differences in attention, children with ADHD/C did not appear to have a deficit in alerting attention, but rather appeared more cognitively impulsive and to have a deficit in auditory attention. Children with SCT were more likely to be rated by their parents as having disrupted sleep.

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Chapter 1: Introduction to Current Study

Attention deficit hyperactivity disorder (ADHD) is the most commonly diagnosed psychiatric disorder of childhood. It is a highly heterogeneous disorder with multiple sub-types, high comorbidity with other disorders, and a variety of associated impairments that affect functioning in multiple domains. Research indicates the existence of two primary symptom domains of inattention and hyperactivity/impulsivity, giving rise to three subtypes recognized by the Diagnostic and Statistical Manual (DSM)-IV (APA, 1994). Children with the diagnosis of ADHD combined type (ADHD/C) have clinically significant impairments in both symptom clusters. This subtype has been associated with deficits in behavioral inhibition (Barkley, 1997) that consequently have an adverse impact on executive functioning (i.e., planning, organizing, self-regulation, and working memory). Most research has focused on ADHD/C, while children displaying significant levels of inattention in the absence of clinically elevated hyperactivity/impulsivity, the primarily inattentive subtype (ADHD/IA), and those with ADHD with only symptoms of hyperactivity/impulsivity (ADHD/HI), have received much less attention.

Research supporting subtype distinctions is based on differences in associated features such as comorbidity patterns, academic and social impairment, age of onset, and sex differences in prevalence (Milich, Balentine, & Lynam, 2001). Enough differences exist that it has been proposed that the ADHD/IA subtype actually represents a distinct disorder rather than a subtype within the broader diagnosis of ADHD (Milich, Balentine, and Lynam, 2001; Barkley, 1997). Nonetheless, data

establishing distinct etiological pathways between the subtypes do not currently exist, and few neuropsychological tests have been found that reliably discriminate between subtypes despite theorized differences in neurocognitive mechanisms.

Because a sex difference in prevalence exists in ADHD, an exploration of androgenic mechanisms that may contribute to ADHD expression could provide further understanding of subtype etiology and presentation. A previous study (McFadden, Westhafer, Pasanen, Carlson, & Tucker, 2005), discovered a potential link between early androgen exposure and ADHD among boys with the Inattentive subtype, as indicated by large group differences in two hypothesized physiological markers of prenatal androgen exposure: otoacoustic emissions (OAEs) and finger length ratios (FLRs). This pattern was not detected among the male ADHD/C group, suggesting a unique etiological pathway for the ADHD/IA group that has not been previously explored.

Current Study

The aim of the current study was to further elucidate the role that abnormal prenatal exposure to androgens may play in the expression of ADHD by comparing children with ADHD/C, ADHD/IA, and controls on previously measured physiological variables (OAEs, FLRs) along with measures of neurocognitive ability and additional tasks sensitive to androgen exposure. Children with ADHD between the ages of 7-12 were recruited from a local neurological clinic (Austin Neurological Clinic) to participate in this study. Control children were recruited from a local community website and by word-of-mouth. In addition to obtaining OAEs and FLRs, sex-linked

disorders and cognitive functions that are believed to be hormone mediated rather than chromosome mediated (i.e., sleep disorders, spatial ability, conduct disorder), and neurocognitive measures (e.g., the Stop-Signal task, a measure of impulsivity) that have been reported to distinguish between ADHD subtypes were assessed. It was hoped that comparing groups on these measures would further explicate the role androgen exposure may play in the expression of ADHD. In addition, establishing physiological measures that reliably distinguish between children with ADHD and controls, or between subtypes, could aid diagnostic and nosological understanding and have implications for prevention and treatment.

Outline of this Document

Chapter 2 presents an overview of ADHD, including a history of the diagnosis, associated features, etiological factors, and symptom domains, including the potential role of Sluggish Cognitive Tempo (SCT) in refining the subtype distinction. Chapter 3 provides a discussion of potentially related disorders and correlates of prenatal androgen exposure. Chapter 4 is a statement of the rationale and hypotheses for the current study. Chapter 5 presents the methodology employed in this study. Chapter 6 presents the hypotheses. Chapter 7 presents data analyses and results, and Chapter 8 provides a discussion of the study findings.

Chapter 2: Overview of ADHD and Associated Features

Attention Deficit Hyperactivity Disorder (ADHD) affects approximately 3 to 7% of school age children between the ages of 5 and 11, with characteristic core symptoms of impulsivity, hyperactivity, and inattention (Willcutt, Lahey, Pennington, Carlson, & Nigg, in submission, Barkley, 1997, APA, 1994). Estimates of the ratio of boys to girls with ADHD range from 9:1 to 6:1 among clinic-based samples, and between 2:1 and 3:1 in population-based samples (DSM-IV-TR, 2000). While this disparity between sexes exists for both the ADHD/C and ADHD/IA subtypes, the sex difference is not as great within the ADHD/IA subtype (Gaub & Carlson, 1997). Symptoms of inattention, hyperactivity, and impulsivity are manifested in social, academic, and occupational domains. Symptoms typical of inattention are failure to give close attention to detail, sloppiness, making careless mistakes, difficulty sustaining attention or persisting on a task, and the appearance of not listening, or of a wandering mind. Characteristic symptoms of hyperactivity are fidgeting or squirming while seated, difficulty in playing quietly, excessive talking, and inappropriate running or climbing. Impulsivity in children with ADHD is characterized by impatience, difficulty waiting in line, blurting out answers to questions, and interrupting or intruding upon others. Cluster analyses indicate that ADHD symptoms are best accounted for by grouping symptoms of hyperactivity and impulsivity into one cluster with deficits in attention forming a second cluster. Currently, the DSM-IV recognizes 3 subtypes of ADHD based upon these clusters: individuals with primarily hyperactive/impulsive

symptoms (ADHD/HI), with primarily inattentive symptoms (ADHD/IA), and with combined hyperactive/impulsive and inattentive symptoms (ADHD/C) (APA, 1994). Because the ADHD/HI subtype has received comparatively little study and its status as a valid subtype of ADHD remains controversial (Barkley, 1998), it was not considered for exploration in this study. Diagnostic criteria are met when a child has evidenced six or more of the nine possible symptoms in both clusters (ADHD/C), or only within the inattentive cluster (ADHD/IA) or only within the hyperactive/impulsive cluster (ADHD/HI). In addition to meeting symptom requirements, ADHD diagnostic criteria require that children must show persistent difficulties of inattention and/or hyperactivity/impulsivity before the age of 7 that occur in at least two settings (typically home and school), and that interfere with development of social or academic functioning. Symptoms typically worsen in situations requiring mental effort, sustained attention, or those that lack novelty or intrinsic appeal. Approximately 70-80% of children diagnosed with ADHD will continue to show dysfunction related to the disorder throughout their lifespan (Barkley, 1998).

Historical Description

Early conceptualizations of ADHD clearly included hyperactive motor activity as the hallmark characteristic of the disorder [for example, the DSM-II (APA, 1968) only provided for hyperactivity]. However, with the publication of the DSM-III (APA, 1980), the perceived core dysfunction of ADHD shifted to attention processes, and the disorder was labeled Attention Deficit Disorder (ADD). At that time the DSM-III also recognized two separate subtypes based on the presence or absence of hyperactivity,

labeled ADD with hyperactivity (ADD/H) and ADD without hyperactivity (ADD/WO), respectively. With the publication of the DSM-III-R (APA, 1987) came a return to a unidimensional category, relabeled Attention Deficit Hyperactivity Disorder, and again was a core feature. However, accumulating research demonstrated that the disorder was best conceptualized as multidimensional in nature, so the DSM-IV reintroduced subtypes within ADHD. Despite early research (Carlson, Lahey, & Neeper, 1986) indicating a cluster of symptoms of "sluggish cognitive tempo" (SCT) among a significant proportion of children with ADHD/IA, potentially indicative of a contrast in the expression of inattention between subtypes, this cluster was not included in the final diagnostic criteria of the DSM-IV. Further analyses of the expression of these symptoms may provide a means of clearly defining specific subtype deficits in attention, or even indicate the presence of a second inattentive subtype within ADHD (Carlson & Mann, 2002).

Etiological Model for ADHD/C

Substantial documentation for the role of biological factors in the etiology of ADHD can be found in studies examining genetics, neurological dysfunction, and physiology (see Wilens, Biederman, & Spencer for review, 2002). For example, high heritability estimates (approximately h^2=0.75) from twin and adoption studies suggest a strong genetic component (Willcutt, in submission), with recent studies using molecular genetic techniques identifying aberrations in genes that control the transport of dopamine (DAT1; Waldman et al., 1998) and dopamine receptors (DRD4; Swanson et al., 2000). In another line of work (Durston et. al. 2004), children with ADHD were

found to have overall volumetric reductions in white and grey matter, and diminished right cerebellar volume not found in their siblings or controls. Non-disordered siblings of children with ADHD had some similar morphological differences that were not found in controls, including significant decrements in right prefrontal grey matter, plus diminished grey matter and up to 9.1% diminished white matter in the left occipital lobe. These neurological differences eventually may help to elucidate both the role of specific biological factors, as well as the role that heritability plays in the expression of ADHD.

Neuropsychological studies have helped to explicate what impact neurological differences have on behavioral and cognitive functioning (e.g., Roth & Saykin, 2004) in this population. Hypotheses of differential neuropsychological functioning have concentrated on the executive functions responsible for goal-directed behavior and the frontal-striatal-thalamic-cortical circuitry associated with these functions. Executive functions are primarily the abilities to create, choose, execute, and continue efficient strategies while inhibiting extraneous information and less efficient strategies (Roodenrys, Koloski, & Grainger, 2001, Schachar & Logan, 1990).

Contemporary models of ADHD/C view attention as a secondary deficit to a more primary deficit, which may best be conceptualized as a deficit in executive processing (Roodenrys, Koloski, & Grainger, 2001). Research demonstrates the utility of this concept in understanding ADHD, with observed deficits in planning and organization (Grodzinsky & Diamond, 1992, Koziol & Stout, 1992), executive processing (Borcherding, Thompson, & Kruesi, 1988), response to attentional demands (Ceci & Tishman, 1984, Sonuga-Barke, Taylor, & Hepinstall, 1992), and performance

on tasks requiring self-regulation (Chee, Logan, Schachar, Lindsay, Wachsmuth, 1989, Schachar & Logan, 1990). Barkley (1997) provided the most comprehensive and widely accepted theory linking the core inhibitory deficit to specific executive functioning deficits in ADHD. Following is a brief overview of his model.

Barkley's core hypothesis is that deficits in behavioral inhibition underlie the perceived deficits in executive function as well as deficits in attentional processes associated with ADHD/C. Behavioral inhibition is believed to be comprised of three interrelated processes: a) stopping an ongoing response, b) interference control, and c) the ability to inhibit a prepotent response. The behavioral inhibition system is considered to be distinct from the executive functions, but they are hierarchically dependent upon inhibition for their operation (Barkley, 1997). The behavioral inhibition system is in greatest use when the individual is confronted with tasks that require temporal delays, the generation of a new response, or resolution of temporally related events. Behavioral inhibition provides the necessary delay between initial input and action allowing executive functions to operate and alter behavioral responses.

Barkley's theory includes the following executive functions: a) working memory, b) self-regulation of arousal/motivation/affect, c) internalization of speech, and d) reconstitution. Working memory serves as a temporary scratch pad that permits results from an earlier response to be held in mind to alter subsequent behavior. This process enables formation of new connections between disparate information and comparison of information to detect error. Self-regulation of arousal/motivation/affect refers to the ability to alter affective states and permits the alteration of arousal or motivational processes to support goal-directed actions. Internalization of speech

permits higher-order processes such as contemplation, depiction, and self-inquiry to control future directed behavior. Proper functioning of the executive functions permits the ability to form rules and plans and to problem- solve. Hierarchical organization and complex behavioral chains result from the formulation of new rules and plans which are made possible by being freed from immediate environmental demands. Reconstitution consists of consideration and construction of behavioral responses within working memory to simulate potential outcomes to hypothesized scenarios.

The impact that deficits in behavioral inhibition have on the executive functions in turn influences motor control, fluency, and syntax, or sequencing behavioral responses. That is, the executive-function deficits will influence the ability to control motor behavior with internally represented information. With well-functioning behavioral inhibition, management of behavior is shifted from the immediate external environment and comes further under the control of self-generated rules and goals based on previously learned behavioral responses. Further, when functioning well, the individual is able to inhibit responses less to relevant stimuli, or to respond to relevant stimuli before resuming the previously planned behaviors.

Noting that differences between the ADHD/C and ADHD/IA subtypes indicate that they may be conceived best as separate disorders (see the following section for more detail), Barkley (1997) explicitly stated that his model only proposed a theoretical framework for the ADHD/C subtype. Many of the hypotheses that result from this theory have been tested and confirmed (Barkley, 1997; Pennington & Ozonoff, 1996), and it is commonly accepted as the most comprehensive and widely discussed theory of ADHD. One of the few neurocognitive studies (Nigg, Blaskey, & Huang-Pollock,

2002) to have supported Barkley's hypothesis of behavioral inhibition was able to demonstrate a specific deficit among children with ADHD/C in inhibiting the ongoing or "prepotent" response to an external cue which was not seen in the ADHD/IA subtype. This finding supported Barkley's view that children with ADHD/C will experience deficits in behavioral inhibition, as well as his hypothesis that there are distinct differences between ADHD/C and ADHD/IA.

ADHD/IA & the Subtype Differences

Considerably less research has explored the ADHD/IA subtype than the ADHD/C subtype. Unlike Barkley's (1997) theory of deficits in behavioral inhibition for the ADHD/C subtype, no comprehensive theory has been put forth to explain the underlying processes leading to the distinct behavioral deficits shown by children displaying inattention in the absence of hyperactive/impulsive symptoms. In part, subtype differentiation is made more difficult by the polytypic nature of ADHD between and within subtypes, and by a lack of sensitivity in neuropsychological measures that could test competing hypotheses.

Behaviorally, individuals with the IA subtype appear more inhibited, hypoactive, internalizing, and sluggish compared to the more energetic, externalizing and disinhibited ADHD/C subtype. The ADHD/IA subtype has been described as socially withdrawn (Maedgen & Carlson, 2000) and passive or behaviorally withdrawn (Hodgens, Cole, & Boldizar, 2000; Baurmeister, Alegra, Bird, Rubio-Stipek, & Canino, 1992; Barkley, 1997). As noted, these disparate behavioral characteristics between subtypes have led researchers to propose that different underlying mechanisms account

for their etiologies (Milich, Balentine, & Lynam, 2001). The following section will further highlight differences between the subtypes, clarify research findings describing the ADHD/IA subtype, and provide potential research guidelines for exploring these factors.

Descriptive Differences

Controversy surrounding the nosology of ADHD continues. The DSM-IV reintroduced subtypes into ADHD diagnoses based on evidence that the two subtypes of interest to this study (ADHD/C and ADHD/IA) have distinct patterns of expression (Barkley, 1997). Supporting evidence came from numerous sources including neuropsychological studies, parent and teacher behavior ratings, and comorbidity differences. Barkley's (1997) theory of ADHD is explicitly instantiated for the Combined subtype only, with Barkley noting distinct differences between the subtypes that would necessitate a separate theory to explain ADHD/IA.

