BRAIN CORTICAL THICKNESS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMBINED SUBTYPE: EFFECTS OF PSYCHOSTIMULANT MEDICATION TREATMENT AND IMPLICATIONS FOR NEUROPSYCHOLOGICAL FUNCTIONING AND BEHAVIOR

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ABSTRACT

BRAIN CORTICAL THICKNESS IN CHILDREN WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER COMBINED SUBTYPE: EFFECTS OF PSYCHOSTIMULANT MEDICATION TREATMENT AND IMPLICATIONS FOR NEUROPSYCHOLOGICAL FUNCTIONING AND BEHAVIOR

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Current etiological mechanisms of Attention-Deficit/Hyperactivity Disorder (ADHD) suggest alterations in the development of prefrontal-striatal-cerebellar networks. Presently it is unclear what relates to the alterations in cortical and subcortical development and thus symptoms of ADHD. Recent studies found reduced cortical thickness and surface area in children with ADHD who have been successfully treated with psychostimulant medication for an extended period of time compared to children with ADHD who have not taken psychostimulants, suggesting therapeutic psychostimulant use may alter trajectories in brain development in ADHD. It is unclear whether these changes in cortical morphology are associated with normalized behavioral outcomes or if changes in cortical morphology predict negative behavioral outcomes. Thus, the purpose of the current study was three-fold: 1) The current study implemented advanced surface-based cortical neuroimaging techniques to determine if cortical thickness differed between children with ADHD compared to typically-developing controls, 2) the study compared cortical thickness in children with ADHD who had been chronically-treated with psychostimulant medication (methylphenidate), children with ADHD who had never received medication, and typically-developing controls, and 3) the study also investigated the relationship between cortical thickness and behavioral and neuropsychological outcomes. The main findings from the current study included significant cortical thinning of the right rostral ACC but non-significant thinning in any region of the prefrontal cortex (PFC) or parietal cortex.

It was also found that medication history did not affect cortical thickness measures. Treated and Not-Treated ADHD groups had reduced cortical thinning in the right rostral ACC with the Treated group ($p = .043$) only slightly different from controls compared to the Not-Treated ADHD group ($p = .017$). Lastly, right rostral ACC thickness predicted a significant amount of the variance in parent and teacher reported symptoms of ADHD. No such relationship emerged between cortical thickness and response inhibition neuropsychological measures. Results of this study are among the first to suggest brain-behavior relationships between ADHD symptoms and regional cortical thickness measures. Furthermore, it is likely that brain morphological differences related to long-term psychostimulant use may depend on both the age of the child and the duration of treatment with psychostimulants.

For my parents, William and Kathryn Bledsoe
and for my best friend and love, Alexia Spanos

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CHAPTER 1: INTRODUCTION AND BACKGROUND

The human brain comprises only 2% of one's total body weight yet consumes 20% of all the body's total energy (Kandel, Schwartz, & Jessell, 2000). Despite being inundated with a multitude of sensory stimuli each second, the brain is able to filter irrelevant stimuli in favor of behavioral goals, maintain or manipulate behavioral goals, and produce an action in accordance with behavioral priorities. The ability to complete these complex processes is largely dependent upon the brains computational structures, neurons. With over 100 billion neurons that are connected to approximately 10,000 other cells in the brain, this network of over 1000 trillion connections is constantly communicating, changing, and manipulating information. While most of us are able to execute complex cognitive tasks with ease, others struggle to maintain attention or inhibit their behavior for even brief periods of time.

The ability to maintain attention and inhibit behavior is part of normal development. In contrast, when one experiences extreme levels of inattention, hyperactivity, or impulsivity, to the extent that it causes clinically significant impairment in functioning, the person meets criteria for ADHD. ADHD is usually diagnosed in children and is currently characterized into three behavioral domains in the DSM-IV: ADHD Predominantly Hyperactive-Impulsive Type (ADHD-H/I), ADHD-Predominantly Inattentive Type (ADHD-P/I), and ADHD Combined Type (e.g., those meeting diagnostic criteria for both ADHD-H/I and ADHD-P/I; ADHD-C).

The cause of ADHD is unknown. Research suggests both neurobiological and genetic factors. For example, children with ADHD have been found to have significantly smaller total brain volume and structural and functional disruptions in the frontal-striatal and cerebellar-frontal networks involved in attention and behavioral modulation. Foundational behavioral theory suggests symptoms of ADHD, including executive functioning impairments, arise out of

impaired functioning and development of these brain networks (Barkley, 1997). It is unclear if these impairments are the result of cortical abnormalities including reductions in cortical thickness in regions important for attention and behavioral modulation. Current research into the causes of brain structural and functional differences in ADHD have looked at psychostimulant medication, the most common treatment modality for ADHD and other disruptive behavior disorders (American Psychiatric Association, 2000). Numerous studies suggest long-term treatment with psychostimulant medication may alter brain volumetric development in children and adults with ADHD (Bledsoe, Semrud-Clikeman, & Pliszka, 2009; Castellanos et al., 2002; Makris et al., 2010; Semrud-Clikeman, Pliszka, Lancaster, & Liotti, 2006; Shaw et al., 2009; Sobel et al., 2010). The behavioral implications of these observed brain volumetric abnormalities in children with ADHD are unknown.

Current Study

The aim of the current study was to examine cortical thickness differences in children with ADHD who have been treated with psychostimulant medication, those with ADHD who have not taken psychostimulants, and typically-developing children. The study sought to understand the relationship between prefrontal, anterior cingulate, and parietal cortex thickness and measures of executive functioning and ADHD symptoms. To date, no such study has been completed. Results from the current study provide evidence for an underlying neurobiological marker for ADHD, demonstrates the impact of chronic psychostimulant treatment on brain structure and behavioral function, and provides clinically important information that may be used to develop symptom-specific treatment interventions.

CHAPTER 2: REVIEW OF THE LITERATURE

Attention-Deficit/Hyperactivity Disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is among the most commonly diagnosed childhood disorders and is thought to affect approximately 5 to 8% of school-aged children (American Psychiatric Association, 2000). Symptoms of ADHD include difficulties with hyperactivity, inattention, and impulsivity. There are currently three behavioral and diagnostic subtypes under the ADHD umbrella: ADHD-Hyperactive/Impulsive (ADHD-HI), ADHD-Predominantly Inattentive (ADHD-PI), and ADHD-Combined Type (ADHD-C). ADHD-HI is characterized by significant levels of hyperactivity and impulsivity without inattention difficulties, ADHD-PI is characterized by significant levels of inattentiveness and forgetfulness without over activity present, and ADHD-C is diagnosed when symptoms of inattention, impulsivity, and over activity are present. Children diagnosed with ADHD, regardless of subtype, display these behaviors to an extent that is inappropriate for their age and developmental level, resulting in a wide range of impairments across multiple settings. While the cause of ADHD is unknown, research focused on identifying neural pathways suggests that ADHD is a brain-based disorder of attention networks.

Attention and ADHD

Inherent in its name, Attention-Deficit/Hyperactivity Disorder is a disorder characterized by difficulties with attention and/or hyperactivity. "Attention", as it is referred to in the DSM-IV-TR, is a construct that encompasses a broad range of behaviors that appear to be caused by a lack of attention. For example, children with ADHD may appear inattentive (e.g., sluggish temperament) or they may seem to have problems paying attention when spoken to because they are unable to sit still or maintain a conversation (e.g., hyperactive behavior caused by the

inability to pay attention for a duration of time) (Barkley, 2005). Although much has changed regarding the nomenclature of ADHD (see Attention Deficit Disorder, APA, (1994), researchers and clinicians still seek to understand how the development of *attention* goes awry in children with ADHD in order to learn more about the cause and potential treatment of ADHD. Numerous forms of attention have been identified and studied in ADHD. They range broadly from selective attention (a cognitive process whereby a given stimulus and its characteristics are selectively processed while other stimuli are ignored) to temporal attention (the recruitment of cognitive resources that allow one to predict the arrival or onset of a stimulus). Selective attention is perhaps the most basic and widely studied form of attention and the most applicable to "attention" defined in ADHD and so will serve as the working definition of "attention" hereafter.

While the construct of attention appears obvious to even the most adroit of scientists ("Everyone knows what attention is." – Williams James) see (James, 1890), attention remains a relatively difficult concept to grasp conceptually, and possibly even more difficult to understand developmentally. Understanding how attention difficulties arise in children and how difficulties with attention become severe enough to impair a child's functioning, and warrant a diagnosis, is the basis for most etiological research on ADHD. The following section briefly discusses the development of attention in typical children. By understanding how attention develops in most children, we are better prepared to understand a potential causal mechanism in children with ADHD. The discussion on typical development of attention is then followed by topics of attention in ADHD, and end by describing theoretical models of attention that will serve as the basis for the hypothesized neurological models of ADHD subtypes. Researchers suggest that the origins of attention can be observed in infants as young as three months when the young infant is able to selectively attend (i.e., recognize and orient towards) to their caregiver's face (Posner &

Fan, 2008). According to these researchers, attention is composed of differential structures and circuits, called an organ system. They suggest that if the rudimentary neural organs/structures involved in alerting (the ability to be aware and respond to a stimulus presented in a measurable medium, such as hearing, seeing, smelling) are not adequately developed, then the infant cannot master higher-order attention functions such as cognitive control and executive attention. Beyond the sensory-dependent alerting phase, there are several steps in the development of attention in the young child.