Further confirmation that ADHD is best conceptualized as having at least two distinct clusters, inattention and hyperactivity/impulsivity can be found in factor-analytic studies of ADHD symptomatology (for a summary, see Lahey, Carlson, & Frick, 1997). When additional symptoms from internalizing or externalizing disorders are added to the analyses, these additional items generally load onto separate factors (Pelham, Gnagy, Greenslade, & Milich, 1992; Wolraich, Hanah, Pinnock, Baumgaertel, & Brown, 1996). However, when symptom clusters believed to be more closely related to ADHD symptomatology (including oppositionality and anxiety) were explored by these studies, characteristic subtype patterns of comorbidity were found. Externalizing

behavior problems such as oppositional behavior were found more commonly among children with ADHD/C, while internalizing symptoms such as anxiety and withdrawal were more common among children with ADHD/IA (Carlson & Mann, 2002). These results support the validity of the two subtypes, and confirm the utility of the inattentive and hyperactive/impulsive clusters. When experimental items such as sluggishness and forgetfulness that purportedly reflect the symptoms of the inattentive subtype are included in analyses, mixed results have been obtained (Lahey, Pelham, & Shaughenacy, 1988; Baurmeister, Alegra, Bird, Rubio-Stipek, & Camino, 1992; Carlson & Mann, 2000). Although items exploring these symptoms (now known as sluggish cognitive tempo, or SCT) were included in DSM-IV field trials, they were dropped from the final symptom criteria list for the DSM-IV in order to provide an identical list of inattention symptoms for all subtypes (Lahey, Applegate, & McBurnett, 1994). The implications of this potential third factor (SCT) for discriminating between the subtypes, and for understanding the ADHD/IA subtype in particular, will be discussed later in this section.

Comorbidity

While overall comorbidity rates for other DSM-IV recognized disorders among ADHD subtypes are estimated to be about 68% (Jensen, Martin, & Cantwell, 1997), there are significant differences between the subtypes in rates of comorbid disorders. Children with ADHD/C receive more comorbid diagnoses of externalizing problems including Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) than

children with ADHD/IA (Eiraldi, Power, Nezu, & Maguth, 1997), and children with ADHD/IA receive more internalizing (e.g., anxiety, depression) diagnoses.

Numerous studies have investigated the rates of comorbidity of ADHD and Learning Disabilities (LD) with inconclusive results. While both subtypes experience greater academic difficulties including being held back, and earlier drop-out rates (Barkley, 1998), a number of studies have indicated that the inattentive type is at greater risk for failure in mathematics (Marshall, Hynd, Handwerk, & Hall, 1997; Carlson, Lahey, & Neeper, 1986). A proposed hypothesis (Marshall et al., 1997) to explain this difference is that the attention deficit in the ADHD/IA group may interfere with the ability to process required abstract symbol systems. When symptom clusters are analyzed, inattentive symptoms predict greater academic failure, while hyperactive and externalizing symptoms show little or no relation to academic success (Swanson et al., 2000, Chhabildas, Pennington, & Willcutt, 2001). Further, across subtypes, inattentive symptoms as a whole are more highly correlated with academic impairment than are hyperactive or impulsive symptoms (Gaub & Carlson, 1997).

Neurocognitive Differences

Distinguishing between the subtypes of ADHD using neurocognitive measures has been difficult. Barkley (1997) highlighted the subtype differences by proposing inattention and disorganization as the primary deficits within the ADHD/IA subtype, while other researchers have emphasized more specific executive-function deficits such as deficits in set-shifting, planning, and interference control (Pennington & Ozonoff, 1996; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). While conclusive etiological

evidence of the deficits seen in ADHD/IA is unavailable, some support for these proposed mechanisms has been found. It appears that the inattentive behaviors seen in children with ADHD/IA arise from difficulty in shifting set, overall arousal, and a deficit in processing speed that may be due to difficulties with automatized processes (Milich, Balentine, Lynam, 2001). In an early study comparing children with DSM-III diagnoses of Attention Deficit Disorder/Without Hyperactivity (ADD/WO) and Attention Deficit Disorder/With Hyperactivity (ADD/H), the ADD/WO group performed more slowly on a measure that assesses automatized processes involved in confrontation naming (Hynd, Lorys, & Semrud-Clikeman,1991). This task requires rapid alternating naming (for example, identifying alternating colors or letters) and rapid alternating stimulus naming (for example, identifying alternating colors and letters). Slower latencies among the ADD/WO group were purported to be deficits in automatized processing. A second study comparing children diagnosed using DSM-IV criteria for ADHD/C and ADHD/IA found that children with ADHD/IA did not show evidence of a deficit in behavioral inhibition as seen in the ADHD/C group (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). This study found that these difficulties in set-shifting appeared on a task requiring alternation between numeric and alphabetic stimuli (the Trail-making task from the Halstead-Reitan battery). Overall, the ADHD/IA group evidenced difficulty with shifting set and in naming speed on the Stroop Task.

Diagnostic Issues and SCT

While symptoms of hyperactivity and impulsivity appear to diminish somewhat over the lifespan, inattention appears to persist at a more stable level (Barkley, 1997). Currently, it is possible for a child to meet DSM-IV diagnostic criteria for ADHD/C and later in life, as hyperactive/impulsive symptoms diminish, to be diagnosed as ADHD/IA. DSM-IV diagnostic criteria require the presence of six or greater inattentive symptoms to be endorsed while having as many as five hyperactive/impulsive symptoms, easily allowing a child with diminishing hyperactive/impulsive symptoms to be reclassified as ADHD/IA. The question of whether these individuals should be placed in the same research groups as children who have never met criteria for ADHD/C is critical, and remains unaddressed. It is possible that these children have the cognitive deficits seen in ADHD/C and not those observed in ADHD/IA, and would thus be inappropriately assigned to the ADHD/IA group. Inclusion of these children into ADHD/IA groups may account for some of the difficulties experienced in subtype differentiation and clarification of ADHD/IA symptomatology. Further, with the apparent heterogeneity of the inattentive group (Carlson & Mann, 2000; Milich, Balentine, & Lynam, 2001) with regards to degree of HI symptom levels, studies may identify more homogenous subtypes by including only "pure" cases in the inattentive group. That would potentially entail inclusion in the inattentive group only those children showing fewer (e.g., three or fewer) of the hyperactive/impulsive symptoms. Application of this classification process in a recent study resulted in the recognition of distinct subtype differences in attention at the neurocognitive level (Booth, Carlson, & Tucker, 2007).

Another diagnostic issue that may have obscured potential differences between the subtypes is the exclusion of sluggish cognitive tempo (SCT) items from the current DSM. Factor analyses that included relevant items, such as "sluggishness," "drowsiness," and "daydreaming," have found these SCT items to load on a unique factor, separate from the other inattention and hyperactive/impulsive items (Lahey, Pelham, & Stein, 1998; McBurnett, Pfiffner, & Frick, 2001). Similar items had been part of the DSM-IV field trials for ADHD and were found to correlate with ADHD/IA, but they were eliminated from final diagnostic criteria due to poor predictive validity (Frick et al., 1994) plus the decision to maintain a single list of inattentive symptoms.

While the concept of SCT remains controversial in the ADHD literature (Todd, Rasmussen, Wood, Levy, & Hay, 2003), some research suggests that this symptom dimension may lead to refinement of the current ADHD/IA classification. When the ADHD/IA group from a large population was divided into those children with high SCT and those with low SCT (based on teacher ratings), several interesting differences were noted (Carlson & Mann, 2002). Children with ADHD/IA rated as high in SCT were also rated higher on internalizing problems and lower on externalizing problems than the ADHD/IA with low-SCT and ADHD/C groups. The low-SCT group had a pattern of fewer internalizing and greater externalizing problems than the ADHD/IA high-SCT group that was similar to, but demonstrated less absolute impairment than, the ADHD/C group. The authors noted that the similarity between the low-SCT and ADHD/C groups on these measures suggested that the ADHD/IA low-SCT group may actually represent subthreshold cases of ADHD/C. This identification of a more homogenous subgroup within the ADHD/IA subtype that is characterized by sluggish cognitive processes and

greater internalizing problems provides further evidence that these symptoms may aid in identifying a "true" inattentive group. Overall, these studies demonstrate the heterogeneity of the inattention symptoms, and suggest that these findings need to be corroborated and expanded to include a greater analysis of SCT and its accompanying neurocognitive and behavioral profile.

Neuropsychological Task Differentiation

Despite Barkley's (1997) well-articulated theory delineating specific cognitive deficits within the ADHD/C subtype, differentiation of ADHD subtypes on neuropsychological assessments has had mixed results. Numerous factors may serve to obscure these potential differences including poor neuropsychological task sensitivity, heterogeneity within the recognized subtypes, and greater than expected variability of task performance within all subtypes. For example, Klorman, Hazel-Fernandez, and Shaywitz (1999) found that children with ADHD/C committed more non-perseverative errors on the Wisconsin Card Sorting Task (WCST), and solved fewer puzzles and broke more rules when completing the Tower of Hanoi. However, other studies have found no differences between children with ADD/H and ADD/WO on the WCST (Barkley, Grodzinsky, & DuPaul, 1992), and no differences in performance between children with ADHD/C and ADHD/IA on the Tower of London (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). Despite the historical inconsistencies, there are only a few measures that have begun to show promise of confirming the hypothesized neuropsychological differences.

Because of the purported role of inhibition as an underlying deficit in ADHD/C (Barkley, 1997), a number of studies have assessed inhibitory deficits in this group, typically using stop-signal paradigms. The stop-signal or stop task is predicated on a "race" model in which response inhibition depends on competing processes involved in executing or inhibiting a response (Logan, 1994). The inhibitory process is triggered in reaction to feedback that tells the individual to stop or change the current behavior. The first process to finish determines behavioral output, allowing an investigation of the inhibitory processes by varying the timing between stimuli and inhibitory signals. Because the motor inhibition involved relies on an orbito-prefrontal cortex network (Fuster, 1997), it has been hypothesized that measures that tap this process will discriminate between controls and children with hypo-active prefrontal cortices (i.e., the ADHD subtypes). In a meta-analytic study of stop-signal performance among children with ADHD (Oosterlaan, Logan, & Sergeant, 1998), consistent findings of a deficit in inhibitory processes were reported within the ADHD population when compared to controls. While this meta-analysis did not differentiate between subtypes, it has been reported that among a sample of boys with ADHD the stop-signal task has successfully demonstrated a motor inhibition deficit only in boys with ADHD/C (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). The authors interpreted this finding as a deficiency in motor inhibition among boys with ADHD/C, but did not rule out cognitive inhibitory deficits in the ADHD/IA group.

Researchers have further attempted to discern subtype differences with the Trail-Making test of the Halstead-Reitan battery because it requires the use of executive functions and attention, and the ability to shift perceptual set (Spreen & Strauss, 1998). The

first task of the Trail-making test requires the respondent to connect a series of numbers by drawing a continuous line from one to the next in numeric order as fast as possible. This is considered to be a test of sustained attention to an internally generated, over-learned sequence, visual scanning, and motor speed. The second task requires the subject to draw a continuous line that alternates between numeric and alphabetic stimuli (i.e., A-L, 1-13). This task combines the demands of the first task with the ability to alternate between internal representations. By examining both sets of scores, it is possible to measure the ability to alternate between internal processes (i.e., "set-shifting"). Impairment in this process has been implicated in the ADHD/IA subtype, but not the ADHD/C subtype (Pennington & Ozonoff, 1996). A recent examination of executive functioning in ADHD demonstrated a specific difficulty among boys with ADHD/IA in set-shifting using the Trails task (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). These findings argue for a specific deficit for each subtype rather than a general impairment. However, it is likely that each subtype shares many neuropsychological characteristics as well as inattentive behavioral characteristics.

Posner (1980) defined alerting as the ability to achieve and maintain an alert state, an attentional domain believed to be deficient among children with ADHD/IA. A recent study (Booth, Carlson, & Tucker, 2007) assessed processes of attention based on Posner's concept of attentional systems. This study found that children with ADHD/IA showed stronger alerting effects than children with ADHD/C. Namely, when provided with a cue alerting the subject to the upcoming stimuli, children with ADHD/IA were able to make greater use of the cue in responding than were children with ADHD/C. Interestingly, the performance of controls on this measure fell between that of the two

ADHD groups (though without showing a statistically significant difference), further highlighting the performance discrepancy between the ADHD subtypes. The facilitated improvement in alerting experienced by the ADHD/IA group on this measure provides further evidence that vigilance and arousal are deficient in this population. When children with ADHD/IA were categorized as either having a high SCT status or low SCT status, those children with high levels of SCT were found to have greater alerting effects than the pooled ADHD/IA group. This effect was not robust, but does serve to provide support for the SCT construct to identify a more homogeneous subgroup within ADHD/IA.

Chapter 3: Disorders and Correlates of Early Androgen Exposure

Androgens play an important role in the normal development of the male fetus. Male embryos carry an X and a Y chromosome, unlike the female embryo which carries two X chromosomes. During the first trimester of prenatal development, a gene on the Y chromosome (SRY) which is responsible for the development of the embryonic testes is activated. As the testes begin to mature and produce androgens, including testosterone, the body, brain, and behavior of the embryo is masculinized. Androgen levels in the fetus peak between the 10^{th} and 22^{nd} week following conception (Smail et al., 1981), and subsequently decline until hormone levels of male and female infants at birth are nearly identical. A second surge in androgen production is observed at birth and lasts for approximately 20 weeks (Smail et al., 1981), before androgen production again subsides to approximately those levels observed in females. This suggests that sex differences related to hormone exposure in physiological or behavioral traits that are observed between the sixth month of life and before adolescence result from sex differences in androgen exposure experienced in prenatal or early postnatal development.

Preliminary evidence suggests a correlation between ADHD and an abnormal androgenization process that occurs within boys with ADHD/IA (McFadden, Westhafer, Pasanen, Carlson, & Tucker, 2005). This relationship implies an alteration in the prenatal environment that contributes to the expression of inattentive behavior among these children. While a direct causal connection has not been established, the connection between androgenization and ADHD can be explored by examining the connection between ADHD and other physiological, developmental, and cognitive

domains believed to be affected by androgenization. Androgenization plays a clearer role in several disorders [e.g., Reading Disability (RD; Tallal & Fitch, 1993)] as well as cognitive and physiological differences [e.g., handedness; Geschwind & Galaburda, (1985)]. Each of these factors is associated with disproportionate male-female prevalence rates and is believed to be indicative of hyper-androgen exposure. While exact mechanisms of action are unknown, the differences in symptomatic expression among these populations may be due to such factors as the timing of androgen exposure at different stages of fetal development, different rates of aromatization, or to the number of androgen receptors present in some brain locations at certain times in fetal development. Geschwind and Galaburda (1985) laid the theoretical framework to explain how this process may work, and indicated several physiological differences that may serve as neurological "soft signs" of perturbations in the androgenization process. The expectations of this theory were that a higher incidence of left-handedness, or left-sided dominance in general, and even differences in hair and eye color, would be associated with abnormal androgen exposure. Beyond simple markers of lateralization, Geschwind predicted that neurological lateralization will occur such as the development of language in the right hemisphere rather than the left hemisphere, leading to greater difficulty with language, and possibly resulting in learning disabilities. Among the primary hypotheses that will be tested by the proposed research are this lateralization of function (e.g., as expressed by handedness) and the prevalence of androgen-related disorders and physiological markers within ADHD. The following sections describe these factors and their relationship to ADHD, and briefly describe how they will be measured.

Reading Disability

Learning disabilities are estimated to affect 5-17% of school-age children in the U.S. (Lyon, 1995; Shaywitz & Shaywitz, 1994). While there are three categories of learning disabilities (Reading, Mathematics, Written Expression), the disorder of reading ability (RD) has received the majority of research focus. As in other disorders discussed in this section, a notable sex difference exists in the prevalence of RD with an estimated ratio of 3:1 boys to girls (Lambe, 1999). A study that assessed the handedness of boys and girls with and without reading difficulties (Neils & Aram, 1986) found that boys with reading difficulties were more likely to be non-right handed. Girls were not found to display this same pattern of findings, but the authors reported that the low number of girls with reading difficulties was a significant confound for their study. This relationship between handedness and reading disabilities supports the lateralization hypothesis (Geschwind and Galaburda, 1985) that posited a relationship between prenatal androgen abnormalities and handedness and developmental difficulties such as reading disabilities.

The majority of research in reading deficits has focused on the role that phonemic awareness, the process necessary for segmenting, manipulating, or identifying the phonemes in words, plays in decoding. Evidence demonstrates that slow, inefficient decoders make poor comprehenders (Perfetti, 1985), but much less research has delved into the difficulties good decoders may experience in comprehension. No research provides a direct causal link between decoding and good comprehension (Coles, 2000). In fact, training poor readers to recognize words more

quickly did not have a beneficial effect on their comprehension beyond an intervention designed to increase comprehension through questioning (Fleisher and Jenkins, 1983). Thus, these appear to be related but distinct processes that may or may not both be present within a reading-disordered individual.

Children with ADHD are at greater risk than the general population for decoding deficits (Willcutt & Pennington, 2000), and it is possible that the overlap of ADHD and RD may be due to a common genetic basis (Willcutt, Defries, Pennington, 2003). This commonality may be a shared predisposition towards deficits in auditory processing, verbal working memory, and language development (Willcutt & Pennington, 2000). While both groups may have deficits in working memory, these difficulties appear to have different bases. Children with RD appear to have an impaired phonological loop (a factor of working memory that is responsible for rehearsal and manipulation of verbal material), while examinations of children with ADHD that did not take into account subtype status did not find similar impairments (Korkman & Pesonen, 1994; Benezra & Douglas, 1988). Rather, children with ADHD likely have deficits in the central executive of working memory (a process theorized to be responsible for resource allocation) that lead to impairment in controlled information processing such as modifying and accommodating new information (Roodenrys, Koloski, & Grainger, 2001). Deficits in learning and memory for recently acquired information are related to ADHD rather than RD while deficits in naming speed are specific to RD. ADHD has been found to be a major source of additional cognitive impairment in RD populations (Felton, Wood, & Brown, 1987).

Further support for the distinction of disordered cognitive processes in ADHD and RD can be found in the association between deficits in Color naming and ADHD that could not be attributed to the comorbidity with RD (Tannock, Martinussen, & Fritjers, 2000). Color naming (non-alphanumeric stimuli) benefited from stimulants, but letter- and number-naming speed (alphanumeric) were unaffected, indicating controlled, semantic-processing deficits in ADHD. In a related study, children with both ADHD and LD, and those with just ADHD, were shown to have invested the same degree of mental effort on the study's measures, but children with LD did best on an effortful task while performing worse on an automatic task (Hazell, Carr, & Lewin, 1999).

To examine the potential contribution that a component of the LD spectrum makes to overall impairment among children who have been exposed to androgen-rich prenatal environments, Reading Disability (RD) status (as quantified by two decoding measures) will be assessed. Group differences in decoding measures will be examined, and, if warranted, these measures can be used as a covariate in data analyses of the connection between androgen exposure and ADHD.

Sleep-Related Breathing Disorders

The majority of all children will experience difficulties with sleep that often do not receive formal clinical diagnoses, but do cause familial distress and diminished functioning (Mindell, 1993). Diagnosable sleep disorders affect a significant proportion of children (7%), and have been found to be even more prominent in children with ADHD (25-50%) according to parent report (Corkum, Tannock, & Moldofsky, 1998).

Males are more likely than females (approximately 2:1) to have symptoms of sleep disorders in general (Quine, 2000), as well as to experience such discrete disorders as enuresis more frequently (Mindell, 1993). These sleep disturbances are likely related to androgenic differences that lead to physiological alterations such as narrowing of the air passageways that interfere with appropriate sleep (Popovic & White, 1998).

While there are many recognized sleep disorders, they are typically divided into two primary clusters: parasomnias and dysomnias. The branch of sleep disorders to which parasomnias belong is characterized by inappropriate activation of sleep-related physiological mechanisms at times that disrupt or negatively impact sleep-stage transitions, arousal, and partial arousal. Dysomnias are disturbances of quality, duration, or timing of sleep due to dysfunction of the processes involved in initiating or maintaining sleep, or due to excessive sleepiness.

Some research indicates that children suffering from sleep problems or disorders may exhibit behavioral problems similar to those seen in ADHD (for review see Chervin et al., 2002). These behaviors may include hyperactivity and impulsivity as well as inattention. However, in a recent exploration of these factors (Chervin et al., 2002), among those children for whom their parents were reporting behavioral sequelae to sleep disturbances, none of the children were found to have clinically significant levels of problem behavior. Further, sleepiness and hyperactivity were not found to be related to each other. An examination of children with ADHD, children who snore, and controls indicated a minimum of cognitive deficits in children who snore despite mild behavioral deficits in attention (Chervin et al., 2002), further indicating that the observed behaviors are related to sleep difficulties rather than ADHD.

While the most reliable means of diagnosing sleep-related breathing disorders (SRBD) is with polysomnography, parent report has demonstrated adequate sensitivity and specificity with good correlations to polysomnography data (Chervin, Hedger, Dillon, & Pituch, 2000). This study will focus on sleep-related breathing disorders such as sleep apnea, and easily observed sleep disorders like enuresis that are amenable to parent report rather than the more intensive and expensive polysomnography methodology. These symptoms have been demonstrated to be among the most prevalent sleep difficulties found among children with ADHD (Chervin, Dillon, Bassetti, Ganoczy, & Pituch, 1997).

It appears, then, that sleep disorders and ADHD are discrete phenomena that may be found together at higher than expected levels, but which nonetheless likely have different etiologies. Analysis of group differences in sleep-related breathing disorders and ADHD may help to understand the role of androgens in the etiology of SRBDs and ADHD. These findings may contribute to an understanding of the timing of necessary androgen-related processes in fetal development and the etiology of ADHD, or the role SRBDs play in symptom expression in ADHD.

Mental Rotation

Strong support exists for a sex difference that is apparent from childhood (Levine, Huttenlocher, Taylor, & Langrock, 1999) and preadolescence (Johnson & Meade, 1987) in the ability to quickly and accurately mentally rotate objects. Ample evidence suggests that males and females recruit distinct neurological regions in performing this task (Seurinck, Vingerhoets, de Lange, & Achten, 2004). However,

when no time limit is placed on task completion, females may perform as accurately as males (Voyer, 1997; but compare with Peters, 2005). This appears to reflect a less efficient process among females that is still capable of performing the task at low to moderate levels of difficulty. It has been postulated that these differences are related to differences in neurological organization that favor males on spatial relation and mental-rotation tasks, while females are more adept at some linguistic skills (Maccoby & Jacklin, 1974; Hyde & Linn, 1988).

Evidence exists for both activational (transitory) as well as organizational (ontological) influences of hormones on mental rotation processes. An activational influence can be found in studies of mental-rotation ability during different phases of the menstrual cycle (Hampson & Kimura, 1988). At midluteal phase when estrogen levels are at their highest, females perform more poorly at mental rotation, while at menses when estrogen levels are at their lowest, they perform significantly better (more like males). Organizational influences of hormones on mental rotation abilities are demonstrated in studies that compare mental-rotation ability across the lifespan. Children as young as four years of age (Levine, Huttenlocher, Taylor, & Langrock, 1999) have been found to demonstrate this sex difference and it is maintained throughout adolescence and adulthood. Therefore, it appears that this sex difference can be related to hormonal events occurring prenatally rather than during puberty (Williams & Meck, 1991), but it is influenced by current hormonal status.

Spatial-ability tasks such as the mental-rotation task have a demonstrated ability to differentiate between the sexes, and are influenced by hormonal variations (Hampson & Kimura, 1988). Comparisons of physiological markers of abnormal prenatal

androgen exposure with mental-rotation performance (McFadden & Shubel, 2003; Loehlin & McFadden, 2003) have provided evidence that, among heterosexual males and females, the factors responsible for masculinizing these markers appear also to play a minor role in the masculinization of mental-rotation abilities. The weak relationship between these variables may provide a broad background for comparison against which it may be possible to draw further conclusions as to the role of androgens in ADHD symptoms.

Physiological Markers of Androgen Exposure and the Auditory System

Otoacoustic Emissions

Otoacoustic emissions (OAEs) are sounds that are produced by the cochlea and detected using a microphone placed in the external ear canal (Probst, Lonsbury-Martin, & Martin, 1991). A primary contributor to these emissions is the outer hair cells of the cochlea. There are several varieties of OAEs and procedures with which to measure them. Spontaneous otoacoustic emissions (SOAEs) are OAEs that the cochlea generates in the absence of acoustic stimuli. Two other forms of OAEs that are produced in response to stimuli are click-evoked otoacoustic emissions (CEOAEs), and distortion product otoacoustic emissions (DPOAEs). CEOAEs can be experimentally induced by presenting click stimuli in the external ear canal. The echo-like waveform produced by the cochlea in response to each click is the CEOAE. DPOAEs are OAEs that result from presentation of two sinusoidal tones to the ear, designated f1 and f2 ($f1<f2$). The distortion product of greatest interest is $2(f1)-f2$.

In humans, SOAEs and CEOAEs have been found to be stronger in females than in males (McFadden, 1998; McFadden, Loehlin, & Pasanen, 1996), and to be indicative of better hearing acuity (Probst, Lonsbury-Martin, & Martin, 1991). These sex differences in OAEs are present in newborns and continue throughout the lifespan (Morlet et al., 1996) suggesting an early physiological alteration that is not dependent upon pubertal maturation, but rather, is an organizational effect of early hormones. Research indicates that certain special populations, such as homosexuals, exhibit characteristic OAEs (McFadden, Loehlin, & Pasanen, 1996; McFadden, & Pasanen, 1998; McFadden, Pasanen, Weldele, Glickman, & Place, 2003). Further, OAEs of other mammals have been found to have sex differences similar to those in humans (McFadden, Pasanen, Raper, & Wallen, 2003). Of particular interest to this study is the finding that differences in OAE patterns exist within the ADHD subtypes (McFadden, Westhafer, Pasanen, Carlson, & Tucker, 2005). These data suggest an organizational change may occur to the cochlea from increased prenatal androgen exposure (McFadden, 2002), found across several species and special populations of humans.

Finger-Length Ratios

Finger-length ratios have shown promise as a marker of prenatal androgen exposure (Manning, 2002). Smaller FLRs in males than those observed in females such as the ratio of the lengths of the index and ring fingers (the "2D:4D ratio") have been found to mirror differences in OAEs in these subjects. Because correlations between OAEs and FLRs appear to be weak (McFadden & Shubel, 2003), these appear to be distinct measures of prenatal androgen exposure that may reflect similar androgenic

processes with either different "windows" of operation, or potentially, an interaction of exposure and individual characteristics.

FLR sex differences can be found to exist in children as young as two years of age (Manning, 2002, p. 15), and can be found in other FLRs such as the 2D:5D and 3D:4D (McFadden & Shubel, 2002). Further, sex differences can be found in other mammals such as the mouse (Brown, Finn, & Breedlove, 2002; Manning, Callow, & Bundred, 2003), baboon (McFadden & Bracht, 2002; Roney et al., 2004), gorilla and chimpanzee (McFadden and Bracht, 2002), as well as the zebra finch (Burley & Foster, 2004).

Androgen Markers, ADHD, and the Auditory System

Previous analysis of OAEs within a population of children with ADHD indicated that boys with ADHD/IA have CEOAEs with smaller amplitudes than boys with ADHD/C or controls (McFadden, et al., 2005). In addition, boys with ADHD/IA showed a pattern of FLRs that mirrored the OAE findings. Thus, support for the argument that boys with the ADHD/IA subtype may have experienced an androgen-rich prenatal environment was found for both OAE and digit-length variables.

Interestingly, children with the ADHD/C subtype have been shown to differ from controls on a number of other auditory tasks (Gray, Breier, Foorman, & Fletcher, 2002; Breier, Gray, Klaas, Fletcher, & Foorman, 2002). Also, clinical experience reveals holds that it is common for children with ADHD to experience multiple ear infections and to have their ears intubated at a young age. Whether a connection

between this pattern of childhood ear infections and later auditory and attentional difficulties exists remains to be established.

A measure of central auditory processing and auditory attention (SCAN-C) has demonstrated some ability to discriminate between children with ADD-H (Keith, Rudy, Donahue, & Katbamna, 1989) or ADHD (Shapiro & Herod, 1994) and controls. Whether these differences are the result of comorbid central auditory processing disorder (CAPD) or problems of attention has yet to be explained. Given the importance of adequate sensory functioning for students within academic settings, these findings highlight the necessity of further analysis.

Chapter 4: Study Rationale

Preliminary evidence suggests a connection between prenatal androgen exposure and the etiology of ADHD/IA among male children (McFadden et al., 2005). To further examine this connection, the current study expanded upon the previous study by examining a sample of boys with ADHD and included multiple forms of OAEs (CEOAE, DPOAE, and SOAE). Physiological differences (i.e., OAEs and FLRs), and disorders (i.e., SRBDs and RD) believed to be associated with abnormal prenatal androgen exposure also were examined to provide further evidence of such exposure and to assess their potential contribution to variability within ADHD expression. Measures that have demonstrated the ability to discriminate between ADHD subtypes (i.e., the Stop-Signal task, Trail-Making Task) also were included to determine the potential effects of androgen exposure on neuropsychological processes related to ADHD.

Links between the factors that were studied and androgen exposure have been established previously (e.g., McFadden et al., 2005; Levine, Huttenlocher, Taylor, & Langrock, 1999; Lamb, 1999), and further, Geschwind and Galaburda (1985) predicted a number of physiological markers that would be related to androgen exposure. These links provide the basis for hypotheses regarding the connection between ADHD and abnormal androgen exposure. However, it is possible that ADHD is related to androgen exposure through processes (e.g., specific "windows" of exposure) that are distinctly different from other disorders. It also may be possible that androgen exposure globally

affects numerous pathways, the cumulative effect of which may disrupt attention, specific processes of attention, or only secondarily affect attention by disrupting processes that are needed for successful attentive behavior (e.g., a learning disability that increases classroom frustration leading to poor attention). This study further attempted to explore Geschwind's hypotheses (Geschwind & Galaburda, 1985) regarding the role of androgen exposure in physiological differences. Several factors (e.g., handedness, eye color) were examined to assess the fit of this proposed model to this population.

To fully understand the role that androgen exposure may play in the etiology of ADHD, several factors were assessed. While the exact mechanism and timing of androgen exposure is still not understood, some tentative hypotheses can be made. Relative finger length is typically established by the 13th week of fetal development (Malas, Dogan, Evcil, & Desdicioglu, 2006). Aural development begins at approximately this time with growth of the receptor cells of the cochlea and is complete by the 28th week (Rubel, 1978; McFadden & Shubel, 2003). Therefore, a similar pattern of OAE and FLR ratios found in boys with ADHD/IA (McFadden, et al, 2005) indicating hyper-masculinization and this difference in developmental timing suggest that there may be a protracted and heightened exposure to prenatal androgens in the womb for these children. Prolonged abnormal androgen exposure further suggests there should be higher levels of androgen-related factors in this population. By assessing such varied factors as sleep disturbance, handedness, FLRs, and OAEs, it may be possible to begin the process of identifying the window(s) during which abnormal androgen exposure occurs. Presumably there is not a perfect 1:1 relation between

androgen exposure and these factors, so we should not expect that all children experiencing abnormal androgen exposure should develop all of the factors under study. Future studies might be able to determine when a fetus is most susceptible to adverse hormonal influences. Further, an analysis of developmental timing and hypothesized androgen exposure would have implications for future theory-driven studies that attempt to discern which processes would be implicated in the development of ADHD, and/or developmental timing of such processes as inhibition and attention. Again, it should also be noted that androgen levels per se may not be the driving factor in these androgen-related differences. It may be that a factor such as the number or sensitivity of androgen receptors is actually more important. An additional aim of this exploratory study was to elucidate the pattern of group differences to provide future projects with the framework to discern the actual mechanism of action.

This study explored a wide range of effects that abnormal androgen exposure can have on the developing fetus. This study had the following specific aims: 1) to provide further evidence of an androgen-ADHD link, 2) to specify which children with ADHD are most likely to have experienced this exposure, 3) to assess the effect(s) androgen exposure may have in the symptomatic expression of ADHD, and 4) to document comorbid diagnoses that may occur in children with ADHD that have been exposed to abnormal prenatal levels of androgens.