Orienting to a Stimulus. The first step in attention development beyond alerting is orienting (e.g., directing attention towards the caregiver). Orienting towards the caregiver provides not only a bond between the child and caregiver but also ensures resources such as food, attention, and safety. Harman, Rothbart, and Posner (1997) showed that when an infant was distressed, the ability to orient toward the caregiver provided relief to the child. For this reason the ability of an infant to self-attend to a stimulus is considered a milestone in early development (Posner & Fan, 2008). Some argue that the most fundamental function of attention involves an infant's ability to become alert to their environment and respond in a way that promotes the acquisition of resources, and ultimately, survival.

Furthermore, as a child matures during preschool and early elementary school years, attention response grows into the ability to self-regulate (i.e., adjust one's emotional state/behavior depending on the demands of the environment) in a changing and dynamic environment. For example, children with intact self-regulation know when to avoid or attend to stimuli that are important. In addition, they come to learn and understand that stimuli or events often change with context (they learn to be flexible to changes in the environment). Children with ADHD, however, tend to struggle with shifting attention either from one subject to the next

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or even within aspects of the subject they are attempting to focus on (Barkley, 1997). Most children, once they master the ability to self-regulate, partly due to social demands and also due to the brain maturation of the prefrontal cortex, can then engage in higher level attention abilities, often described with the term "executive functions." In Posner and Fan's (2008) model, self-regulation leads to the second stage in attention development, the executive network.

Executive Attention/Control. The executive network consists of multifaceted functions that are more sophisticated and include systems of decision-making (i.e., weighing the strengths and weaknesses of a response in order to achieve a desired outcome), reward processing (i.e., a behavioral or physiological response to a reward or anticipation of a reward), response inhibition (i.e., inhibiting an automatic response in favor of a better response), working memory (i.e., ability to hold and manipulate information in one's mind) , and self-regulation (defined previously as the ability to adjust one's emotional state/behavior depending on the demands of the environment) of behavior. It is here, at this executive level, that the breakdown in attention is thought to be specific to ADHD (Barkley, 1997). Research on executive measures of attention, however, suggest that even a subset of typically developing children, that is, without a diagnosis of ADHD, are found to significantly struggle with neuropsychological tests of attention (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). These networks involve neural circuits (e.g., frontal-striatal) that work in concert to perform these higher-order functions. Developmentally, the skill of self-regulation or inhibitory control is seen in normally developing children between the ages of two and five (Posner & Fan, 2008). Others, using a Simple Simon task (Backen-Jones, Rothbart, & Posner, 2003) have shown that the development of selective attention takes place rapidly between 36 and 48 months of age.

During the ages of 5 to 9, children with deficits in self-regulation and attention are noticed by teachers and parents, as their behaviors deviate from what would be developmentally appropriate. The symptoms are generally recognized at this time as the child begins formal schooling and is required to abide by rules and conduct expected in a classroom (APA, 2000). It is believed that difficulties with attention and impulsivity are present earlier but they do not pose considerable difficulty for the child prior to school entry (Barkley, 2005). The underlying developmental course and cause of ADHD is not fully understood at this time.

The Etiology of ADHD

ADHD is understood by most researchers and clinicians as a neurobiological disorder. The precise mechanism or biological marker, however, remains elusive. Numerous theories have hypothesized the cause of ADHD (Barkley, 1997; Dougherty et al., 1999; Nigg, et al., 2005; Sagvolden & Sergeant, 1998; Sonuga-Barke, 2002, 2003, 2005; Swanson, Kinsbourne, et al., 2007). While some argued that ADHD is a disorder characterized by executive function deficits moderated mostly by the prefrontal cortex (Barkley, 1997), others suggest that ADHD manifests via a general deficit in the dopaminergic system of the brain that is responsible for prefrontal, striatal, and brain stem functions(Solanto, 2002). The latter theory is based on a large number of neuroimaging studies that have observed abnormalities in brain structures rich in dopamine receptors in children and adults with ADHD (Castellanos et al., 2001; Castellanos et al., 1994; Castellanos et al., 1996; Castellanos, et al., 2002; Durston et al., 2004; Hill et al., 2003; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Mostofsky, Cooper, Kates, Denckla, & Kaufman, 2002; Semrud-Clikeman, et al., 2006). Table 1 features a brief summary of structural neuroimaging studies from 1990 through 2009.

-Insert Table 1-

In addition to structural neuroimaging evidence, genetic research suggests a high degree of heritability for ADHD (Biederman, Faraone, Keenan, Knee, & Tsuang, 1990; Faraone, 2004; Thapar, O'Donovan, & Owen, 2005). Specifically, genetics studies estimate the heritability of ADHD to be around 70% (Biederman & Faraone, 2002) and implicate catecholamines such as the dopamine transporter (DAT), D4 and D5 dopamine receptors, and dopamine β-hydroxylase in ADHD symptomology (Faraone et al., 2005). In addition, methylphenidate, which blocks the re-uptake of dopamine pre-synaptically, has proven one of the most effective treatments for ADHD symptoms (MTA, 2001). Thus, the dopamine deficit theory of ADHD remains a consistent and prominent model of ADHD etiology.

This body of research, however, does not come without limitations. For example, it does not explain why nearly half of those with ADHD may not suffer executive function impairments which are modulated by dopaminergic neuroanatomy (Nigg, et al., 2005), why some children show a positive response to stimulant medication (Konrad, Gunther, Hanisch, & Herpertz-Dahlman, 2004; Vaidya et al., 1998), while others with the disorder do not (DuPaul & Rappoport, 1993), and why some find abnormalities in structures thought to be involved in ADHD (Castellanos, et al., 1994; Castellanos et al., 1996; Castellanos et al., 2001; Castellanos et al., 2002; Durston, Hulshoff Pol, Schnack, Buitelaar, Steenhuis, Minderaa, et al., 2004; Semrud-Clikeman et al., 2006), yet others do not (Wellington, Semrud-Clikeman, Gregory, Murphy, & Lancaster, 2006). In addition, dopaminergic abnormalities have been observed in many forms of psychopathology from depression (Dunlop & Nemeroff, 2007) and schizophrenia (Ma et al., 2008) to eating disorders (Frank et al., 2005), alcohol use (Ray et al., 2009), and obsessive-compulsive disorder (Camarena, Loyzaga, Aguilar, Weissbecker, & Nicolini, 2007). Thus,

dopaminergic abnormalities may not be specific to ADHD but may underlie a predisposition to many forms of brain-based psychopathology.

Because the brain proves a very difficult organ to study given its plasticity (i.e., structural and functional changes over time and development) and complexity between individuals (i.e., people may use different neural networks to solve similar problems), there are many variables which must be addressed by ADHD researchers interested in understanding the cause of ADHD. The following section presents important variables which appear to complicate a clear-cut understanding of ADHD etiology and attempts to address issues that may account for ADHD heterogeneity.

Comorbidity. Many potential explanations exist for the widespread inconsistencies in causal models of ADHD and the studies that support them. ADHD can manifest by itself or in the company of other psychological disorders making it difficult to tease apart the "true" behavioral and neurological components of ADHD. For example, Oppositional Defiant Disorder (ODD), characterized by defiant and hostile behavior, occurs in the presence of ADHD in approximately 60% of clinical cases (Gillberg et al., 2004). In addition, Conduct Disorder (CD), a more severe externalizing disorder found to develop in adolescence, is thought to co-occur with ADHD in nearly half of clinical samples (Gillberg, et al., 2004). Also, studies suggest that ADHD and tic disorders occur together roughly 13% of the time (Gadow, Sverd, Sprafkin, Nolan, & Grossman, 1999). Researchers have also studied the co-occurrence of ADHD and internalizing disorders. Specifically, mood disorders (e.g., major depressive disorder) have been found in roughly 20% of children with ADHD (Gillberg, et al., 2004). Lastly, learning disabilities are common in nearly 50% of children with ADHD (Barkley, 1990; Pliszka, 2000; Semrud-Clikeman et al., 1992). Thus with so many combinations of psychopathology and

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behavioral heterogeneity, it is difficult to define the ADHD phenotype, and studies with heterogeneous samples may account for the wide variety of findings.

Studies have attempted to determine how comorbidity affects behavioral outcomes for children with ADHD. For example, Nigg, Hinshaw, Carte, & Treuting (1998) found that motor difficulties remained in children with CD after controlling for ADHD symptomology. Executive function impairments have been found to persist in physically aggressive children even after controlling ADHD symptoms (Seguin, Nagin, Assaad, & Tremblay, 2004).