Chapter 5: Methods

Recruitment and Screening

ADHD subjects were primarily recruited from the neuropsychology practice of David M. Tucker, Ph.D. and his colleagues at the Austin Neurological Clinic, although several were recruited from a pediatrician practice (Byron Kocen, M.D.) and one from the Austin Child Guidance Center. Ratings of ADHD symptoms from at least one parent and one teacher were used in conjunction with a semi-structured clinical interview to determine ADHD diagnoses. Control subjects were recruited from friends of the ADHD subjects and through advertising in the Austin area. An initial attempt was made to obtain at least 15 children of both sexes for each group, with over-sampling of the ADHD/IA group to provide children that qualify for the sluggish cognitive tempo (SCT) group. Recruitment efforts were made to provide comparable female groups. Because performance on a number of the proposed measures is known to be affected by sex hormones, female participants were only included if they had not reached menarche. Parents were asked during an initial recruitment phone call if their daughters had reached menarche, and only girls under 13 years of age were sent recruitment letters. To keep male and female samples comparable in age, male participants were required to be younger than 13 years of age. Due to low recruitment of female subjects, their data will not be considered in the following analyses.

Because one of the major goals of this study was the identification of subtype differences within ADHD, the diagnostic standards for inclusion as an ADHD/IA or control subject were modified to maximize these differences. Children included in the control group were required to have three or fewer total DSM-IV symptoms of

inattention and/or hyperactivity/impulsivity and not to have previously received a diagnosis of ADHD or a learning disorder. As in the McFadden et al., 2005 study, to meet inclusion criteria for this study, children with ADHD/IA were required to have four or fewer symptoms of hyperactivity/impulsivity, and as specified in the DSM-IV, six or more symptoms of inattention. No changes in diagnostic criteria from the DSM-IV-TR were made for children in the ADHD/C group; they were required to display six or more symptoms of both inattention and hyperactivity/impulsivity. Because of the controversial status of the ADHD/HI subtype as a discrete manifestation of ADHD (Barkley, 1998), those subjects were not included in this study.

Further exclusion criteria included a prorated full-scale IQ of less than 80, current use of psycho-active drugs other than those for ADHD, a history of psychosis, evidence of a neurological disorder such as epilepsy, or a history of head injury. Children currently taking medication for ADHD were required not to have taken their medication on the test day. While a "wash-out" period during which children do not receive medication is common practice in ADHD research, it can produce transitory emotional and cognitive changes (e.g., Dalley, 2007) similar to "withdrawal effects" which may somewhat alter the study findings. However, children commonly do not take their medications on weekends and the possibility of cognitive effects secondary to the wash-out period is preferable to testing children on medication as the stimulants affect the cognitive processes being assessed. Because they have been shown to adversely impact OAEs, all children were required not to have used analgesics such as aspirin or antihistamines during the previous 48 hours. Children exposed to loud noise (e.g., a loud concert) within the previous 24 hours were asked to return for testing on a

subsequent day. Children also had to pass an initial hearing screening (described in OAE Measurements) to participate.

Procedure

General

All testing for each subject took place during a single 2.5-hour session in the lab of Dr. McFadden at the University of Texas at Austin. Order of assessment can be found in Appendix E. Consent and Assent forms were signed by parents and children prior to the test session. Parents then completed diagnostic, descriptive, and experimental forms while children underwent testing in a sound-proofed room. Subjects were initially paid $40, but this amount was later raised to $50 to meet enrollment goals.

The parents of all participants consented to permit the researchers to contact their child's school teacher to obtain diagnostic and experimental behavioral ratings (see Appendix E) by completing the Teacher Consent form (Appendix D). A packet was then mailed to the participant's teacher. Included in the packet was a self-addressed, stamped envelope in which to return the forms. Teachers who participated by returning the forms received a $5 gift certificate to a local business. If no reply was received from the initial mailing, a second mailing to that teacher was mailed after 2-3 months. For those children who participated during the summer while school was in recess, a mailing was sent to their teacher from the previous school year. If no reply was obtained from that teacher, a second mailing was sent to the child's current teacher approximately 3 months after the new school year began to permit the new teacher to

become familiar with the child. Due to a low total return rate of these behavioral rating form packets from teachers (23%), these ratings were not included in the current study to maintain similar diagnostic ratings for all children.

Questionnaires

ADHD Diagnostic Checklist

The ADHD diagnostic checklist (see Appendix A) is based on the DSM-IV criteria for ADHD and ODD, and quantifies symptoms of inattention, hyperactivity, impulsivity, and oppositional behavior. Impairment on each symptom is rated on a four-point severity scale. An endorsed score of 2 (pretty much) or 3 (very much) was taken to indicate the presence of that symptom, while scores of 0 (not at all), and 1 (just a little) was taken to indicate the absence of that symptom.

Sluggish Cognitive Tempo was examined with four items chosen from the previous literature (McBurnett, Pfiffner, & Frick, 2001) suggesting that these descriptors characterize the attention style of a subset of children with ADHD. These are daydreams, apathy, underactivity, and one item retained in DSM-IV, forgetfulness. Eight more potential sluggish cognitive tempo items were included to further assess this construct. These 12 items were included on the diagnostic symptom questionnaire which both parents and teachers were asked to complete.

Demographics, Androgen Exposure, Birth Order, and Noise Exposure

One form was used to collect responses from parents on an assortment of demographic and descriptive characteristics (Appendix B). Due to their brevity,

straightforward manner, and lack of psychometrics, they will be presented together in this section. The demographics section was used to record data such as the child's age, grade level, height, weight, sex, race, and parent's education level and occupation. Several brief questions that assessed potential indicators of prenatal androgen exposure first suggested by Geschwind & Galaburda (1985) such as eye and hair color and handedness were included to explore their relationship to other study variables. Because the womb environment is believed to change (Blanchard, 1997) with successive births (particularly with male children), birth order and the number of previous male and female siblings born to the child's biological mother were recorded to provide information that may be valuable in understanding the effects of birth order upon the outcome measures. Finally, questions about recent exposure to loud noises and medications that may affect hearing acuity were asked. Exposure to these events may affect OAE measurements even if the child's hearing acuity falls within normal levels. As such, endorsement of these items necessitated rescheduling 1 male control and 1 male ADHD/IA group subject to complete the study.

Pediatric Sleep Questionnaire

Parents were asked to complete the Sleep Related Breathing Disorders (SRBD) subscale of the Pediatric Sleep Questionnaire to assess sleep disorders among subjects (Chervin, Hedger, Dillon, & Pituch, 2000). The SRBD consists of 16 questions that were found to correlate well with a physiological measure (polysomnography) of sleep-related breathing disorders. The items are phrased in a simple "yes/no" format, and scored as present or absent. The SRDB score is calculated as a proportion of symptoms

that are present. This subtest has demonstrated adequate sensitivity (0.81) and specificity (0.87) among a population of children with confirmed diagnoses of SRDB compared to children at a general pediatrics clinic (Chervin et al., 2002). Subscales (Appendix C) exist for snoring (items 1-5), and excessive daytime sleepiness (items 11, 12), and include individual items for issues such as enuresis.

Intellectual and Achievement Assessment

The Block Design and Vocabulary subtests from the Wechsler Intelligence Scale for Children- Third Edition (WISC-III; Wechsler, 1991) were administered to obtain a prorated IQ score for each child (Sattler, 2004). The Wide Range Achievement Test-Revision 3 (WRAT-3; Jastak & Wilkinson, 1993) reading subtest and the Word-Attack subtest from the Woodcock-Johnson R tests of achievement were administered to assess reading achievement levels. These measures require reading either real or manufactured single words out loud to the examiner who scores the item as passed or failed.

Hand, Foot, and Eye Lateralization

Hand, foot and ocular dominance was assessed by asking the participant to demonstrate two motor activities that indicate dominance for each category. For hand dominance, subjects were asked to demonstrate throwing a ball and writing with a pencil. Foot dominance was determined by having the child mimic kicking a ball and stomping on a bug. Asking the child to imitate looking through a telescope, and sighting down a rifle was used to determine ocular dominance.

OAE and Audiometric Measurements

Auditory testing occurred within a soundproofed room in the lab of Dennis McFadden, Ph.D. All children were required to have hearing within the normal range binaurally as assessed by a hearing evaluation conducted with a screening audiometer (Maico MA 40). Hearing was tested from 125 to 8000 Hz, and children were required to be able to detect a pure tone at 20 dB hearing level (HL) or less to participate. Those children found to have hearing at below-average levels were asked to return at a future date to undergo a second hearing screening and subsequent testing if they passed. Five children (1 female control, 1 female with ADHD/C, and 3 male with ADHD/C) were asked to return based on these criteria. The female control was found to have hearing below average levels at follow-up, the female with ADHD/C and two males with ADHD/C declined to return, and one male with ADHD/C returned and was allowed to participate when he was found to have adequate hearing. Compensation in the form of $20 was provided to those children who were screened but unable to participate.

Measures of OAEs have been demonstrated to be more reliable after the subject has spent time ("initializing effect") within the testing environment (Whitehead, 1991). As in the McFadden et al. (2005) study where children spent 15 or more minutes in quiet activity, in this study, those children who were found to have adequate hearing participated in other quiet measures for this study for 20-25 minutes immediately preceding the OAE testing period. After this initializing period, subjects were asked to lie still on a cot with their head supported by a pillow in the sound room. The examiner stayed in the room with the children during testing to run the analyses and provide

encouragement. Video monitoring at the rate of 1 frame/second continued throughout testing to provide the child's parent(s) a chance to observe the session. A hollow eartip covered with a foam pad was then inserted into the external ear canal of the ear. An attempt was initially made to counterbalance the first ear tested across subjects, with approximately equal proportions of subjects across groups having a given ear tested first. However, the first several children in the study expressed anxiety about the procedure and requested to observe the examiner and the testing protocol and apparatus during the first trial, necessitating testing the left ear because of room configuration. This was continued for subsequent children.

One small plastic tube passing through the hollow eartip and attached to an Etymotics ER-10B+ microphone permitted measurement of the OAEs present in the ear canal, while two other small plastic tubes conducted sound from the two Etymotics ER-2 earphones to the ear canal for CEOAEs and DPOAEs. An Apple G4 computer was used for stimulus presentation and data collection. LabView software was used to run an in-house created program (written by Edward G. Pasanen) that used the built-in sound system of the computer and the sound card installed in the computer to generate stimuli for CEOAE and DPOAE measurements. Results from OAE data collection were analyzed off-line.

Click-Evoked Otoacoustic Emissions (CEOAE)

Stimuli consisted of a series of electrical pulses about 91 us in duration delivered to the earphone. A 2-ms delay before collection of data was imposed after each click to eliminate the click stimulus and ringing in the ear canal and middle-ear

system. This ringing is not part of the cochlear response to the click. After the initial delay, 40-ms of the cochlear response was collected and summed with responses from previous clicks.

The echo-like responses to the click stimuli were delivered to the microphone's preamplifier and then to a low-noise amplifier/filter device that amplified the collected waveform by approximately 14 dB with a high-pass at approximately 400 Hz (to minimize non-OAE body sounds). Using a National Instruments PCM/CIA card, this output was then digitized at a sampling rate of 50,000 sample points per second.

Stimuli were presented in approximately one-second bursts of 10 clicks with approximately 500 ms separating each set of clicks. If the noise level within the ear canal exceeded a predetermined level, the presentation of clicks was paused and the succeeding set postponed until the noise level was once again below the criterion value. Recorded click responses were eliminated if they were larger than an established ceiling value under the rationale that they likely reflect extraneous body noise (McFadden & Shubel, 2003). A minimum of 250 individual cochlear responses to the click stimuli were collected and averaged before proceeding to other OAE collection for that ear.

Analysis of the CEOAE data eliminated the first 4 ms of the averaged waveform to further eliminate mechanical ringing of the middle-ear system in response to the stimuli. The following 20.5 ms of the collected waveform was then bandpass-filtered between 1.0 and 5.0 kHz. The rms level of this waveform was calculated and transformed into decibels sound-pressure level (dB SPL). CEOAE waveforms were collected at two click levels (0 and -6 dB). The initial peak-equivalent sound-pressure

level (peSPL re 20 muPa) was set at 75 dB as in McFadden et al., 2005. Thus, the second peSPL was -6 dB lower or 69 dB.

The resulting waveforms were then examined to detect those cases where the resulting waveform was indistinguishable from the background noise floor, or for possible procedural errors such as the improper placement of the microphone or mechanical error which may have led to atypical waveforms. CEOAE levels at 7 and 20 ms delays were transformed into powers and the 20 ms level was subtracted from the 7 ms level. The difference was then converted back into decibels, and if the value was less than 0, that ear was removed from further analyses. With this method, one control boy and one boy with ADHD/C were eliminated from all four CEOAE comparisons (left and right ear, 0 and -6 dB). Two children from each group were removed from left ear analyses at both click levels, and two boys with ADHD/C and two control boys did not contribute right ear data at either click level. Three children with SCT and one control provided data for only one of the four comparisons (right ear), and one control and one child with ADHD/C contributed data for only a single left ear comparison and no right ear comparisons.

Spontaneous Otoacoustic Emissions (SOAE)

Two-minutes of recorded time consisting of four 30-second runs of each ear interspersed with brief rest periods were taken. For analysis, the recording was broken into 743-ms overlapping sections with approximately 186 ms between the onset of each segment (approximately 75% overlap). Fast Fourier transformations (16k FFTs, Hanning window) were calculated and averaged for the quietest 25% of these

measurements (those with the lowest rms values). These averaged segments (the initial spectrum) were recorded in frequency bins 1.35 Hz in width. A smoothed baseline is created by scanning through the spectrum and replacing those spectral values deemed to be extreme values (Pasanen & McFadden, 2000). This decision is made by creating regression lines based on the spectral value of the immediately surrounding regions. These lines are extrapolated to provide an estimate of the value being examined. Any values that are further than three standard deviations away from the regression line are replaced by the value determined by the extrapolated regression line. Peak deviations are then calculated within the initial spectrum using those peaks that were not replaced during the smoothing process. These values are used to determine the distribution of deviation values that will be used in comparison of all observed peaks. Selection of peak values as SOAEs is made by comparing every peak within the initial spectrum with the peak deviations. Any peak that is greater than this deviation score by more than 5 standard deviations and is greater than any other peak within 0.1 octave is selected as an SOAE. Alternate peaks within 0.1 octaves of the SOAE are deleted due to the belief that it is not possible to have two SOAEs within that range (Zwicker, 1990). The frequency assigned to the identified SOAEs is the frequency of the bin in which its peak was located.

Distortion Product Otoacoustic Emissions (DPOAE)

Two sinusoidal tones (f1 and f2, called the primary tones) with tone frequencies ranging from about 2000-8000 Hz were presented continuously for four seconds. The distortion product frequency (2f1-f2, with f2=1.21f1) was continuously monitored by

the computer throughout this process. The strength of both primary tones was set at six equal levels. Sampling occurred at six frequencies of the distortion product per octave, centered around 5,000 Hz. Analyses compared a baseline without primary tone presentation with two runs from the total sample that have the lowest overall noise floors. Data were obtained from 29 dB to 71 dB in 7 dB increments, but because not all children produce DPOAEs at each level, the 50 dB measurement, the level at which most children produced DPOAEs, was used for analyses. One child with ADHD/C was unable to complete DPOAE testing as he found it too uncomfortable. Data were missing or incomplete for one other child with ADHD/C and one with SCT on the right ear. One child with ADHD/C, one child with ADHD/IA, and two children with SCT were missing data for the left ear.

Finger-Length Measurements

Images of both hands were taken using a digital scanner except for the hands of one male child with ADHD/C which had to be photocopied due to scanner malfunction. Both hands were simultaneously placed lightly on the scanner with the fingers spaced side by side. A white towel covered the hands and forearms in order to provide a high-contrast background. The images were then scanned into Photoshop and saved. These images were later imported into Canvas where measurements of each finger were made within Canvas. The Canvas software allows the rater to place lines at the basal crease and tip of each finger and then Canvas calculates the distance between each pair of lines to provide very precise measurements of finger length. One experienced judge (a research assistant, Jenny Tran) who was blind to the diagnostic status of the children

measured the entire set of hands and the resulting measurements were used to obtain measures of all of the six possible pair-wise length ratios of the fingers were calculated for each hand.

Screening Test for Auditory Processing Disorders for Children (SCAN-C)

The SCAN-C (Keith, Rudy, Donahue, & Katbamna, 1989) is comprised of four auditory-processing tests presented on a compact disc player with headphones: Filtered Words, Auditory Figure-Ground, Competing Words, and Competing Sentences. These measures provide a number of different analyses of central auditory processing including the ability to understand distorted speech, speech in the presence of background noise, and auditory attention. The Filtered Words Test, a measure of auditory closure, requires the subject to discern what word is being spoken when portions of the recording of the word have been deleted. In the Auditory Figure-Ground Test the child must differentiate the presented word from a noisy background (individuals speaking incoherently) and repeat the presented word out loud. The levels of the stimuli (figure) to the background noise (ground) are varied throughout this subtest to provide varying levels of comparison of figure to ground. The Competing Words and Competing Sentences Tests are dichotic listening tests that present the child with different words or full sentences, respectively, in each ear. For the Competing Words Test, the child must repeat the stimulus word presented to the right ear before repeating a different stimulus word presented to the left ear. After 15 trials the task switches demands and requires the child to repeat the left-ear stimulus word before repeating the right-ear stimulus word. For the Competing Sentences Test, the child is

presented with a sentence to the left ear while simultaneously a different sentence is presented to the right ear. The child must then repeat the sentence heard in the right ear. After ten trials the child is asked to repeat the sentence heard in the left ear. These last two measures are purported to assess the development and maturity of the auditory system as well as hemispheric specialization and short-term auditory sequential memory. An "ear advantage" score can be calculated from the Competing Words test, indicating to which ear the child was better able to attend.

For each of the four subtests, the total number of items correct is recorded and converted to scale scores with a mean of 10. A composite score with a mean of 100 and a standard deviation of 15 will be calculated from the sum of the individual test's scaled scores. Across age ranges, the SCAN-C Cronbach's alpha reliability coefficients for the composite range from .86 to .92, across subtests the coefficients range from .56 to .89 (Keith, Rudy, Donahue, & Katbamna, 1989). Test-retest reliability for the composite score was not reported, but subtest reliability (corrected *r*) ranges from .65 to .83 among 5- to 7- year-olds, and .67 to .78 among the 8- to 11-year-olds. The SCAN-C demonstrated adequate discriminant validity when measuring group differences between children with central auditory processing disorder (CAPD) and children with no previous history of speech or language disorder (Keith, Rudy, Donahue, & Katbamna, 1989).

Mental Rotations Test

The Mental Rotations Test used for this study is an on-line (http://www.uwm.edu/People/johnchay/index.htm) version consisting of 30 10-cube

pairs of blocks. The beginning angle of orientation difference for each pair range randomly from 0 to 280 degrees in 20-degree intervals. The child is asked to place the left index finger on a key labeled “Same,” the left ring finger on a second key labeled “Different,” and the left thumb on the space bar of the keyboard. Instructions are read to the child and a practice trial is then administered. Task instructions direct the child to press the “Same" key if the two figures presented on the computer screen are congruent (i.e., if the arrays of blocks for the two figures are mentally rotated to assume the same orientation and are similar to each other). That is, if the arrays of blocks for the two figures are mentally rotated to assume the same orientation and are similar to each other, the child is asked to press the "Same" key. If the two arrays are not congruent, the child is asked to press the "Different" key. To advance to the next trial the child is asked to press the space bar. Latencies are recorded for each of the 30 trials. Dependent variables include time to completion for each item within the trial and total number of items answered correctly.

Stop-Signal Task

The stop-signal task to be used for this study is a computerized choice-reaction-time task that is a tracking version of the stop task (Logan, 1994). Children sit in front of a computer monitor and respond to the presented stimuli (an "X" or an "O") by pressing a corresponding key on the keyboard using two fingers of their dominant hand. Two practice trials are administered before six sets of stimuli which are administered by alternating between trials and other cognitive tasks. The instructions are explained to the child by a trained supervisor who stays with the child throughout testing.

The first two sets consist of the child responding as quickly as possible to either the "X" or the "O" during 32 practice trials. Children are then asked to continue responding as quickly as possible to the stimuli during the second set, but they are asked not to strike a key if they hear a tone. They are asked to respond to every stimulus without waiting to hear if a tone is presented and informed that they will be unable to successfully stop every time. On 25% of the trials the "stop" tone sounds for 100 ms. Initially, the delay between stimulus and signal is set at 250 ms; this is the "stop signal delay." Every time the child is able to inhibit the response, the next time the tone sounds the stop-signal delay will be shortened by 50 ms. For every presentation in which the child cannot inhibit the response, the next time the stop signal delay is increased by 50 ms. With this procedure, stop-signal reaction time is maintained at approximately 50%. In this way the primary dependent variable, a "stop signal reaction time" (SSRT), is calculated by subtracting the mean stop signal latency from the mean go response time (i.e., the time taken to respond to the go stimuli).

Trail-Making Test

The Trail-Making Test (Halstead-Reitan Neuropsychological Battery) consists of two separate forms, A and B, containing numeric (1-15), or alphabetic (A-G) and numeric (1-8) stimuli, respectively. Form A presents the subject with a small practice trial on one side and the full numeric trial on the other. The subject is instructed to trace a line from the circled number “1” to each successive number in numeric order without raising the pencil from the paper. After demonstrating rule comprehension on the practice trial, the subject is presented with the test trial consisting of the numbers 1

through 15 and told to work as quickly as possible while the administrator records time-to-completion and notes any errors made. Form B presents the subject with alpha-numeric stimuli and requires alternation between alphabetic and numeric stimuli in successive numeric and alphabetic order (e.g., 1, A, 2, B, etc.). As in Form A, a practice trial introduces the task followed by the actual timed test. Number of errors and time to completion will be recorded by the examiner. Time to completion for Form A (a measure of overall graphomotor speed) was compared to the time to completion of Form B to obtain a measure of the ability to shift cognitive set (i.e., repeated switching from alphabetic and numeric stimuli).

Chapter 6: Hypotheses

Primarily, it was expected that boys with ADHD/IA would demonstrate the same hyper-masculinized pattern of OAE and FLR findings seen previously (McFadden, et al, 2005), perhaps indicating exposure to abnormally high levels of prenatal androgens. Our knowledge of ADHD and androgen exposure suggested the following hypotheses:

1. On the SCAN-C, the impaired attention of children with both ADHD/C and ADHD/IA will lead to their performing more poorly than controls on those subtests with greater attention demands (i.e., Competing Words, Competing Sentences), as well as having poorer scores on the composite measure.

2. Children with ADHD/IA will experience greater difficulty with set-shifting (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002), which will manifest as slower times to completion of Form B of the Trail-Making test either both controls or children with ADHD/C.

3. Children with SCT will have the slowest "go" response times on the Stop-Signal Task. Due to the slower processing speed and poor alerting attention within this group, these children are more likely than others to experience slow responses to such external stimuli as the “go” signal.

4. This same impaired alerting and sluggish cognition will also lead to greater time to completion for the Mental Rotations task.

5. It is expected that children with ADHD/C will experience greater difficulty with behavioral inhibition than all other groups (Barkley, 1997). This will manifest as

larger stop-signal response times on the Stop Task (Nigg, Blaskey, Huang-Pollock, & Rappley, 2002). That is, the difference between actually inhibiting a behavioral response (i.e., stopping from pressing the button, or, more technically, inhibiting the prepotent response) and starting that response will be greater for these children than others.

6. The higher incidence of sleep disorders among boys implicates the role of androgens in their etiology. Because it is believed that boys with ADHD/IA have experienced at least a window of time in which they were exposed to greater than normal levels of androgens (McFadden et al., 2005), it is likely that they will be at greater risk for sleep disorders than other children.

7. Based on previous research, both ADHD groups are predicted to have lower reading ability scores. Due to greater exposure to prenatal androgens, and the link between such exposure and learning disabilities, it is expected that boys with ADHD/IA will have the poorest scores on measures of reading ability.

8. Finally, exploratory analyses will be conducted to examine the relationships among ADHD symptoms, neuropsychological measures, birth order, OAEs and digit ratios, and other androgen-influenced factors (i.e., handedness, reading scores, sleep disorders, mental rotation).

Chapter 7: Results

Participant Characteristics

Original participants included females (7 ADHD/IA, 3 ADHD/C, and 10 controls); however, they were not included in the final analyses as it was decided that these small cell sizes would not permit adequate group comparisons. In addition, among the boys, 5 who had previously received diagnoses of ADHD were rated by their parents on the day of testing as no longer meeting behavioral diagnostic criteria for ADHD. Another 6 boys were unable to complete testing for various reasons (e.g., equipment failure, medication taken that morning). Based on the criteria described in the Methods section, the final groups included 13 controls, 19 boys with ADHD/C, and 21 boys with ADHD/IA (10 assigned to the ADHD/IA group and 11 to the Sluggish Cognitive Tempo (SCT) group).

Children with ADHD/IA were then divided into those with and without SCT. This categorization was accomplished with 12 items from the symptom rating questionnaire (items 21-32, Appendix A). Each item was scored by parents from 0-3 and these scores were used to create a total SCT score for each child ranging from 0 to a possible 36. Based on parent ratings, 10 children with the lowest scores (ranging from 2-12) were kept in the ADHD/IA group, while 11 children receiving the highest ratings (ranging from 13-30) were placed in the SCT group. The resulting ADHD/IA group had an average rating of 7.1 (SD=3.3) of the possible 36 points on the SCT items, while the SCT group had an average rating of 20.0 (SD=5.7) on these items.

These four groups (control, ADHDD/C, ADHD/IA, and SCT) were compared on demographic and descriptive characteristics (age, prorated IQ, reading ability, handedness, and ethnicity). The results of these comparisons revealed no group differences in IQ [F (3, 52) =.525, p=.667]. Each group had mean prorated IQ scores in the High Average range (i.e., an IQ standard score of 110-120) of intellectual functioning. In terms of age, a group difference [F (3, 52) =4.565, p=0.007] was observed; boys with ADHD/C were younger those with ADHD/IA without SCT (see Table A). Age was used as a covariate in later analyses to determine the effect this group difference may have had on neurocognitive variables. Age was not expected to affect OAE or finger-length ratio comparisons as these variables are established early (prenatal or, possibly, perinatal) and do not vary as a direct function of body size (Lippa, 2003).

Analyses of single-word reading ability (WRAT-III) indicated no group differences [F (3, 52) =.718, p=.546]. Similarly, ability to read pseudo-words (WJ-R, Word Attack) did not differ between groups [F (3, 52) =1.147, p=.340]. Individual scores on these measures were compared to the child's prorated IQ score to assess for the presence of a reading disability. Determination of reading disability status was made by considering children who scored 85 (1 standard deviation below the mean; Low Average ability) or lower on the WRAT-III or WJ-R reading tasks and had a prorated IQ 15 points or higher than their WRAT-III or WJ-R scores as having a reading disability. No children in this study met these criteria.

Number and percentage of right-handed children and Caucasian children were calculated for each group. Approximately equal ratios of Caucasian to non-Caucasian

children were recruited in each cell (ranging from 70.0 to 78.9%). Handedness did vary across groups, however. All children in the control group were right handed, whereas each proband group contained children rated as non-right handed (i.e., left handed or ambidextrous). Children with ADHD/IA had the greatest number of non-right handed children with only 50% (5/10) being right handed, which is quite unexpected and lower than the 85% recorded in the McFadden et al (2005) study for children with ADHD/IA who participated in the OAE study. Data from demographic comparisons are summarized in Table 1.

Table 1

	Control	ADHD/C	ADHD/IA	SCT
N	13	19	10	11
Age: Mean (StdDev) Months	129.8 (22.3)	112.4 (18.0)*a*	134.2 (14.1)*b*	113.8 (17.9)
IQ: Mean (StdDev)	113.0 (14.6)	114.6 (11.3)	112.5 (13.3)	119 (16.1)
WRAT-III: Mean (StdDev)	113.1 (13.7)	107.2 (9.6)	108.9 (17.0)	111.6 (10.5)
WJ-R: Mean (StdDev)	108.8 (14.2)	105.8 (9.5)	105.3 (13.1)	113.6 (12.8)
Right Handed: # (%)	13 (100)	15 (78.9)	5 (50.0)	10 (90.9)
Caucasian: # (%)	10 (76.9)	15 (78.9)	7 (70.0)	8 (72.7)

(Groups with subscripts differ at p<.05)

Physiological Measures.

Otoacoustic Emissions

To examine group differences in OAEs (CEOAE, SOAE, DPOAE), a one way ANOVA comparing the groups was computed for each type of OAE. Post hoc, pair-wise Tukey tests were then computed. While there is no evidence that CEOAEs vary with ethnicity, African-Americans and Asian-Americans may have more numerous

SOAEs (Whitehead, Kamal, Lonsbury-Martin, Martin, 1993). We conducted analyses with all ethnicities included, and again with only Caucasian boys, our largest group. Inclusion of children from all ethnicities did not materially affect the analyses; therefore, only the results of analyses with all children are presented here. Data are shown in Table 2.

Analyses comparing DPOAE results at 50 dB for each ear revealed no group differences for the left [F (3, 47) =.465, p=.708], or the right [F (3, 49) =1.429, p=.247] ear. Although DPOAE data were collected across 7 levels for each ear (7 dB intervals from 29 dB to 71 dB), only those descriptive data obtained at 50 dB are presented here as this is the frequency level at which most children produced a DPOAE. At 29 dB children produced the weakest DPOAEs which became progressively stronger up to 71 dB. However, at no level did differences between groups approach statistical significance.

Analyses of SOAEs included both the strength of SOAEs detected as well as their number. No group differences in SOAE strength were noted for the left [F (3, 40) =1.626, p=.200], or the right ear [F (3, 36) =1.397, p=.261]. Similarly, examination of the number of SOAEs for the left [F (3, 51) =.744, p=.531] and right [F (3, 48) =.527, p=.666] ear did not demonstrate group differences.

For CEOAE measurements, data were collected for two click levels for each ear (0 and -6 dB). Left ear CEOAEs did not differ between groups at either the standard click presentation level [F (3, 39) =.143, p=.934], or at the -6 dB level [F (3, 34) =.524, p=.669]. Right ear CEOAEs were similarly unrevealing at the standard level [F (3, 43)

=1.042, p=.385], and the -6 dB level [F (3, 42) =1.004, p=.401]. Post-hoc Tukey tests failed to demonstrate pair-wise differences for either ear, at either level.

Table 2

	Left Ear			Right Ear	
	DPOAE 50 db			DPOAE 50 dB	
	N	Mean	Std Dev	N	Mean	Std Dev
Control	13	0.825	7.868	13	-5.531	9.192
ADHD/C	17	-3.179	9.727	17	-3.256	10.291
ADHD/IA	9	-1.267	12.067	10	2.665	12.646
ADHD/SCT	9	-0.654	7.399	10	0.549	10.041
	SOAE Strength			SOAE Strength	
Control	9	-8.176	8.567	8	-7.308	11.769
ADHD/C	16	-6.892	6.633	13	-1.214	8.138
ADHD/IA	8	-7.968	8.791	9	-5.532	10.422
ADHD/SCT	8	-0.436	10.282	7	1.834	10.030
	SOAE Number			SOAE Number	
Control	12	1.917	1.730	13	1.923	3.013
ADHD/C	19	1.895	1.410	17	2.647	2.178
ADHD/IA	10	1.300	0.949	10	2.300	2.058
ADHD/SCT	11	2.273	1.794	9	3.222	2.635
	CEOAE 0 db			CEOAE 0 dB	
Control	10	11.617	3.573	9	11.692	2.371
ADHD/C	13	11.122	3.499	16	9.673	4.089
ADHD/IA	8	11.420	0.710	10	11.922	4.330
ADHD/SCT	9	12.058	4.203	9	11.637	3.657
	CEOAE -6 dB			CEOAE -6 dB	
Control	8	7.740	3.359	9	9.221	4.013
ADHD/C	12	8.998	4.516	16	6.984	3.780
ADHD/IA	7	7.343	1.373	9	9.687	4.448
ADHD/SCT	8	9.273	4.006	9	9.273	5.794

Finger-Length Ratios

Finger-length ratios have been shown to vary across ethnic groups (Manning, 2002). For this reason, all non-Caucasian children were removed from FLR analyses. One-way ANOVAs were computed to examine group differences in FLRs for each of the 12 possible ratios (i.e., 6 ratios for each hand). Follow-up post hoc, pair-wise Tukey tests were then computed. Data are shown in Table 3.