Symptom Severity and Research Samples. What about the other half of children that have only a diagnosis of ADHD and do not appear to suffer from comorbid disorders? ADHD with comorbid externalizing disorders are more likely to be noticed by a teacher, school counselor, or clinician. For this reason the child will be referred for treatment and enter research studies via clinical referrals (Barkley, 2005). Other children, with a sole diagnosis of ADHD alone, are more likely to come from a community sample (i.e., primary care, school/educational setting). Thus, clinical and community samples may be different, making research studies that include both difficult to interpret. Most studies of ADHD, be it behavioral (e.g., academic performance, oppositional behaviors, social skills), neuropsychological (e.g., measures of memory, planning ability, attention ability, etc.), or neuroanatomical/functional (e.g., volumetric measures of brain structures, functional measures of brain activity) include a heterogeneous amalgam of subjects ranging from ADHD alone to ADHD with comorbid Major Depressive Disorder (MDD). Exploring the differences between clinically referred and community samples of children with ADHD can assist in our understanding of the role that severity plays in response to treatment and outcome.

Effects of Chronic Medication. Historically, research on ADHD has been carried out in both chronically-treated and treatment naïve children. Unfortunately, most studies do not mention what percent of their subject pool had a history of medication treatment or if they were on stimulant medication during testing (see Table 1). It is estimated that approximately 12% of children with ADHD are prescribed stimulant medication (Jensen et al., 1999), and that children receiving treatment evince greater symptom severity and are more likely to be clinical samples compared to community samples.

Researchers have also observed differences in neuropsychological (Kempton et al., 1999; Konrad, et al., 2004; Mehta et al., 2000; Semrud-Clikeman, Pliszka, & Liotti, 2008), neuroanatomical (Bledsoe, et al., 2009; Castellanos, et al., 2002; Semrud-Clikeman, et al., 2006), and neurofunctional (Pliszka et al., 2006) performance in children with ADHD who have a history of stimulant medication treatment. Thus, given that a subsample of children with ADHD receive medication, and chronic medication has been linked to structural and functional changes in brain anatomy, treatment history is an important variable that likely affects the outcome of research findings and more importantly, our ability to determine the cause of ADHD. Other variables, such as age/development, could also potentially explain the heterogeneity in ADHD research literature.

Age and Developmental Heterogeneity. Brain structure changes significantly over time. We know from numerous studies that the prefrontal cortex and cerebrum in general develop non-linearly in childhood and adolescence (Barkovich, 2005; Barnea-Goraly et al., 2005; Giedd, 2004; Gogtay et al., 2004). In addition, researchers have observed significant group differences in anatomical volumes (overall brain volume, cerebellum, caudate, etc.) at age 10, but noted that developmental trajectories normalized when measured at 10-year follow up (Castellanos, et al.,

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2002). Thus, it is difficult to ascertain significant group differences over time in neuropsychological and neuroimaging studies of ADHD when researchers allow such generous age ranges (e.g., 4.5 years to 19 years). Simply co-varying age (statistically removing/controlling the variance in brain volume accounted for by age) to compare mean group differences may not reveal important developmental changes in gray and white brain matter (Giedd et al., 1996) that occur throughout childhood and adolescence. This uneven development has made it difficult to compare neuroimaging studies in general. For example, numerous studies have reported reductions in caudate volume in children with ADHD (Castellanos, et al., 2001; Castellanos, et al., 1994; Castellanos, et al., 1996; Filipek et al., 1997; Hynd et al., 1993; Semrud-Clikeman, et al., 2006; Semrud-Clikeman et al., 2000), but differed in agreement as to whether reductions were found in the left (Filipek et al., 1997; Hynd et al., 1993; Semrud-Clikeman et al., 2000) or right caudate (Castellanos et al., 1994, 1996). In addition, some studies used ADHD samples with a mean age of 9.7 years (Castellanos et al., 2001) while other studies used samples with a mean age of around 12 years (Castellanos et al., 1996; Semrud-Clikeman et al., 2006), further complicating findings due to differences in normal brain maturation/development. Therefore, neuroimaging studies need to be replicated in specified developmental cohorts in order to determine what structural or functional abnormalities persist in development and how they affect specific aspects of functioning.

ADHD as a Brain-Based Neuropsychiatric Disorder

Neuroimaging techniques provide an accurate way to measure the relationship between behaviors/symptoms and underlying brain morphology and brain functioning. Structural (i.e., measures of the volume or area of a brain structure or region) and functional (i.e., measures of regional blood flow that indicate neural activity during a behavioral task) neuroimaging

techniques have improved vastly over the last thirty years especially in their use for children. There have been notable advancements; magnetic resonance imaging (MRI) provides excellent spatial resolution, uses no ionizing radiation (unlike computed tomography, CT), and thus can be used in pediatric samples of clinical and non-clinical typically developing controls. For these reasons, MRI and functional MRI studies have burgeoned in pediatric literature of ADHD.

While MRI techniques provide information about the volume of a brain structure/region, they do not imply, by themselves, information about the functioning of the structure/region or implications for behavior. There are many reasons for this. A surplus of cerebral white matter may indicate stronger neural connections/integrity between brain structures and regions, or may indicate a lack of synaptic pruning and a less efficient pathway such as in Autism (Courchesne et al., 2001). The same is true for gray matter; thinning of the cortical mantle may predict disease such as Alzhiemer's Disease (Kuperberg et al., 2003), whereas thickening of cortical gray matter has been observed in adolescents with Autism (Brieber et al., 2007). Thus, it is difficult to predict the functional importance of gray or white matter volume without also including behavioral measurements. It is for this reason that most structural neuroimaging studies attempt to connect volumetric measurement with behavioral outcome measures (e.g., correlating brain matter volumes with test performance or symptom severity). In addition, functional MRI (fMRI) allows researchers to measure brain activation, in-vivo, while subjects undergo behavioral tasks. In plain terms, the amount of deoxygenated blood is measured while one attempts a behavioral task. The brain region(s) containing more deoxygenated blood is thought to indicate the neural location (or network) of the behavioral task.

The following section presents major MRI and fMRI studies in children and adults with ADHD and is organized by brain region/structure. The purpose of discussing these studies is to

1) review what is known about the ADHD brain in terms of structural and functional abnormalities, 2) provide a background for establishing ADHD as a biological disorder, and 3) use what is known from this body of research to support the hypotheses and rationale for the current study.

Speculations on Anatomical Heterogeneity in ADHD

ADHD as a Biological Disorder. While viewing the relatively large number of studies on anatomical/biological correlates of ADHD in Table 1, it likely that ADHD is a brain-based disorder. The difficulty however is in articulating exactly what *mechanism* is responsible for the manifestation of the disorder and each of its symptoms. Is the disorder caused by a dysfunctional right hemisphere? Perhaps ADHD is caused by impairments in fronto-striatal neurocircuitry? Part of the difficulty in explaining the biological etiology of a psychological disorder is that there is no tangible lesion or rash that one gets that would indicate the cause of an illness. Indeed, psychological science is based on this premise and does not usually prescribe to a purely medical model of causation. The medical model, however, does provide an empirical approach to understanding psychological phenomena such as ADHD that allows for hypothesis-driven research that is quantifiable and can explain why or how a disorder develops.

Although this often is the assumption: that abnormal psychological symptoms are caused purely by biological mechanisms. Psychology, however, was developed *because* biological explanations of psychological phenomena were not adequate. For example, until the middle of the 19th century most believed that those with psychological illnesses (hysteria, amnesia, dissociation, and later, "shell shock" or symptoms of PTSD in the early 20th century) were the product of malingering patients as doctors found no observable physiological or biological injury. Thus, given that no gross anatomical lesion or tangible injury occurs consistently in all

children with ADHD, finding a biological mechanism that explains ADHD in its entirety proves

a very difficult task. The following sections discuss likely "take-home" messages regarding the

anatomical and neurological underpinnings of ADHD reviewed in Table 1. In addition,

explanations for heterogeneity and methodological constraints are described.

Right Hemisphere. Nearly all anatomical studies that looked at hemispheric abnormalities

in ADHD observed abnormalities in the right hemisphere. While it would not be practical or

appropriate to discuss all of the functions of the right hemisphere, much can be hypothesized

given the consistent right hemisphere abnormalities in ADHD. Children with ADHD appear to

have reductions in right prefrontal gray matter and left occipital gray and white matter (Durston,

et al., 2004), reduced right anterior superior white matter and parietal-occipital white matter

(Filipek, et al., 1997), smaller prefrontal gray and white matter volume, emphasized in the right

hemisphere (Kates et al., 2002; Mostofsky, et al., 2002), thinning of the right inferior parietal

cortex (Makris et al., 2007), smaller right gray matter volume in superior frontal gyrus and right

posterior cingulate (Overmeyer et al., 2001).

These findings are not without functional importance. For example, the right hemisphere

appears to be involved in attention and vigilance. Specifically, theories suggest that the

noradrenergic system of the locus coeruleus of the brainstem, intralaminar thalamic nuclei, and

the right prefrontal cortex are involved in sustained attention and vigilance (Parasuraman &

Greenwood, 1998; Posner & Petersen, 1990). In addition, arousal has been found to be a right-

hemisphere function that is speculated to be involved in early detection/information processing

(Posner & Petersen, 1990; Sergeant, 2000). Further, children with ADHD appear to respond and

perform better to tests and tasks when they are novel rather than over-learned or practiced tasks

(Barkley, 2005; Nigg, 2005). Thus, it is likely that a right-hemisphere dysfunction is involved in

ADHD and may explain difficulties with attention, arousal, and vigilance. Current theory also speculates that the right hemisphere is more involved in recovery from ADHD symptoms (Halperin & Schulz, 2006) and may moderate the effectiveness of subcortical neural circuitry in adolescence and early adulthood when it reaches full development (i.e., synaptogenesis). Lastly, right hemisphere dysfunction may explain the inattentive symptoms that are required for a diagnosis of both ADHD-C and ADHD-PI. Further anatomical and neuropsychological studies should attempt to differentiate left vs. right hemisphere dysfunctions in ADHD and in executive attention in general.

Prefrontal Cortex. The prefrontal cortex (PFC) is connected with nearly every structure and area of the central nervous system (Fuster, 2008). In humans, the PFC makes up nearly 30% of the total cerebral cortex, and is phylogenetically the last structure to develop (Fuster, 2008). The PFC is implicated in nearly all aspects of human personality and cognition. Damage to the PFC has been implicated in severe personality changes (Anderson, Bechara, Damasio, Tranel, & Damasio, 2002). For example, Phineas Gage, the railroad construction worker who lost nearly his entire orbitomedial PFC after being impaled by a steel tamping rod was said to show changes in personality, thought, memory, and impulsivity (Blumer & Benson, 1975; Harlow, 1868).

The PFC has received much attention in the ADHD literature given neuropsychological research that found impairments in tests thought to tap PFC functioning (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Nigg, Blaskey, Stawicki, & Sachek, 2004; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). In addition, the PFC appears to be important for inhibitory control (Aron, Dowson, Sahakian, & Robbins, 2003; Rubia et al., 1999), attention, working memory, and planning (Fuster, 2008; Posner & Petersen, 1990). Further, because of the

abnormalities in the PFC mentioned above and here, many etiological theories were developed to explain ADHD (Barkley, 1997; Nigg & Casey, 2005; Seidman, Valera, & Makris, 2005).

Numerous studies reported statistically significant reductions in PFC volume in children with ADHD (Castellanos, et al., 1994; Castellanos, et al., 1996; Castellanos, et al., 2002; Durston, et al., 2004; Filipek, et al., 1997; Hesslinger et al., 2002; Hill, et al., 2003; Hynd, et al., 1990; Mostofsky, et al., 2002; Overmeyer, et al., 2001; Sowell et al., 2003), and reductions in cerebral glucose metabolism in adults with ADHD (Zametkin et al., 1990). However, due to small sample sizes and inconsistencies, effect sizes for volumetric reductions in the PFC have been small to moderate, $d = .30$ to $.90$ (Halperin & Schulz, 2006). Thus, more studies are needed that replicate findings with respect to volumetric abnormalities of the PFC in children with ADHD. New research using morphometric mapping and quantification of the cerebral cortex which allows for a finer analysis of cortical volume has revealed abnormalities in PFC volume in ADHD. Specifically, researchers have observed thinning of the dorsolateral PFC in adults with ADHD (Makris, et al., 2007) and left medial PFC (Shaw et al., 2006). Functional studies of working memory ability (using a Sternberg match-to-sample task) in girls with ADHD reported increased recruitment of the PFC in order to complete the working memory task compared to healthy controls (Sheridan, Hinshaw, & D'Esposito, 2007). Thus, the group ADHD appeared to recruit a less efficient pathway in the PFC than non-ADHD comparisons. Such a study has not been completed using samples of boys with ADHD. Studies of response inhibition (go/no-go task; Durston, 2003; Schulz et al., 2004; Schulz, Newcorn, Fan, Tang, & Halperin, 2005) reported increased activation of the lateral PFC in children with ADHD compared to age-matched controls without ADHD. They also found children with ADHD used a more diffuse network of brain regions while performing the go/no go task, further supporting the theory of

inefficient PFC functioning in ADHD. Others reported decreased activation of the ventrolateral PFC in children with ADHD-C compared to controls while performing an inhibitory task (Pliszka, et al., 2006). Overall, structural and functional evidence suggests impairments in the PFC in ADHD.

Researchers hypothesize a new role for the PFC in children with ADHD. It is suggested that the PFC is likely involved in the recovery from ADHD via its modulation of subcortical networks (Halperin & Schulz, 2006). Further, they suggest that top-down control of the PFC may act to compensate for dysfunctions in the striatum. They also point out that because the PFC develops cytoarchitecturally later than other areas (striatum/basal ganglia), it is not necessarily involved in the cause of ADHD but more so in the recovery and remission as evidenced by numerous studies that found symptoms of ADHD improved with age (Barkley, 1990; Biederman, Mick, & Faraone, 2000; Kessler et al., 2005; Manuzza, Klein, Bessler, Malloy, & LaPadula, 1998). More research that empirically supports this view of the PFC is needed and would provide new insights into ADHD etiology and regarding treatment options.

Anterior Cingulate Cortex. The anterior cingulate cortex is a key structure described in Posner and Petersen's (1990) model of the anterior attention network. The anterior cingulate cortex is activated for a host of cognitive operations including response inhibition, processing of reward, motivation, target detection, and decision making (Bush, Luu, & Posner, 2000). Functional neuroimaging studies suggest hypoactivation of areas of the anterior cingulate in children and adults with ADHD (Bush et al., 1999; Ernst et al., 2003; Pliszka, et al., 2006; Zametkin, et al., 1990). Studies observed decreased activation of the anterior cingulate in tasks thought to require behavioral inhibition (e.g., counting Stroop task) in children with ADHD compared to controls (Bush et al., 1999). ADHD subjects recruited frontal-striatal and insular

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regions during the task suggesting that performance was not the result of global hypoactivation. Pliszka et al., (2006) also reported reduced activation of the anterior cingulate during tasks of behavioral inhibition (e.g., stop signal task) in children with ADHD-C. In addition, structural neuroimaging studies have observed volumetric reductions in the anterior and posterior cingulate in children with ADHD-C compared to typically developing controls (Overmeyer et al., 2001; Semrud-Clikeman et al., 2006). Further, cortical thinning of the anterior cingulate cortex has been demonstrated in adults with ADHD (Makris et al., 2007). Therefore the anterior cingulate appears abnormal structurally and functionally in children with ADHD. Due to the structural reductions and hypofunctionality in the anterior cingulate in children with ADHD, symptoms of ADHD may be related to abnormal development of this cortical region.

While the anterior cingulate cortex is likely involved in the biological etiology of ADHD very few studies have been done at this point making it difficult to conclude on any specific role of impairment. Studies on response to reward and delay aversion in ADHD have implicated the anterior cingulate in ADHD etiology (Sagvolden & Sergeant, 1998; Tripp & Alsop, 1999, 2001). These and other studies suggest that children with ADHD may be more sensitive to reward than typically developing age-mates, thus providing further impetus for the involvement of the anterior cingulate in ADHD symptomology. This line of research is relatively new and replication is warranted. Of particular importance, these theories may provide information regarding the development of ADHD symptoms and treatment interventions. For example, if children with ADHD do indeed struggle with delayed reward and exhibit impaired response to reward, behavioral treatments that target these symptoms may help children navigate interpersonal relationships and also academic settings. Lastly, that the role of the anterior cingulate regarding potential differences between ADHD subtypes needs further exploration. For

example, studies which evaluate whether children with ADHD-C and ADHD-PI evince similar impairments in functional MRI and structural MRI studies would be helpful. Indeed, the fMRI studies by Bush et al., (1999) and Pliszka et al. (2006) provided very compelling evidence for hypofunctioning of the anterior cingulate during behavioral inhibition tasks in children with ADHD-C.

  Parietal Cortex. The parietal cortex is implicated in the posterior attention network in Posner and Petersen's (1990) model. They hypothesize that the parietal lobe involves noradrenergic modulation of orienting and selective attention. Research has found the posterior parietal lobe to be important for shifting attention (Sapir, Hayes, Henrik, Danziger, & Rafal, 2004). Due to its connections with the thalamus (among other areas) the parietal lobe plays a significant role in attention. Research, however, on the parietal lobe in those with ADHD is scant. One of the first to report abnormalities in the parietal lobe found reduced white matter at the parietal-occipital junction (Filipek et al., 1997). Further, they found that children who benefited least from stimulant medication were those with significantly less white matter in the parietal lobe. Other studies involving measurement of cortical volume found general thinning of the right parietal lobe in adults with ADHD (Makris et al., 2007). In studies in children with ADHD, Shaw et al., (2006) found that normalization of the right parietal lobe was associated with better outcomes (measured by Children's Global Assessment Scale scores) than children with abnormal right parietal and left prefrontal volumes. Other studies observed initial reductions in posterior parietal volume in children with ADHD (Castellanos et al., 2002) yet volumes normalized after 10-year follow-up suggesting potential developmental explanations of parietal cortex dysfunctions in ADHD. In contrast, other studies have found increased cortical volume of

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the inferior parietal lobe in children with ADHD, yet not significantly larger when compared to typically developing controls (Sowell et al., 2003).