No statistically significant group differences were noted on left hand analyses. Examination of the right hand indicated differences at the trend level for the 2D:3D ratio [F (3, 39) =2.503, p=.075], as well as for the 4D:5D ratio [F (3, 39) =2.274, p=.096]. Pair-wise analyses indicated that children with SCT had smaller (more masculine) means than controls at the trend level (p=.091) on the 2D:3D ratio, while none of the pair-wise comparisons on the 4D:5D ratio were statistically significant. A group difference was observed on the 2D:5D ratio [F (3, 39) =3.394, p=.028]. Post-hoc analyses revealed that children with ADHD/IA had larger ratio means (less masculine) than children with ADHD/C and SCT. Thus, in our sample, some evidence emerged to suggest that children with SCT represent a masculinized subset of children, while the opposite pattern (i.e., a more "feminized") pattern emerged for those with ADHD/IA.

We conducted effect-size analyses on the one measure (FLRs) that provides the most directly comparable results to those reported by McFadden et al. (2005). The analyses are based on unpaired, two-tailed t-test comparisons and are reported in Table 4. These comparisons were made with only Caucasian boys. As shown, these effect sizes suggest a stronger pattern of masculinization for the SCT group.

Table 3 Finger Length Ratios

Left	N		2D:3D	2D:4D	2D:5D	3D:4D	3D:5D	4D:5D
Control	10	Mean	0.90	0.96	1.18	1.06	1.31	1.23
		Std	0.03	0.04	0.09	0.02	0.08	0.06
ADHD/C	15	Mean	0.89	0.97	1.18	1.10	1.33	1.22
		Std	0.04	0.07	0.08	0.13	0.12	0.07
ADHD/IA	7	Mean	0.90	0.96	1.21	1.07	1.35	1.26
		Std	0.02	0.03	0.02	0.03	0.03	0.03
SCT	8	Mean	0.90	0.96	1.16	1.07	1.29	1.20
		Std	0.01	0.01	0.06	0.02	0.08	0.07
Right	N		2D:3D	2D:4D	2D:5D	3D:4D	3D:5D	4D:5D
Control	10	Mean	0.92	0.97	1.19	1.06	1.30	1.23
		Std	0.03	0.05	0.05	0.04	0.04	0.03
ADHD/C	15	Mean	0.9	0.96	1.18 *a*	1.07	1.32	1.23
		Std	0.02	0.03	0.06	0.02	0.08	0.06
ADHD/IA	7	Mean	0.91	0.98	1.25 *b*	1.07	1.37	1.28
		Std	0.02	0.04	0.04	0.03	0.04	0.03
SCT	8	Mean	0.89	0.96	1.17 *a*	1.08	1.32	1.23
		Std	0.02	0.02	0.02	0.02	0.04	0.04

(Groups with subscripts differ at p<.05)

Table 4	Hand	2D:3D	2D:4D	2D:5D	3D:4D	3D:5D	4D:5D
Controls vs. ADHD/C	Left	0.49	-0.10	0.06	-0.34	-0.24	0.15
	Right	0.71	0.44	0.21	-0.16	-0.27	-0.20
Controls vs. ADHD/IA	Left	0.22	0.10	-0.41	-0.11	-0.63	-0.64
	Right	0.27	-0.11	-1.16*	-0.38	-1.78*	-1.61*
Controls vs. SCT	Left	0.27	0.02	0.35	-0.36	0.26	0.41
	Right	1.07*	0.40	0.44	-0.57	-0.50	0.01
ADHD/C vs. ADHD/IA	Left	-0.37	0.17	-0.55	0.31	-0.15	-0.80
	Right	-0.64	-0.65	-1.28*	-0.31	-0.90	-0.92
ADHD/C vs. SCT	Left	-0.36	0.13	0.32	0.27	0.44	0.26
	Right	0.37	-0.11	0.12	-0.60	-0.07	0.19
ADHD/IA vs. SCT	Left	0.04	-0.14	1.11	-0.19	0.99	1.15*
	Right	1.28*	0.63	2.12*	-0.16	1.27*	1.47*

Positive entry designates greater masculinization. Unpaired t-test, two-tailed: *=p<.05
Ns: Control=10, ADHD/C=15, ADHD/IA=7, SCT=8

Neurocognitive Measures

As with previous analyses, ANOVAs were used to compare all groups, with Tukey tests used to make follow up pair-wise comparisons for significant effects. For variables with which age correlated significantly, additional analyses are reported with age as a covariate. Data are shown in Table 5.

Stop-Signal Task

Results of the Stop-Signal Task provides choice-reaction time (the mean time to observe the "X" or "O" stimulus and choose) and signal-reaction time (the mean time to inhibit the prepotent response on half of the auditory signal trials). Stop-signal reaction time (SSRT) is calculated by subtracting signal reaction time from choice reaction time. Our primary outcome variable is stop-signal reaction time, but choice-reaction time also was examined. SSRT means differed significantly at the group level [F (3, 52) =2.898, p=.044], but examination of pair-wise comparisons yielded only a trend (p=.068) towards children with ADHD/C having longer (worse) SSRTs than controls. Choice-reaction time analyses also yielded group differences [F (3, 52) =3.547, p=.021]. Pair-wise analyses indicated that children with SCT were slower in deciding than controls (p=.018), with trends towards their also showing slower choice reaction times than children with ADHD/C (p=.075), or with ADHD/IA (p=.090). Age correlated significantly with SSRT scores (r=-0.33, p=0.02) and choice-reaction time scores (r=-0.38, p=0.01). When analyses were run with age as a covariate, the SSRT findings became a trend [F (3, 52) =2.537, p=.052], although the trend for children with

ADHD/C to have higher scores than controls remained (p=.055). Choice-reaction time findings remained significant [F (3, 52) =5.150, p=.002] when age was used as a covariate, although the pattern of between-group differences changed somewhat. Under these conditions, the children with SCT had longer choice-reaction times than controls and children with ADHD/C, but the trend towards longer latencies than children with ADHD/IA disappeared.

Woodcock-Johnson III: Decision Speed

Analyses of Decision Speed scores (number correct in 3 minutes) failed to produce significant differences at the group level [F (3, 52) =.495, p=.687], or with post-hoc Tukey tests. As expected, age did not correlate with Decision Speed scores because these standard scores were obtained from age-based norms.

Trail-Making Test

The Trail-Making Test provides standard scores for performance (based on latency) on Trails A (connecting dots in numeric sequence) and for performance on Trails B (connecting dots in alternating and increasing alphabetic and numeric sequence). Numbers of errors on these measures also were recorded. The primary outcome variable for this study was Trails B (a measure of cognitive flexibility), although the other outcome variables also were assessed. Groups did not differ on either Trails A [F (3, 52) =.574, p=.635] or Trails B [F (3, 52) =1.179, p=.328]. On both Trails A and B, children with ADHD/C made the greatest number of errors, but these differences did not approach statistical significance. While these scores were

obtained from age-based norms, performance on Trails A did correlate with age (r=-0.32, p=0.02). After covarying for age on Trails A, a group difference was noted [F (3, 52) =2.654, p=.044], and post-hoc analyses indicated trends for children with ADHD/C (p=.059), and those with SCT (p=.069) to complete this task more slowly than controls.

WISC-IV: Digit Span

While groups did not differ in prorated IQ scores, their performance on the Digit Span subtest of the WISC-IV did differ [F (3, 52) =2.972, p=.041], with children with ADHD/C performing more poorly than controls (p=.044). This task is normally considered a measure of primary auditory attention (as measured by total number of digits the child can recite from memory forward) and working memory (digits backwards). When reciting digits forward [F (3, 52) =3.935, p=.014], children with ADHD/C performed more poorly than controls (p=.015). A group trend [F (3, 52) =2.373, p=.082] was observed on digits backward, with a trend (p=.067) for children with ADHD/C to perform more poorly than controls. This suggests a decrement in overall auditory attention for these children rather than a focal deficit in working memory as has been proposed (Barkley, 1997).

Mental Rotation Test

The Mental Rotation Test is a computerized measure which provided both total number of correct responses as well as average latency across 30 trials. Groups differed significantly [F (3, 52) =3.565, p=.021] in total number of correct responses, with children with SCT providing more correct responses than children with ADHD/C.

However, groups did not differ in average response time [F (3, 52) =1.573, p=.208]. Age correlated positively with number of correct responses (r=0.43, p=.001), and negatively with latency scores (r=-0.30, p=0.03); that is, older children were both more accurate and quicker. When covarying for age, number of correct responses continued to show statistically significant group mean differences [F (3, 52) =6.630, p=0.00], and response time showed a non-significant trend [F (3, 52) =2.280, p=.074]. In pair-wise comparisons with age as a covariate, boys with SCT were more accurate than boys in all other groups, with a trend (p=.063) for boys with ADHD/C to respond more quickly than those with SCT.

SCAN-C

The SCAN-C consists of four central auditory processing subtests which generate a single Composite total based on the scaled scores of the subtests. The Composite score is based on norms for children ages 5-11; older children's scores are based on adult norms. There was not a group difference for Composite score [F (3, 52) =1.809, p=.158], but analysis of the Filtered Words subtest indicated a significant difference [F (3, 52) =3.263, p=.029], as did the Auditory Figure-Ground subtest [F (3, 52) =3.476, p=.023], while the Competing Words [F (3, 52) =.707, p=.553] and Competing Sentence subtests did not [F (3, 52) =.381, p=.767]. Examination of pair-wise post-hoc tests indicate that on the Filtered Word subtest, children with ADHD/C performed more poorly than children with SCT, while on the Auditory Figure-Ground subtest, controls performed more poorly than children with ADHD/IA. Age correlated significantly with the Composite score (r=-0.37, p=0.01) and the Auditory Figure-

Ground (r=-0.28, p=0.05), Competing Words (r=-0.31, p=0.03), and Competing Sentences (r=-0.34, p=0.01) subtests. After covarying for age, a group difference was observed on the Composite score [F (3, 52) =4.291, p=.005], and the Auditory Figure-Ground subtest [F (3, 52) =4.811, p=.002], while the Competing Words subtest showed a trend toward significance [F (3, 52) =2.062, p=.100], but the Competing Sentences failed to show a group difference [F (3, 52) =1.958, p=.116]. Post-hoc analyses revealed between-group differences on the Composite and Auditory Figure-Ground scores. On both tests children with ADHD/IA scored more highly than children with ADHD/C, while on the Auditory Figure- Ground subtest they performed better than controls, with a trend (p=.089) toward better performance than controls on the Composite score. Children with SCT demonstrated a trend (p=.072) toward better performance than controls on the Auditory Figure-Ground, as well as on the Composite score (p=.056) compared to children with ADHD/C. Covarying for age did not affect the pattern of between-group relationships on the Competing Words subtest.

Table 5

		Control	ADHD/C	ADHD/IA	SCT
	N	13	19	10	11
Stop Signal: SSRT	Mean	209.18	280.96	221.93	273.97
	Std	60.21	87.69	53.46	98.48
Stop-Signal: Choice-Reaction Time	Mean	637.13*a*	667.56	657.07	758.15*b*
	Std	82.76	97.41	113.08	93.16
Decision Speed	Mean	99.92	95.74	94.40	100.73
	Std	7.8	20.13	12.84	13.78
Trails A	Mean	108.31	104.05	101.7	103.00
	Std	11.00	15.11	12.15	12.27
Trails B	Mean	107.31	108.32	100.4	100.36
	Std	11.44	14.46	13.85	17.31
WISC-IV Digit Span	Mean	11.23*a*	9.00*b*	10.70	10.73
	Std	2.17	2.19	2.41	2.49
Mental Rotation: Number Correct	Mean	21.85	18.89*a*	21.30	24.09*b*
	Std	5.24	3.96	3.09	4.59
Mental Rotation: Response Time	Mean	5.51	5.28	4.92	6.48
	Std	2.4	1.82	1.33	0.93
SCAN-C: Composite	Mean	86.92	90.79	96	101.09
	Std	22.2	14.94	13.36	9.76
SCAN-C: Filtered Word	Mean	9.62	9.00*a*	10.6	11.54*b*
	Std	2.53	2.67	1.58	1.63
SCAN-C: Auditory Figure-Ground	Mean	6.77*a*	8.11	9.70*b*	9.36
	Std	2.95	2.49	1.77	2.29
SCAN-C: Competing Words	Mean	8.46	9.37	9.90	10.45
	Std	4.72	3.35	2.77	2.46
SCAN-C: Competing Sentences	Mean	8.38	8.42	7.80	9.45
	Std	5.25	3.39	2.97	1.86

(Groups with different subscripts differ at p<.05)

Exploratory Analyses

Sleep-Related Breathing Disorders

The Sleep-Related Breathing Disorders Questionnaire consists of 24 items which ask the parent to indicate the presence or absence of symptoms of sleep disturbance in their children (see Appendix C). Question 17 asked parents to report the total number of hours slept by their child each evening. This question was removed from the analyses to permit a composite score based on the remaining 23 items scored as "0" or "1" if the symptom was absent or present, respectively. A group difference was observed on these items [F (3, 52) =2.905, p=.044]. Examination of pair-wise comparisons indicated that the children with SCT were rated by parents as having a greater number of sleep-related symptoms than controls. Parents also reported more sleep-disturbance symptoms among younger than older children (r=-0.38, p=0.00). However, when the effects of age were statistically controlled, a group difference in number of symptoms remained [F (3, 52) =3.196, p=.021], and children with SCT were still rated as having a greater number of symptoms than controls. Children were also asked to rate the presence of symptoms of sleep disturbance in themselves; these ratings did not show group differences [F (3, 52) =1.827, p=.155]. Data are shown in Table 6.

Table 6

		Control	ADHD/C	ADHD/IA	SCT
	N	13	19	10	11
Parent Sleep Ratings	Mean	2.38*a*	4.74	4.10	5.73*b*
	Std	2.36	3.68	1.66	2.83
Child Sleep Ratings	Mean	1.92	3.05	2.70	2.27
	Std	1.38	1.61	0.95	1.42

(Groups with subscripts differ at p<.05)

Birth order

Parents were asked to report the total number of previous male births to the child's biological mother. While children with ADHD/C and SCT had the largest group means, a group difference was not noted [F (3, 52) =1.053, p=.378]. The means (Std Dev) for each group were: controls=.62(.768), ADHD/C=1.11(1.696), ADHD/IA=.60(.699), SCT=1.45(1.695). Number of older brothers was negatively correlated with CEOAEs in the left ear (r=-.375, p=.017), but did not show statistically significant correlations with other physiological measures. With Bonferroni correction (Darlington, 1990; pg. 249+) using the 10 possible OAE correlations, the correlation with CEOAEs was no longer significant (adjusted p=.170). Birth order did not correlate with symptoms of ADHD or SCT.

Correlations

Exploratory analyses included correlations to further understand the relationships between variables. Of primary interest here were correlations of ADHD and SCT symptoms and our physiological variables with neurocognitive measures to determine what effects ADHD status or masculinized FLRs and OAEs may have on cognition. For all children, symptoms of hyperactivity/impulsivity (r=0.35, p=0.01), inattention (0.41, r=0.00), and SCT (r=0.39, p=0.00) were positively correlated with Stop-Signal Reaction Time latencies. That is, the more symptoms of ADHD or SCT a child was rated as having, the more likely they were to perform poorly. SCT symptoms were negatively correlated (r=-0.31, p=0.02) with performance on Trails B of the Trail-

Making Test. Symptoms of hyperactivity/impulsivity were negatively correlated (r=-0.38, p=0.01) with number of correct responses on the Mental Rotation Test. When only children with ADHD/IA or SCT were considered, SCT symptoms were negatively correlated with all fifth digit ratios (i.e., 2D:5D, 3D:5D, 4D:5D) on both the left and right hands. Specifically, on the left hand the correlations were: 2D:5D (r=-0.45, p=0.04), 3D:5D (r=-0.45, p=0.04), and 4D:5D (r=-0.46, p=0.04). On the right hand the correlations were: 2D:5D (r=-0.53, p=0.01), 3D:5D (r=-0.56, p=0.01), and 4D:5D (r=-0.62, p=0.00). This pattern suggests that children with high ratings of SCT are more likely to appear masculinized on 5th digit ratios bilaterally.

Finally, parent ratings of sleep disturbance were correlated with other variables. Sleep ratings were positively correlated with symptoms of hyperactivity/impulsivity (r=0.35, p=0.01), inattention (r=0.42, p=0.00), and SCT (r=0.39, p=0.00), suggesting that children with ADHD are more prone to sleep disturbance than other children as has been previously reported (Corkum, Tannock, & Moldofsky, 1998). Three blocks of Stop-Signal performance were recorded for each child. Across each of these blocks as well as the composite SSRT score, parent ratings of sleep disturbances were positively correlated with longer SSRT latencies (e.g., composite SSRT: r=0.35, p=0.01).

Follow-Up Analyses

High Masculinization vs. Low Masculinization

Children with ADHD were rank ordered, regardless of ADHD diagnostic group, based on their right hand 5th digit (2D:5D, 3D:5D, and 4D:5D) ratios. Comparisons were made only with Caucasian children as FLRs have been observed to vary across

ethnicities (Lippa, 2003). In doing so, 10 non-Caucasian children were removed. Two groups, each with 15 children, with either high or low masculinization on these FLRs were formed. The High group contained 4 non-right-handed children and 5 non-right-handed children were placed in the Low group. As expected, comparisons on individual FLRs were generally in the expected direction, with High group FLRs being smaller (more masculine) and the Low group having larger ratios. Specifically, group differences were noted on the left hand 2D:5D and 3D:5D ratios with Tukey tests indicating the High and Low groups differed from each other, but did not differ from controls on these ratios. Main effects were observed for the right hand 2D:3D, 2D:5D, 3D:5D, and 4D:5D ratios. On the 2D:3D ratio, the High group had a smaller mean ratio than controls. High and Low groups differed from each other and controls on the 2D:5D ratio, while on the 3D:5D and 4D:5D ratios the Low group differed from the High group and controls.

Comparisons of the High and Low groups on other variables yielded few differences. Groups did not differ in terms of age, IQ, or reading scores. There were no group differences in OAEs. On neurocognitive comparisons, a main effect was observed for parent ratings of sleep disorders, with children in the High group being rated by parents as having more sleep problems than controls.

Comparison with McFadden et al., 2005

In order to better understand our data and to permit comparison with previously published data (McFadden, et al, 2005), DSM-IV ADHD diagnostic criteria (i.e., no SCT group was used) were used to classify Caucasian participants. Analyses of our

data based on these groupings failed to demonstrate differences for FLRs on either the left or right hand. Similarly, pair-wise analyses did not indicate statistically significant differences at this level. Methodology was somewhat different in collection of CEOAEs, but data were compared and no group differences were observed. In the McFadden et al. (2005) study CEOAEs were made using a laptop computer at the Austin Neurological Clinic in a quiet room which was not sound-proofed as in the current study. FLR data for the revised (i.e., three group) comparisons are shown in Table 7.

Table 7 Finger Length Ratios

Left	N		2D:3D	2D:4D	2D:5D	3D:4D	3D:5D	4D:5D
Control	10	Mean	0.90	0.96	1.18	1.06	1.31	1.23
		Std	0.03	0.04	0.09	0.02	0.08	0.06
ADHD/C	15	Mean	0.89	0.97	1.18	1.10	1.33	1.22
		Std	0.04	0.07	0.08	0.13	0.12	0.07
ADHD/IA	15	Mean	0.90	0.96	1.18	1.07	1.31	1.23
		Std	0.02	0.02	0.06	0.02	0.07	0.06
Right	N		2D:3D	2D:4D	2D:5D	3D:4D	3D:5D	4D:5D
Control	10	Mean	0.92	0.97	1.19	1.06	1.30	1.23
		Std	0.03	0.05	0.05	0.04	0.04	0.03
ADHD/C	15	Mean	0.90	0.96	1.18	1.07	1.32	1.23
		Std	0.02	0.03	0.06	0.02	0.08	0.06
ADHD/IA	15	Mean	0.90	0.97	1.21	1.08	1.34	1.25
		Std	0.02	0.03	0.05	0.02	0.05	0.04

(Groups with subscripts differ at p<.05)

Chapter 8: Discussion

A growing body of research suggests abnormalities in prenatal androgen exposure can be detected with analyses of otoacoustic emissions and finger length ratios (Manning, 2002), that these physical markers reflect an organizational influence of these hormones on the developing fetus (Falter, Arroyo, Davis, 2006; McFadden, 2002), and that they may affect adult behavior (e.g., Loehlin, McFadden, 2003). Results of studies conducted examining women's performance on cognitive tasks during different phases of their menstrual cycle (Hampson & Kimura, 1988) suggest that fluctuating levels of hormones can have temporary effects on cognition. If fluctuating levels of hormones can affect cognition and prenatal androgen exposure has an organizing effect that alters adult behavior, it is likely that those behavioral changes are reflected in underlying cognitive processes. In fact, there is some evidence to suggest that this is the case (e.g., Bull & Benson, 2006; Burton, Henninger, Hafetz, 2005). Therefore, if a group of individuals has shown common behavioral characteristics and abnormal OAEs and FLRs, it may also be the case that they share unusual cognitive processes. Children with ADHD have been found to have differences in OAE and FLR ratios suggestive of prenatal androgen influence (McFadden et al., 2005) and exhibit cognitive and behavioral differences from children without ADHD (Gaub & Carlson, 1997) possibly reflecting alterations in these processes secondary to androgen exposure.

This study sought to replicate and extend our previous work suggesting an association between abnormal androgen exposure and ADHD/IA (McFadden et al., 2005) by comparing ADHD and control groups on OAEs, FLRs, ADHD symptoms, and numerous neurocognitive processes. Further, there is a growing body of literature to

support the argument that prenatal androgen exposure is related to symptoms of hyperactivity (Williams, Greenhalgh, & Manning, 2003), or even diagnosable ADHD (de Bruin, Verheij, & Wiegman, 2006). Animal models appear to also provide some support for this argument (Li & Huang, 2005; King, Barkley, Delville, & Ferris, 2000). Based on previous clinical diagnosis and current parent ratings of their behavior, boys who participated in the ADHD groups were assigned to one of three groups: ADHD Combined Type, ADHD Inattentive Type, and a third, experimental ADHD group, drawn from the children with ADHD/IA with high sluggish cognitive tempo (SCT).

As discussed below, expected group differences on physiological variables were not obtained, although an experimental construct (SCT) may identify a more masculinized subgroup of children with ADHD/IA. Group differences were observed on neurocognitive and other variables further suggesting that children with SCT may represent a homogenous group of children with ADHD/IA. This pattern, and exploratory analyses conducted in an effort to determine those factors affecting the pattern of results, are explicated below.

Group Characteristics

Groups did not differ on obtained prorated IQ scores or on measures of reading achievement. This was somewhat unexpected as children with ADHD have been found to have elevated rates of learning disabilities (Willcutt & Pennington, 2000). Further, boys have been found to be at greater risk for developing a reading disability than girls (Lambe, 1993), suggesting the possibility of an androgen influence on reading ability. The relatively high IQ group averages (all groups in the high average range of

intellectual functioning) may have decreased the incidence of comorbid LD, because our criteria required children to show significantly below average (85 or lower) reading scores to be so designated. Nonetheless, the lack of group differences on IQ and reading ability indicate that, in this sample, our hypothesis that boys with ADHD, and more specifically, boys with ADHD/IA, would have higher rates of learning disabilities, was not supported.

Roughly equal proportions of Caucasian to non-Caucasian children were observed in each group, with percentages ranging from 70.0% (7/10) in children with ADHD/IA to 78.9% (15/19) in children with ADHD/C. While all children within the control group were right handed, fewer right-handers were observed in children with ADHD (78.9% ADHD/C, 50% ADHD/IA, and 90.9% SCT). Ethnicity has been demonstrated to effect finger-length ratios (although the pattern of male/female differences typically remains; Manning, 2002) and possibly some types of OAEs (Whitehead, Kamal, Lonsbury-Martin, Martin, 1993), while Geschwind (1985) proposed that handedness would be related to abnormal androgen exposure. However, while a greater number of non-right-handed boys were observed in children with ADHD than in controls, suggesting a greater prenatal exposure to androgens, the only observed group difference was related to children with ADHD/IA actually appearing less masculine than other children (see below). Further, handedness did not correlate with any of the physiological variables.

Physiological Measures

Previous research has suggested that children with ADHD will appear more masculinized on measures of otoacoustic emissions and in their patterns of finger-length ratios (McFadden et al., 2005). However, analyses of our current results failed to demonstrate group differences in OAEs. When controls were compared to children with ADHD/C and those with ADHD/IA, no group differences were observed for FLRs. After subdividing children with ADHD/IA into groups based on SCT symptoms, one finger-length ratio demonstrated a group difference, with boys with ADHD/IA having a larger ratio than boys with ADHD/C or those with SCT. This is contrary to our expectations and our previous research showing that boys with ADHD/IA have smaller FLRs as well as weaker and less numerous OAEs. That is, previous research suggested that these children had been exposed to higher levels of prenatal androgens, leaving them with hypermasculinized FLRs and OAEs. However, our current findings suggest that boys with ADHD/IA, at least on this one finger-length ratio, actually appear less masculine than other children. In contrast, at the trend level, children with SCT had a smaller (more masculine) right hand 2D:3D ratio than controls. Effect-size comparisons provided a somewhat stronger picture of this pattern of masculinization differences in the ADHD/IA and SCT groups. A possible interpretation of these findings is that children with SCT represent a subgroup of children with ADHD/IA who are more masculinized on physiological measures. The initial study by McFadden et al. (2005) did not subdivide children into ADHD/IA and SCT groups, and this cannot be done reotrospectively, and may have had a greater number of children who would meet this study's criteria for SCT. Children with SCT may, therefore, actually represent a

somewhat more masculinized group. Corroborating this possibility, among children with ADHD/IA and SCT, SCT symptoms were found to correlate negatively with FLRs involving the 5th digit on the left and right hands. In other words, greater parent ratings of SCT symptoms were related to lower (more masculine) 5th digit ratios.

Neurocognitive Variables

In an attempt to understand the effects prenatal androgen exposure may have on cognitive processes, participants completed measures of attention, executive functioning, visuospatial ability, and central auditory processing. One measure of executive functioning requiring rapid visual analysis of stimuli and creation of category relationships (WJ-III Decision Speed) did not discriminate between groups. From a cognitive perspective, this is a complex task requiring recruitment of several underlying processes (e.g., attention, working memory, processing speed) to create cognitive sets and it may not be as sensitive to deficits in any one of those processes as more focused measures may be.

In looking at performance on measures of attention and executive functioning, several observations suggest possible subtype differences in these processes. There was a trend for children with ADHD/C and those with SCT to perform more slowly than controls on a task requiring rapid visual search and graphomotor speed (Trail-Making Test A). Children with SCT may be expected to do more poorly on this task due to their proposed deficits in alerting attention (rapidly focusing on new stimuli) and recruitment of resources to perform quickly on speeded tasks. Similarly (and somewhat

surprisingly), children with ADHD/C have consistently shown slower performance across a variety of cognitive tasks (Willcutt et al., in submission).

Performance on the Stop-Signal Task was somewhat more revealing of subtype differences in attention. In responding quickly to simple visual stimuli on the Stop-Signal Test, children with SCT had the slowest overall reaction times and differed significantly from controls and children with ADHD/C on this measure. This may represent a hesitancy to respond until more accurate appraisals can be made. Alternatively, it may represent a general slowing in behavioral responses that incidentally permits greater accuracy as cognitive processes continue to assess new information. Because their ability to inhibit the prepotent response (response to the initial stimulus) did not differ from other children, this appears to reflect an overall slowing in alerting or initial attending to new visual stimuli, but adequate inhibition of response. Evidence for a deficit in attention has been proposed as a core cognitive deficit in children with ADHD/IA (Barkley, 1997) and has recently found support in theory-based cognitive testing (Booth, Carlson, Tucker, 2007). Barkley (1997) proposed that children with ADHD/C would have greater deficits in inhibition than other children and our current data hinted ($p=.055$) at these children having greater difficulty than controls at inhibiting the prepotent response on the Stop-Signal Test, providing some support for that hypothesis and the prediction that subtypes of ADHD have differences in underlying cognitive processes which had previously been considered an undifferentiated deficit in attention.

Children in our sample did not differ in terms of prorated IQ, nor did their performance on subscales that assessed visuoconstructional abilities (WISC-IV Block

Design) and developed lexicon (Vocabulary) used to calculate prorated IQ scores. However, children with ADHD/C performed more poorly than controls on a task requiring immediate auditory attention and working memory, an aspect of executive functioning that acts as a mental "scratch pad" and permits simultaneous manipulation of multiple ideas or pieces of data. Their performance on this task indicated poorer primary auditory attention with a trend towards poorer working memory. This suggests an overall deficit in auditory attention rather than an impairment in working memory as has been proposed by Barkley (1997).

While children did not differ in visuoconstructional abilities as measured by the WISC-IV, their performance on the Mental-Rotation task further suggests differences in underlying cognitive processes required to complete this task. There was a trend ($p=.063$) for children with ADHD/C to complete this task more quickly than those with SCT, but they had the fewest number of total correct responses. Children with SCT on the other hand had the slowest times to completion, but were more accurate than all other groups in their responses. These data support the findings from the Stop-Signal Task that children with SCT are slower to alert to new stimuli and make rapid decisions, but that other cognitive processes may be engaged during this interval allowing more accurate appraisals.

Performance on a measure of central auditory processing (SCAN-C) indicated a trend ($p=.089$) for controls to perform more poorly overall than children with ADHD/IA. Controls also performed worse than children with ADHD/IA and those with SCT on a subscale (Auditory Figure-Ground) used to obtain overall composite scores. Overall performance of children with ADHD/C was lower than children with

ADHD/IA, with a trend (p=.056) for lower performance than those with SCT. An initial hypothesis of this study was that children with ADHD would perform more poorly than controls due to deficits in attention. While children with ADHD/C performed relatively poorly on this measure than other children with ADHD, the performance of controls was unexpected and is difficult to explain. Examination of group means on tasks with well-established norms indicated that controls performed within normal limits for the populations used to standardize these tasks. However, their performance on the SCAN-C was nearly a standard deviation below the mean on the composite score with reduced performance on three of the four subscales used to calculate the composite score.

Exploratory Analyses

Data on several other topics of interest, including sleep disturbance and birth order, also were collected. When considering inclusion of quality of sleep and sleep behaviors in the study, it was expected that children with ADHD would have higher rates of sleep disturbance than children without ADHD as has been previously reported (Corkum, Tannock, & Moldofsky, 1998). Further, because boys have been found to have higher rates of sleep disturbance than girls, it was expected that sleep disturbance might, in part, be related to prenatal androgen exposure and would be related to OAEs and FLRs. Children with SCT were rated by their parents as having greater numbers of problematic sleep behaviors than controls on this measure. However, physiological variables did not correlate with parent ratings of sleep disturbance. This suggests that children with SCT either may be at risk for developing sleep disorders, or, potentially,

children with sleep disorders may be at risk for being misdiagnosed as having ADHD rather than deficits in attention that are secondary to poor sleep.