The posterior attention network has not received much attention in ADHD literature with respect to DSM-IV subtype differences. Some suggest this network is not impaired in children with ADHD-C (Nigg, 2005). To date, only one study has looked at the functioning of this system in ADHD-PI (Huang-Pollock, Nigg, & Carr, 2005). While the authors did not find results in support of a late selection deficit using the visuospatial orienting task in ADHD-PI, they did note a trend towards significant group differences when children were classified using the Sluggish Cognitive Tempo criterion (Huang-Pollock, et al., 2005; McBurnett, Pfiffner, & Frick, 2001). Another investigation attempted to differentiate ADHD subtypes used measures of executive functioning, learning and attention (Solanto et al., 2007). It was reported that children with ADHD-C performed worse than both ADHD-PI and controls in response inhibition, visual-spatial working memory, planning, and on observational measures of motor disinhibition. Findings are suggestive of differences in the functioning of the anterior attention network in ADHD subtypes.

Caudate Nucleus. The caudate nucleus is a subcortical structure that is responsible for motor coordination and inhibition of motor response. Further, the caudate receives cortical inputs from nearly all aspects of the brain, with prominent afferent connections to the PFC and efferent connections from the thalamus (Kandel et al., 2000). Most studies on ADHD-C have found reversed asymmetry of the caudate and reductions in size, however, it is unclear if it is the right or left caudate nucleus that is abnormal (Figure 1). In addition, because the caudate contains dense dopaminergic receptors, it remains an important fixture in dopamine theories of ADHD etiology (see Swanson et al., 2007). Further, studies suggest those with ADD with hyperactivity

are more receptive to stimulant medication (a stimulant that works on the dopaminergic system) than those with ADD without hyperactivity (Goodyear & Hynd, 1992). It is therefore hypothesized that symptoms of ADHD-C arise via impairments in areas rich in dopamine, such as the caudate, whereas those with inattentive symptoms have impairments in other areas (e.g., brain stem nuclei, posterior attention areas). More studies are needed in order to determine if the caudate is abnormal in those with ADHD-C *and* ADHD-PI.

-Insert Figure 1-

Cerebellum. The cerebellum appears to be abnormal in children with ADHD (Berquin et al., 1998; Bledsoe et al., 2009; Bussing et al., 2002; Castellanos et al., 2001; Hill et al., 2003; Mostofsky et al., 1998). Given that the cerebellum is important for a wide range of motor and non-motor operations, connected with nearly all cortical and subcortical brain architecture, the cerebellum presents an interesting, complex, and potentially significant role in explaining ADHD etiology. For example, children with ADHD have been found to have motor coordination impairments (Pitcher, Piek, & Hay, 2003). Some estimates suggest that nearly 50% of children with ADHD also meet criteria for a developmental coordination disorder (Gillberg, 2003). By extension, it can by hypothesized that if one were to look at gross motor impairments in ADHD there would be an emphasis in children with ADHD-C, given symptoms of hyperactivity and motor dysregulation, which are not present in those with ADHD-PI. Children with ADHD-C show volumetric reductions in the posterior inferior vermis of the cerebellum (Bledsoe, Semrud-Clikeman, & Pliszka, In Press). Reductions in the vermis significantly predicted parent and teacher reported levels of hyperactivity and attention problems (Figure 2). Results suggest symptoms of ADHD may be related to abnormal development of dopamine-rich regions of the cerebellar vermis and its connections with the cortex. Another more nuanced way of viewing the

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cerebellum's role, above and beyond that of a motor coordination center, in ADHD, is discussed

via its connections with fronto-striatal neurocircuits that are involved in executive control.

-Insert Figure 2-

Some theorists surmise the role of the cerebellum in ADHD via temporal processing

theory (Nigg & Casey, 2005). Temporal processing theory suggests that children with ADHD

have difficulty with managing correctly timed responses to their environment. Further, Nigg and

Casey (2005) suggested that fronto-striatal/cerebellar circuits were responsible for encoding and

the "what and when" of environmental information (such as those in classroom settings as well

as that which is required during neuropsychological tests), and the amygdaloid complex was

responsible for interpreting and encoding the emotional salience of the stimuli. Future work

should investigate temporal information processing in children with ADHD, especially as it

pertains to neuropsychological/executive functioning. Because the cerebellum is a structure that

is sensitive to pediatric injury (Soto-Ares et al., 2001; Volpe, 1995), it may be a better candidate

for understanding the typically early-onset of ADHD. Therefore, it is likely that arousal

abnormalities coupled with cerebellar abnormalities may cause deficits in temporal processing

efficiency.

Long-Term Psychostimulant Medication May Complicate Anatomical Studies of ADHD.
The majority of neuroanatomical studies of ADHD have used subjects chronically treated with

stimulant medication (see Table 1). Because chronic stimulant use has been associated with

reductions in the density of dopamine transporters in animal models, it was hypothesized to have

a similar effect on developing neuroanatomy of children with ADHD taking methylphenidate

(Moll, Sause, Ruther, Rothenberger, & Huether, 2001). Specifically, reductions in the anterior

cingulate cortex in treatment-naïve children with ADHD-C were observed (Semrud-Clikeman et

al., 2006) as well as significant reductions in the posterior inferior cerebellar vermis in treatment-naïve children with ADHD-C (Bledsoe et al., 2009). Other studies, however, reported statistically significant reductions in many areas of the brain in children with ADHD-C in childhood but noted no significant differences between ADHD-C and control subjects when brought back after a 10-year interval (Castellanos et al., 2002). The results from this longitudinal study suggested that the neuroanatomical abnormalities studied in children with ADHD (most of those presented in Table 1) may be explained via a developmental delay.

Thus, one might suggest that all of the structural studies on ADHD would produce the same results of Castellanos et al. (2002) if followed longitudinally. If this were true then we would certainly be better able to predict the prognosis of ADHD, understand more regarding the biological etiology, and could devise specific psychopharmacological treatments for symptoms of ADHD. Unfortunately, more studies are needed in order to draw firm conclusions. Given that pharmacological treatment is among the most common and effective (MTA Study, 1999) intervention for children with ADHD, researchers should continue to focus on how/if stimulant medication affects the development of key brain structures involved in ADHD.

Sample Size and Effect Size. Most anatomical studies of ADHD include a small sample size, making group comparisons difficult and potentially fortuitous. The number of subjects in a study not only has implications for external validity, but it can affect the effect size. The effect size is a statistic that tells us how much one group differs, on average, from another group (Cohen, 1988). Effect sizes are based on standard deviation units, thus, $d = .8$, suggests that two groups (mean performance) under study vary by nearly one full standard deviation. In ADHD research, effect sizes for neuroanatomical studies have been relatively low. For example, most anatomical imaging studies of ADHD show effect sizes for structures in what Cohen (1988)

would classify as "medium" (e.g., $d = .5$, approximately 6% of the variance in brain structure is explained by having ADHD) to "small" (e.g., $d = .2$, approximately 1% of the variance in brain structure is explained by having ADHD) (Valera, Faraone, Murray, & Seidman, 2007). In addition, the research literature as a whole, collectively suggest the use over 1,200 subjects in anatomical neuroimaging research on ADHD. However, if one were to observe the frequency of studies that shared ADHD subjects, or included subjects in more than one study, the actual number of subjects under study is reduced to nearly half. Therefore, conclusions regarding neuroanatomical abnormalities in the literature are based on a much smaller overall sample of subjects that what is presented by looking at the studies individually. Lastly, while MRI scans represent a costly methodology for ADHD researchers, more studies are needed, with increased and diversified samples in order to present more evidence for the neurological underpinnings of ADHD.

Surface-Based Cortical Mapping. New ways of acquiring structural measurements of the brain allow for more nuanced studies of brain growth and abnormalities. Cortical and surfaced-based neuroimaging techniques improve on conventional volumetric analysis by allowing for a direct measure of cortical area, cortical thickness, and cortical/gyral formation (see Figure 3). Studies have already been carried out longitudinally in children that have revealed much regarding cortical/gray matter development (Sowell, Thompson, Leonard, Welcome, Kan, & Toga, 2004). Others have used such techniques to understand the development of cortical areas implicated in disease and psychopathology. For example, research using cortical/gyral mapping (Figure 4) is being used to study a host of disorders and diseases from Alzheimer's disease (Dickerson et al., 2009), Schizophrenia (Goghari, Rehm, Carter, & MacDonald III, 2007),

ADHD (Makris et al., 2007; Shaw et al., 2008; Sowell et al., 2003; Wolosin et al., 2007), and multiple sclerosis (Sailer et al., 2003).

-Insert Figure 3-

Premature or significant thinning of the cortex has been observed in children and adults with ADHD (see Table 1). For example, Sowell et al., (2003) reported reduced cortical morphology bilaterally in the inferior dorsal prefrontal cortex and in the anterior temporal cortex in children with ADHD compared to typically developing control children. Alternatively, they found prominent increases in cortical gray matter bilaterally in the inferior parietal and posterior temporal cortex. Longitudinal studies observed global thinning of the cerebral cortex in children with ADHD (Shaw et al., 2006). In addition, when their sample (n = 163) was divided into "better" or "worse" clinical outcome, they observed persistent thinning of the left medial prefrontal cortex in the worse outcome group and normalized cortical thickness (converging thickness trajectories with control subjects) of the right parietal cortex in children in the better clinical outcome group. Thus, this study suggests that the development of the right parietal cortex may be responsible in the remission or recovery from ADHD symptoms. It is also notable that these authors observed persistent thinning in the left medial prefrontal cortex given the high frequency of other studies reporting abnormalities localized in the right prefrontal cortex. Others using cortical folding and area analyses report reduced cortical area of the right inferior parietal cortex, dorsolateral PFC, and anterior cingulate cortex in adults with ADHD (Makris et al., 2007). These researchers found no significant differences in cortical thickness between adults with ADHD and adults without. While these studies provide important information regarding cortical abnormalities in ADHD, the studies, collectively, did not use behavior or

neuropsychological measures. Thus, it is unclear what relationship cortical abnormalities have with behavioral and/or functional outcomes.

Cortical and surface based analyses provide a new way of assessing the neurological correlates of attention and attention disorders. Previous morphological methods do not allow for spatial mapping of cortical area and cortical thickness, and in essence, rely on 2-dimensional measurements of the cortex. This new body of research suggests new findings regarding brain development in ADHD that is in opposition to previous research. For example, previous longitudinal studies of cortical and subcortical morphology in ADHD reported significant gray and white matter reductions in childhood but normalization by late adolescence (Castellanos et al., 2002). In contrast, longitudinal research using cortical-based morphometry observed significant thinning in the medial and superior prefrontal and precentral cortex in children with ADHD (Shaw et al., 2006). Thus, cortical surface analytic methods may present a more sensitive tool for understanding and measuring brain abnormalities in children with ADHD. Lastly, only one study has used cortical surface mapping analyses to compare ADHD subtypes and effects of comorbidity on cortical area (Wolosin et al., 2007). These researchers were unable to find any evidence of subtype differences but did observe a trend for abnormal cortical folding in those with comorbid ODD compared to those with only ADHD.

Effects of Psychostimulant Medication on Behavior in ADHD

Stimulant medication is the most common treatment intervention for ADHD (American Psychiatric Association, 2000). Stimulants, such as methylphenidate, have been found to inhibit the re-uptake or recycling of dopamine pre-synaptically, thereby increasing the amount of dopamine available to areas of the brain that are thought to be related to ADHD symptoms (Challman & Lipsky, 2000; Volkow et al., 2001). Many different types of stimulant medication

are prescribed for ADHD including methylphenidates (Ritalin, Concerta) and dextroamphetamines (Adderall, Dexedrine). The focus of this discussion will be on methylphenidate, as it remains the most commonly studied stimulant medication (see Table 1).

Methylphenidate (MPH) appears to improve many of the symptoms associated with ADHD and when paired with parent training and child-focused treatments the effects are even more robust. In a large randomized clinical trial of treatment interventions for ADHD (n=579), researchers showed that over 14 months, medication combined with behavioral treatment was the most efficacious treatment for ADHD (MTA Group, 1999). In addition, Hinshaw (1992) found that stimulant medication decreased externalizing behaviors such as stealing, vandalism, and cheating in children with ADHD. In the same vein, stimulant medication has been shown to alleviate aggressive behavior (Hinshaw, Heller, & McHale, 1993; Murphy, Pelham, & Lang, 1992), and improve effort and sustained attention (Barkley, 1977; Barkley, DuPaul, & McMurray, 1991; Wilkison, Kircher, McMahon, & Sloane, 1995).

Executive functioning is also thought to improve in children with ADHD who are treated with stimulant medication. Five studies found children with ADHD who were treatment naïve (i.e., never took medication for ADHD symptoms) performed worse on a host of behavioral, academic, and executive domains compared to ADHD children treated with stimulant medication (Barnett et al., 2001; Kempton, et al., 1999; Semrud-Clikeman, et al., 2008). Kempton et al. (1999) found children chronically treated with stimulant medication performed better on computer administered executive function measures (assessing spatial memory, planning, impulse control) than treatment naïve children. This finding suggests chronic medication may improve neuropsychological functioning when children continue to take stimulants. Beneficial effects of acute stimulant medication on neuropsychological functioning have been reported for

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visual-spatial working memory (Barnett, et al., 2001; Bedard, Martinussen, Ickowicz, & Tannock, 2004; Berman, Douglas, & Barr, 1999; R. Elliott et al., 1997; Kempton, et al., 1999; Mehta, Goodyear, & Sahakian, 2004; Mehta, et al., 2000), planning (R. Elliott, et al., 1997; Kempton, et al., 1999; O'Driscoll, Depatie, Holahan, Lemieux, & Barr, 2005), and response inhibition (Aron, et al., 2003). Thus, the majority of studies show that acute medication improves many areas of neuropsychological functioning. Other studies have found improvements on similar executive functioning tests even after children have discontinued medication during testing (Semrud-Clikeman, et al., 2008). This finding suggests that the benefits of stimulant medication for attention and executive ability may persist even after medication washout (i.e., medicine discontinued at least 24 hours before testing).

Semrud-Clikeman et al. (2008) found chronically treated children with ADHD (though not medicated during testing) out-performed treatment naïve children (never treated with psychostimulants) on measures of organized writing, Stroop interference, selective attention, and similar performance on verbal working memory and academic skills as control subjects. Thus, chronically treated children with ADHD may still experience residual benefits of psychostimulant medication even after washout. It is unclear if chronically treated children would continue to perform better than treatment naïve children if follow-up testing was done after over a year of discontinuing medication. It is hypothesized, however, that the improvements observed in those with long-term medication treatment, in terms of behavior and academic performance, would persist to some degree even after discontinuation (Semrud-Clikeman, et al., 2008). In other words, it is unlikely that improvements in behavior and academic skills attributed to medication response would be completely lost if discontinued after successful long-term treatment.

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Psychostimulants may also improve spatial memory in children with ADHD. For example, children with ADHD who were treatment naïve made significantly more search errors (forgetting previously selected boxes or targets) compared to chronically treated ADHD and control subjects on a spatial working memory(SWM) task (Barnett, et al., 2001; Cairney et al., 2001). Chronically treated children with ADHD did not significantly differ from controls on any of the spatial working memory tasks, suggesting that chronic treatment may normalize SWM performance in children with ADHD. It appears chronically treated children with ADHD perform better on spatial working memory tasks when continuing to take their medication compared to age-mates with ADHD who are naïve to treatment.

In general, children with ADHD who take stimulant medication in the long term, show improvements in some aspects of behavior, academic skills, and executive functioning. To date, no study has simultaneously examined the effects of chronic stimulant treatment on brain structure, neuropsychological, and behavioral outcomes. Such a study would provide a better understanding of the brain and behavior relationships in ADHD. Determining how brain cortical structure is related to specific behaviors in children with ADHD would also help in the search and development of the disorder's etiology. If cortical structure and/or behavior is moderated by stimulant treatment history, the results of such a study may engender new treatment interventions for children with ADHD.

Effects of Psychostimulant Medication on Brain Structure in ADHD

The cause of the structural anomalies and developmental delay in ADHD is unknown. One potential confound in the neuroimaging literature is the use of ADHD participants who have been chronically-treated with psychostimulant medication. Psychostimulant medication is the most common treatment for ADHD in the United States, with approximately 9% of boys and 4%

of girls receiving prescriptions (CDC, 2003). Understanding the long-term effects of medication is therefore important for many children with ADHD. Two longitudinal randomized clinical trials found stimulant medication was related to a decrease in 1.3 cm per year in height and between 2.86 pounds per year (in preschool-aged children) and 5.51 pounds per year (in school-aged children) in weight when compared to age normal growth rates (MTA, 2004; Swanson, Elliott, et al., 2007; Swanson et al., 2006). Thus, if growth rates are affected by chronic stimulant treatment the same may also be true for brain development.

A handful of studies have looked at medication history as a potential confound in structural neuroimaging. Castellanos et al. (2002) reported increased white matter volumes in chronically-treated children with ADHD but not treatment-naïve children with ADHD upon entrance in a longitudinal study. The similar lobar volumes in chronically-treated children with ADHD and controls suggest medication may be related to "normalization" of brain development. Others reported abnormal cortical thinning of the right motor cortex, left middle and inferior frontal gyrus, and right parietal-occipital region in treatment-naïve children with ADHD (Shaw, et al., 2009). Further, the anterior cingulate cortex and posterior inferior region of the cerebellar vermis have also been found to be smaller in treatment-naïve children with ADHD (Bledsoe, et al., 2009; Semrud-Clikeman, et al., 2006).