Some evidence exists to implicate birth order in altering fetal development (Blanchard, 1997). While there has been some debate as to psychosocial causes for birth order effects on behavior (e.g., Healy & Ellis, 2007), this study examined birth order to assess the relationship between previous male births and physiological markers of androgen exposure. No group differences were noted in number of older brothers, nor were number of previous male births correlated with hyperactive/impulsive, inattentive, or SCT symptoms. Birth order did negatively correlate with one physiological variable (left ear CEOAEs), but given the number of possible correlations this finding should be interpreted with caution.

Limitations

Several limitations need to be kept in mind regarding the findings presented here. Children in the ADHD groups (ADHD/C, ADHD/IA, and ADHD/SCT) were recruited from a private neuropsychology practice and may represent a select population of children from more privileged socio-economic backgrounds and/or families with greater educational achievement. Further, participation for children often necessitated a parent willing to drive them to the University of Texas campus and wait during the three-hour assessment. Control children were recruited from friends of the children with ADHD, or through a community website (Craig's List) which would necessitate some familiarity with navigating the internet, possibly possession of a home computer, and the ability and willingness of a parent to participate. Therefore, our sample may

represent a select group of children from socioeconomic backgrounds with greater resources or well-educated families, and may help to explain their higher scores on the WISC-IV.

As previously noted, while data were collected for girls, we do not present those data here due to small sample size. Comparison of boys and girls on these measures would help to anchor claims of "masculinized" physiological or cognitive characteristics. Further, examination of group differences among girls might provide additional data regarding the nature of androgen influence on the developing fetus in terms of cognitive abilities or the development of ADHD.

A significant limitation to this study was reliance on parent ratings for symptoms of ADHD. Several attempts were made to contact and recruit the children's teachers, but a surprisingly low number of teachers (26 %) returned rating forms. Previous research of this kind performed from this lab resulted in teacher participation rates at least twice those observed in this study. A decision was made by the University of Texas at Austin's Institutional Review Board to include teacher consent forms (an original and copy for the teacher) resulting in 7 sheets (2 consent forms, 2 pages of behavior ratings, 1 letter of introduction, 1 receipt, and 1 copy of the parent consent form) sent to the teacher in order to obtain two pages of behavior ratings. This required the teacher to read through and sign several pages as well as complete the behavior ratings and may have made teachers less willing to participate.

Power issues are also of concern. While the overall group sizes were likely adequate for detecting group difference, they became quite low for some comparisons once the SCT group was formed, as well as for those analyses excluding non-

Caucasians. Effect-size comparisons showed stronger evidence of predicted differences, suggesting the need for replication using larger samples.

Summary and Future Directions

This study had two primary goals: re-assessment of physiological markers suggesting prenatal androgen exposure among some children with ADHD, and exploration of possible neuropsychological correlates of that exposure. A previous study (McFadden et al., 2005) suggested a link between children with ADHD/IA and abnormal prenatal androgen exposure after these children appeared hyper-masculinized on analyses of otoacoustic emissions and finger-length ratios. Using standard ADHD diagnostic classification criteria, our current findings failed to replicate that study, with no differences detected on these physiological variables. However, when children with ADHD/IA were divided into those with versus without SCT, some- albeit mixed-evidence emerged on FLR comparisons suggesting a more masculinized pattern for the SCT group, with the opposite (i.e., more "feminized") pattern for the non-SCT ADHD/IA group. Further, when only children with ADHD/IA or those with SCT were considered, SCT symptoms were negatively correlated with fifth digit ratios on both hands indicating a more masculinized pattern of results for children high in SCT symptoms.

Other measures yielded results of note. Children with SCT were rated by their parents as having more sleep problems than other children, and as previously noted, SCT symptoms appeared to be related to a more masculinized FLR presentation. This suggests that prenatal androgen exposure may predispose children to deficits in sleep

and/or primary deficits in attention. Finally, neurocognitive measures provided some evidence for subtype differences in children with ADHD, with results fairly consistent with previous findings in the literature. A particularly noteworthy finding was support for a recently reported alerting deficit in children with SCT (Booth, Carlson, & Tucker, 2007).

Further exploration of SCT and sleep disorders to understand the potential role of prenatal androgen exposure in ADHD is clearly warranted. It would be valuable if such work recruited larger sample sizes for comparisons of interest. Finally, expanding outcome measures to further elucidate the neurocognitive factors differentiating subgroups- possibly mapping onto physiological measures- may yield information that could lead to making etiologically-driven ADHD subtyping designations.

Appendix A

Child Behavior Ratings

Parent

Today'sDate:_____

Completed By:_____

Relationship to Child:_____

Please circle the number that best describes the child's behavior during the past six months

0=Rarely or Never, **1**=Sometimes, **2**=Often, **3**=Very Often

1. Fails to give close attention to details or makes careless mistakes	0 1 2 3
2. Has difficulty sustaining attention in tasks or play activities	0 1 2 3
3. Does not seem to listen when spoken to directly	0 1 2 3
4. Does not follow through on instructions and fails to finish tasks	0 1 2 3
5. Has difficulty organizing tasks and activities	0 1 2 3
6. Avoids tasks, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)	0 1 2 3
7. Loses things necessary for tasks or activities	0 1 2 3
8. Is easily distracted by extraneous stimuli	0 1 2 3
9. Is forgetful in daily activities	0 1 2 3
10. Fidgets with hands or feet or squirms in seat	0 1 2 3
11. Leaves seat in the classroom or in other situations in which remaining seated is expected	0 1 2 3
12. Runs or climbs excessively in situations where it is inappropriate	0 1 2 3
13. Has difficulty playing or engaging in leisure activities quietly	0 1 2 3
14. Is often "on the go", or acts as if driven by a motor	0 1 2 3
15. Talks excessively	0 1 2 3
16. Blurts out answers before questions have been completed	0 1 2 3
17. Has difficulty waiting turn	0 1 2 3
18. Interrupts or intrudes on others (e.g. butts into conversations)	0 1 2 3

19. If you indicated that your child has often or very often exhibited any of these behaviors (items 1-18), at what average age did these behaviors first appear? Approximately _____ years old.
20. Did your child ever receive special services in school because of the behaviors listed above? Y N

20a. Did your child ever been to a doctor or counselor because of the behaviors listed above? Y N

20b. If your child has been to a doctor, did the doctor prescribe medication for these difficulties? Y N

20c. If yes, what was the name of the medication? _____

20d. Please rate (circle the number) how well your child has responded to this medication?

1 2 3 4 5 6 7 8 9 10

Very poorly *Adequately* *Extremely well*

21. Is sluggish, slow to respond	0 1 2 3
22. Seems not to hear, needs things repeated	0 1 2 3
23. Seems to be "in a fog"	0 1 2 3
24. Is drowsy or sleepy	0 1 2 3
25. Is easily confused	0 1 2 3
26. Daydreams, stares into space, or gets lost in his/her thoughts	0 1 2 3
27. Is absentminded, forgets things easily	0 1 2 3
28. Is apathetic or unmotivated	0 1 2 3
29. Is underactive, slow moving, or lacks energy	0 1 2 3
30. Is lethargic	0 1 2 3
31. Seems to be unaware of her/his surroundings (for example doesn't notice wet paint or a dangerous situation)	0 1 2 3
32. Has trouble making up his/her mind	0 1 2 3

Did you indicate in item 20 that your child is receiving medication?

Y N

20e. If yes, please rate how effective this medication has been in addressing the behaviors in items 21-32.

1 2 3 4 5 6 7 8 9 10

Very poor *Adequate* *Excellent*

33. Loses temper	0 1 2 3
34. Argues with adults	0 1 2 3
35. Actively defies or refuses adult requests or rules	0 1 2 3
36. Deliberately does things that annoy other people	0 1 2 3
37. Blames others for his or her mistakes or misbehavior	0 1 2 3
38. Is touchy or easily annoyed by others	0 1 2 3
39. Is angry and resentful	0 1 2 3
40. Is spiteful or vindictive	0 1 2 3
41. Is quarrelsome	0 1 2 3

Appendix B

Questionnaire for ADHD, OAE, Neurocognitive Study
Lab of Dennis McFadden, PhD
Department of Psychology
University of Texas

FORM Q

Subject Number _____ Date _____ Time _____
Experimenters_____

Please enter (PRINT)

child's name,_____

name of individual completing _____

relationship to child, _____

current address of child, _____

_____

and telephone number _____

I do ___, do not ___ give permission to be contacted for future or follow-up studies.

If yes, please sign here: _____

_____ I would like to receive group results of this study. Please complete the following if you would like to receive group results of the study sent to a different address than the one noted above:

Name/Address: _____

_____

(street) (city, state) (zip code)

Please carefully remove this page from the remainder of the questionnaire. It will be stored separately to guarantee the confidentiality of your responses on the questionnaire.

Subject Number _____ Date _____

1. What is the child's birth date?_____ 2. Age_____ 3. Sex _____

4. What is the child's natural hair color?_____5. Eye color? _____
   6. Eye Color Number _____
7. How tall is the child?_____ feet _____ inches (Do not answer - experimenter will supply)

8. What is the child's weight?_____

9. Regarding the child's biological mother:
   How many older biological brothers did she have? _____ (Don't know _____)
   How many older biological sisters did she have? _____ (Don't know _____)

10. How many times was the child's biological mother pregnant? _____ D/K
    For those pregnancies not carried to full term, please indicate the sex of the child and how long they were carried:

_____

11. Please list the birth date and sex of each of the biological mother's children:

___/___/___	M/F	___/___/___	M/F
___/___/___	M/F	___/___/___	M/F
___/___/___	M/F	___/___/___	M/F
___/___/___	M/F	___/___/___	M/F
___/___/___	M/F	___/___/___	M/F

12. Has the child ever had problems of any sort with his/her ears or auditory system? Ear infections, lanced
    eardrums, ringing in the ears, temporary or permanent hearing loss, etc.? If so, provide as many details as
    can be recalled.

_____
_____
_____
_____

13. Please indicate any known allergies your child has (e.g., hay fever, allergic reactions to medication, asthma):

_____
_____

14. Does your child suffer from any other respiratory difficulties? _____ If so, please describe:

15. At this moment, is the child suffering from any congestion due to an allergy or cold?
Yes, severe _____ Yes, mild _____ No _____

16. Please indicate any infectious disorders your child has experienced, and the approximate number of times your child has had each disorder. Chickenpox _____ Cold _____ Flu _____
Hand, Foot and Mouth Disease _____
Mononucleosis _____ Other: _____

17. Please note any drugs the child has taken for any reason within the past 24 hours. Include drugs taken for allergies, congestion, pain, upset stomach, dieting, strength or endurance, treatment for ADHD
Products such as aspirin, Cope, Midol, Momentum, Pepto-Bismol and anti-histamines do count as drugs.

	Name, if known	Reason Taken	Dose, if known	When Taken
Prescription Drugs				
Non-prescription Drugs				

18. What is the child's shoe size? _____

Has the child ever engaged in any of the following noisy activities? If so, how often?

	Never	Occasionally	Regularly
19. Ride a motorcycle?	_____	_____	_____
20. Ride in a loud boat?	_____	_____	_____
21. Use another loud vehicle?	_____	_____	_____
22. Play a loud musical instrument?	_____	_____	_____
23. Attend loud concerts or other performances?	_____	_____	_____
24. Listen to loud music?	_____	_____	_____
25. Use a walkman-type listening device?	_____	_____	_____
26. Use noisy power tools?	_____	_____	_____
27. Shoot a rifle or handgun?	_____	_____	_____
How recently? _____			
28. Used a power garden tool (e.g., mower, edger)? _____	_____	_____	
How recently? _____			
29. Used power tools (e.g., saw, drill)?	_____	_____	_____
How recently? _____			

30. The child is extremely sensitive to cold weather (or excessive air conditioning). [circle below]

Strongly Agree	Somewhat Agree	Slightly Agree	Uncertain	Slightly Disagree	Somewhat Disagree	Strongly Disagree

31. Federal reporting procedures request that we ask you to respond to the following with which category(ies) best describe(s) your child:

Ethnic Category:

1. Hispanic, Latino, or Spanish Origin _____
   (Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race) _____
2. **Not** Hispanic, Latino, or Spanish Origin _____
   (please specify, if known)

_____

Racial Category:

1. American Indian or Alaskan Native _____
2. Asian _____
3. Black or African American
4. Native Hawaiian or Other Pacific Islander _____
5. White _____
6. Other or Unknown

32. Has the child previously participated in an experiment on otoacoustic emissions?
Yes ____ No _____ If so, approximately when? _____ (months ago)

33. What is the current level of academic achievement and occupation of the child's primary caregivers?

33a. Mother's education _____, occupation _____

33b. Father's education _____, occupation _____

*If the child's primary caregivers are not his/her biological parents, please indicate for whom the education and occupation for 33a. are _____, and for 33b. _____.

Appendix C

Pediatric Sleep Questionnaire

Please circle the appropriate answer for each question.
Y = Yes
N = No
D/K = Don't Know

While sleeping, does your child…

1) …snore more than half the time? Y N D/K

2) …always snore? Y N D/K
3) …snore loudly? Y N D/K
4) …have "heavy" or loud breathing? Y N D/K

5) …have trouble breathing, or struggle to breathe? Y N D/K

Have you ever…

6) …seen your child stop breathing during the night? Y N D/K

Does your child…

7) …tend to breath through the mouth during the day? Y N D/K
8) …have a dry mouth on waking up in the morning? Y N D/K
9) …occasionally wet the bed? Y N D/K
10) …wake up feeling unrefreshed in the morning? Y N D/K

11) …have a problem with sleepiness during the day? Y N D/K

12) Has a teacher or other supervisor commented that your child appears sleepy during the day? Y N D/K
13) Is it hard to wake up your child in the morning? Y N D/K
14) Does your child wake up with headaches in the morning? Y N D/K
15) Did your child stop growing at a normal rate at any time since birth? Y N D/K
16) Is your child overweight? Y N D/K

17) Approximately, how many hours of sleep does your child receive each night?
_____

18) Has your child ever complained of odd experiences (e.g., hearing or seeing things that were not there) upon waking or just before falling asleep? Y N D/K
If yes, please describe:_____
_____

Does your child...				How Often?
19) ... dream on a regular basis?	Y	N	D/K	_____
20) ... complain of nightmares, or scary dreams?	Y	N	D/K	_____
21) ... have difficulty falling asleep at night?	Y	N	D/K	_____

22) ... ever walk while asleep? Y N D/K _____
23) ... ever talk while asleep? Y N D/K _____
24) ... have restless sleep (e.g., kicks off covers, or tosses or turns)? Y N D/K _____

Appendix D

Sleep Self-Report

Please circle the appropriate answer for each question.
Y = Yes
N = No
D/K = Don't Know

Have you ever:

1) had a dream begin before you fell asleep? Y N D/K
How many times per week does this happen? _____

2) had a dream continue after you woke up? Y N D/K
How many times per week does this happen? _____

3) had a vision or seen something not really there when just falling asleep or waking? Y N D/K
How many times per week does this happen? _____

4) felt paralyzed or like you can't move when going to sleep or on waking? Y N D/K
How many times per week does this happen? _____

Do you often:

5) feel sleepy in the morning? Y N D/K
How many times per week does this happen? _____

6) feel sleepy during the day? Y N D/K
How many times per week does this happen? _____

7) fall asleep in school? Y N D/K
How many times per week does this happen? _____

8) dream? Y N D/K
How many times per week does this happen? _____

Appendix E

Test Order

Complete assent and consent forms

Hearing screening
Stop-signal trials
Trail-Making Test
WRAT-III, WJ-R reading subtests
Mental Rotation
OAEs
    SOAE
    CEOAE
    DPOAE
IQ measures
    Vocabulary
    Block Design
    Digit Span
SCAN-C
Finger-length ratio scan
Thank you and receipt

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