In the aforementioned studies, brain volumes and area differed between chronically-treated children with ADHD-C typically-developing controls. This body of work suggests that chronic psychostimulant treatment may have a protective element for brain development. It is unclear how or why psychostimulants are related to changes in brain development. There is behavioral evidence that may explain the relationship between chronic psychostimulant use and changes in cortical development.

Psychostimulant medication has been shown to improve executive function performance, or at least normalize it in children with ADHD on measures of planning, cognitive flexibility and response inhibition (Elia, Welsh, Gullotta, & Rapoport, 2006; Kempton, et al., 1999; Konrad, et al., 2004; Mehta, et al., 2000; Pietrzak, Mollica, Maruff, & Snyder, 2006; Semrud-Clikeman, et al., 2008; Swanson et al., 2002). Methylphenidate has also been associated with increased blood flow to frontal and striatal regions of the brain which was associated with improved response inhibition ability (Vaidya, et al., 1998). Even in healthy individuals, methylphenidate has been found to improve working memory ability via increased blood flow to the dorsolateral prefrontal cortex and parietal cortex (Mehta, et al., 2000). Therefore, the corrective effects of stimulant medication on executive functioning and behavior in concert with the increased frontal-striatal-parietal blood flow may promote normalization cortical and subcortical development.

Until recently, there were no studies connecting changes in the development of the cortex with neuropsychological or behavioral changes. Most studies utilized either neuroimaging or neuropsychological outcome variables to study the effects of psychostimulants, but rarely were the two combined. It was therefore difficult to determine how changes in the brain influenced or could predict changes in behavior.

One study (mentioned above) has investigated the influence of cortical brain development on behavior in children with ADHD. Shaw et al. (2006) found cortical thinning was different between children with ADHD depending on their level of behavioral functioning. Specifically, after dividing the 97 ADHD participants into better or worse outcome groups (e.g., better outcome group had ≥ 64 score on Children's Global Assessment Scale, CGAS), they reported cortical thinning in the left medial prefrontal cortex in those in the better outcome group. Right parietal cortex thickness was associated with better outcome and may underlie

developmental normalization. They also found that cortical thickness was similar in children with ADHD in the better outcome group and controls, suggesting medication may normalize cortical development in children with ADHD.

There are many confounding variables within this study design worth mentioning. For example, the better outcome group had significantly higher intelligence scores than the worse outcome group, suggesting IQ may moderate clinical outcome possibly in conjunction with cortical thickness. It is also complicated by findings that suggest a negative correlation between intelligence and cortical thickness in childhood and a positive correlation in adulthood (Shaw et al., 2006b). Therefore, it is possible that the ADHD group's thinner left medial prefrontal cortex might have been related to their significantly lower IQ score compared to controls and not accounted for by symptoms of ADHD. While statistical tests were run to control for significant IQ differences between ADHD and controls, the better and worse outcomes groups still differed at $p = .001$. In addition, the worse outcome group had a much higher rate of combined-type ADHD (e.g., 61% of worse outcome group and only 11% of the better outcome group) than the better outcome group suggesting symptom severity may have influenced clinical outcome.

Growing evidence suggests ADHD-Combined Type and ADHD-Predominantly Inattentive subtype represent two distinct neuropsychiatric disorders. Given that those with ADHD-C appeared to populate the worse clinical outcome more than those with ADHD-PI, an analysis of cortical thickness and clinical outcome based on subtypes would have been helpful and also theoretically important. There were also many children in each group that had comorbid diagnoses including oppositional defiant disorder, conduct disorder, mood disorder, anxiety disorder, and/or Tic disorder. Many children with ADHD do not have comorbid diagnoses and it is unclear whether other psychological disorders influence cortical development.

It is unknown if the results of this study would be confirmed in children with ADHD and no comorbid disorders.

While little research exists on the relationship between chronic medication and brain structure, more work has looked at its effects on behavior. Only a few studies have looked at the effects of medication on neuropsychological testing. In general, research suggests chronic medication improves academic skills, interpersonal behavior, and executive functions in ADHD.

Aims of the Current Study

The aims of the current study is to 1) investigate the relationship between the thickness of the cortical ribbon (density of neurons) in children with ADHD 2) determine the extent to which chronic treatment with psychostimulant medication moderates cortical thickness and/or behavior, and 3) assess the relationship between cortical thickness and executive functions and ADHD symptoms.

The Study Questions and Hypotheses

1.) Do children with ADHD have regionally specific cortical thinning compared to children without ADHD?

Hypothesis 1a. Children with ADHD will have significantly thinner anterior cingulate cortex than children without ADHD.

Hypothesis 1b. Children with ADHD will have significantly thinner prefrontal cortex than children without ADHD.

Hypothesis 1c. Children with ADHD will have significantly thinner parietal cortex than children without ADHD.

Rationale. Numerous theories have implicated the prefrontal cortex, parietal cortex, and anterior cingulate cortex in the pathophysiology of ADHD (Castellanos et al., 2008; Nigg &

Casey, 2005; Willcutt, et al., 2005). Children with ADHD have been found to have volumetric reductions and hypoactivation of these regions compared to children who do not have ADHD, thus the underlying mechanisms of ADHD symptomotology are thought to be a product of the abnormal development and functioning of these regions. It is unclear, however, if reductions are specific to cortical volume (the product of cortical surface area *and* cortical thickness) or cortical thickness in children with ADHD-Combined Type. The purpose of these hypotheses is to provide information on the potential underlying brain cortical endophenotypes of ADHD.

2.) Do children with ADHD who have been chronically-treated with psychostimulant medication differ in regionally specific cortical thickness from children with ADHD who have never been treated with stimulant medication and children without ADHD?

Hypothesis 2a. Children with ADHD who have been chronically-treated with psychostimulant medication will have a significantly thinner prefrontal cortex, parietal cortex, and anterior cingulate cortex compared to children with ADHD who have never been treated with psychostimulant medication.

Hypothesis 2b. Children with ADHD who have been chronically-treated with psychostimulant medication will not differ in thickness of the prefrontal cortex, parietal cortex, and anterior cingulate cortex compared to typically-developing control participants without ADHD.

Hypothesis 2c. Children with ADHD who have not been treated with psychostimulant medication treatment will have significantly thinner prefrontal cortex, parietal cortex, and anterior cingulate cortex compared to typically-developing control participants without ADHD.

Rationale. Stimulant medication remains among the most common treatments for ADHD symptoms in children and adults (American Psychiatric Association, 2000). Children with

ADHD who are chronically treated with psychostimulant medication, such as methylphenidate, have been found to be significantly shorter and weight less than children with ADHD who do not take psychostimulant medication (Swanson, Elliott, et al., 2007; Swanson, et al., 2006). Thus, the effects of chronic psychostimulant treatment may also be related to significant changes in the development of the cerebral cortex. One of the central aims of this study is to determine if there are differences in children with ADHD who are chronically treated with psychostimulants and those with ADHD who are not. It is hypothesized that chronic psychostimulant use may normalize abnormal brain developmental trajectories of ADHD (Shaw et al., 2007).

3.) Does cortical thickness contribute to executive functioning performance and symptoms of ADHD?

Hypothesis 3a. Cortical thickness will explain a significant amount of the variance in response inhibition ability.

Hypothesis 3b. Cortical thickness will explain a significant amount of the variance in parent and teacher reported levels of ADHD symptom severity.

Rationale. Finding differences in cortical thickness is important for basic research and allows for theory-driven hypotheses about the underlying neurobiological etiological mechanisms. Unfortunately, such findings are limited with regard to their ability to say anything empirical about the underlying function of a set of symptoms or behavior. To date, only one study has attempted to connect brain cortical thickness measurements with functional outcomes (Shaw, et al., 2006). Results suggested cortical thickness of the parietal cortex differentiated those with ADHD with better behavioral outcomes from those with poorer behavioral outcomes. Therefore, the current set of hypotheses attempts to connect brain structure and function by

assessing the relative influence of cortical thickness on specific executive functions and parent

and teacher reported symptoms of ADHD.

CHAPTER 3: METHOD

Project Approval

The current study utilized neuropsychological and neuroimaging data procedures in compliance with the ethical issues and standards of research of the American Psychological Association (American Psychological Association, 2002). The project was funded by Dr. Margaret Semrud-Clikeman in the Departments of Psychiatry and Psychology at Michigan State University. Participant informed consent forms used in the study are included in Appendix A. The project was funded by the National Institute of Health Grant: NIH: #R01 MH63986.

Permission to use the data for the current study has been obtained prior to any data analysis from Dr. Margaret Semrud-Clikeman in the Departments of Psychiatry and Psychology at Michigan State University, Dr. Steven R. Plizka at the University of Texas Health Science Center at San Antonio, and the Institutional Review Board of Michigan State University under the project title: "Neuroimaging of inhibition and stimulant response," protocol number: IRB#06-903, on September 1st, 2009. The current study used data that was collected as part of a larger study from the University of Texas at Austin and the University of Texas Health Science Center in San Antonio by Dr. Semrud-Clikeman.

Participants

Participation for neuropsychological testing and MRI scanning took place at the University of Texas Health and Science Center at San Antonio. Families of both ADHD and typically developing children were invited to participate in a study on attention, executive functioning, and brain structure and function. Parents and/or primary caregivers were required to fill out behavioral questionnaires and information on their child's developmental history. Referral for participation was conducted through local schools, organizations, and psychological

and psychiatric outpatient clinics and hospitals. Referral was also conducted through advertisements placed in local organizations and psychological and psychiatric outpatient clinics and hospitals.

Procedures

Participant Characteristics

Participants for the study were a total of 47 subjects matched on gender, SES, and ethnicity. All subjects were right-handed. There were three groups: ADHD-Combined Type (ADHD, n =32; 18 chronically-treated with psychostimulant medication and 14 treatment-naïve) and healthy controls (n = 15). 32 boys and 15 girls participated in the study (Table 2). All ADHD subjects met DSM IV-TR criterion for ADHD Combined–type and no other psychiatric or psychological disorder including Learning Disorders, Anxiety Disorders, Mood Disorder, or Oppositional Defiant Disorder. Control participants did not meet any criteria for a psychiatric or learning diagnosis nor have a history of medication treatment. All participants were recruited from a diversity of socioeconomic and ethnic backgrounds in order to control for potential group differences. ADHD participants taking medication for ADHD were subjected to at least a 36-48 hour washout period prior to testing. All participants had less than 15 standard score point differences between general conceptual ability (DAS-GCA) and all achievement measures. The ADHD groups were matched on severity of symptoms as measured by Conners' Ratings Scale *(Conners, 1998a)*. Parent and child informed consent were completed prior to testing. All children were fluent in English.

Group 1: ADHDRx. Participants were diagnosed with ADHD-C using the Diagnostic Interview Schedule for Children –IV-Parent Version (DISC-IV-P with agreement between two investigators from the University of Texas Health and Science Center at San Antonio).

ADHDRx participants were subjected to at least a 24-48 hour washout period prior to testing, and were not taking any other medications during testing. According to parents' ratings of the last six months, ADHDRx participants fell 1.5 standard deviations above the mean for their age and sex while off medication on the parent Conners' Global Index and Restless/Impulsive Index. Ratings on the teacher form of the Conners' for this group fell within one standard deviation on the Global Index and the Restless/Impulsive (RI) index ensuring positive medication response. In addition to the DISC-IV-P, the child's medical history was reviewed with parents to rule out a serious medical illness or developmental difficulties.

Group 2: ADHDTn. Participants were diagnosed with ADHD-C using the Diagnostic Interview Schedule for Children –IV-Parent Version (DISC-IV-P with agreement between two investigators from the University of Texas Health and Science Center at San Antonio). The ADHDTn group had never been treated with medication for any psychiatric condition including ADHD. In addition, participants had never been treated with stimulants for personal reasons of parent/caregiver, and not due to symptom severity. ADHDTn participants were required to have a Restless/Impulsive (RI) index and Global index on the parent and teacher Conners' Global Index ≥ 1.5 standard deviations above the mean for their age and sex. In addition to DISC-IV-P, medical history was reviewed with parents to rule out serious medical illness or developmental difficulties.

Group 3: Control Participants. Participants consisted of 15 healthy age/IQ matched typically-developing controls. Control participants had no history of medication treatment or met any criteria for a learning disorder or other psychiatric diagnoses. Control participants were required to have a Restless/Impulsive (RI) and global score on the parent and teacher Conners Global Index that fell within one standard deviation from the mean for their age and sex.

Neuropsychological Variables of Interest and Screening Measures

The neuropsychological variables of interest were previously collected at the University

of Texas Health and Science Center at San Antonio through the use of a test battery designed to

measure verbal and nonverbal intelligence, academic achievement, executive functioning, and

ADHD symptom severity. Neuropsychological variables for the current study included measures

for general conceptual ability (GCA), academic achievement, executive functioning, and parent

and teacher reported attention and hyperactivity.

Differential Ability Scales (DAS; Elliott, (1990). The DAS was used to assess General

Conceptual Ability (DAS-GCA) a measure of general intellectual functioning. The test for ages 6

– 18 years of age include core measures of Word Definition, Similarities, Matrices, Sequential

and Quantitative Reasoning, Design Recall, Pattern Construction, and three additional subtests:

Digit Recall, Object Recall, and Processing Speed. The DAS was normed on 3,475 children

ages 2.6 years to 17.11 years of age. The DAS used a diverse sample based on gender and

race/ethnicity from the 1988 U.S. Census.

Wechsler Individual Achievement Test (WIAT-II,(Psychological Corporation, 2002). The

WIAT-II was used to rule out learning disorder by assessing current mathematical and reading

abilities. The Mathematical Reasoning and Reading Comprehension subtests were used assess

possible learning disabilities. Subjects with learning disabilities were excluded from this study.

The WIAT-II was normed on a nationally stratified representative sample of 5,586 subjects

based on the 1998 U.S. Census. Internal subtest reliability was satisfactory ($r \geq .70$) to high ($r \geq$

.85), and overall internal reliability of the composite scores was high ($r \geq .85$).

Conners' Rating Scale – Revised (CRS-R, (Conners, 1998a, 1998b). The Conners'

Rating Scale is designed to assess symptoms (inattention, impulsivity, hyperactivity) of ADHD

by using both teacher and parent questionnaire format. The parent and teacher report form of the Conners was used to assess the presence of ADHD symptom. For the purposes of this study, the Conners' Global Index – Restless/Impulsive composite score (CGI-R/I) was used as a measure of ADHD symptom severity. The score index is a proxy for DSM-IV criteria for ADHD and can be used for a wide variety of ages: 3 to 17 years of age. Raw scores are translated to T-scores that are calculated into the Conner's Global Index. Internal reliability is high for both the long form (.73 - .94) and short form (.86 - .94). The normative sample included over 8000 subjects, and was geographically representative (>45 states), and includes both teacher and parent forms.

Delis-Kaplan Executive Functioning System (D-KEFS; (Delis, Kaplan, & Kramer, 2001). The D-KEFS comprises nine tests that measure different aspects of executive functioning. The Color-Word subtest comprises four trials: 1) naming colors of ink, 2) reading color-words, 3) reading dissonant color-words (the word "blue" printed in red ink), and an interference trial 4) reading dissonant color-words or naming ink color when a box is present around the word. The third trial of this test (reading dissonant color-words) is thought to be a measure of response inhibition (inhibiting an automatic response in favor of a response that meets task demands) (Lezak, Howieson, & Loring, 2004). All trials of the Color-Word subtest were used in the analysis of group differences. Response inhibition has been found to be impaired in children with ADHD in numerous meta-analytic investigations (Frazier, Demaree, & Youngstrom, 2004; Hervey, Epstein, & Curry, 2004; Homack & Riccio, 2004; van Mourik, Oosterlaan, & Sergeant, 2005). Effect sizes range from small to large (corresponding order above; 0.56, 0.15, 0.75, 0.35).

Behavior Assessment System for Children, 2nd Edition (BASC-2, (Reynolds & Kamphaus, 2004). The BASC-2 is a comprehensive behavioral questionnaire designed to assess a wide range of behaviors from hyperactivity and anxiety to depression and withdrawal. It

provides not only self-evaluations in these domains but includes parent and teacher perspectives allowing for the assessment of behaviors in different environmental contexts. For the purposes of this study the Hyperactivity and Attention Problems scales were used. These scales have been shown to differentiate children diagnosed with ADHD compared to non-ADHD controls (Sullivan & Riccio, 2006). Furthermore, these scales have been shown to significantly correlate ($r = .83$) with the Global Executive Composite scale on the Behavior Rating Inventory of Executive Function (BRIEF-2). Reliability and validity estimations of the BASC-2 suggest excellent internal consistency (.90 for composite and .80 for individual scales), test-retest reliability (.70 for composite scores and .80 for individual scales).

Magnetic Resonance Imaging Acquisition

MRI images will be acquired at the University of Texas Health Science Center at San Antonio using three-dimensional gradient recalled acquisitions in the study state (3D-GRASS) with a repetition time (TR) = 33msec, echo time (TE) = 12msec, and a flip angle of 60 degrees to obtain a 256 X 192 X 192 volume of data with a spatial resolution of 1mm X 1mm X 1mm. Children wore headphones and watched movies or television programs of their choice in order to help them relax and feel comfortable. DICOM files were burned to CD and then transferred to the Cognitive Imaging Research Center (CIRC) server at MSU and processed individually.

Magnetic Resonance Imaging Preprocessing

All MR images were processed using the FreeSurfer image analysis suite (Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000) by the author on a Linux platform at MSU. FreeSurfer was specifically designed to analyze the thickness of the human cortical ribbon, the morphology of gyri and sulci, the volume of white and gray matter structures (see Figure 4 visualization), and in the analysis of functional MRI data. FreeSurfer also features built-in statistical analysis

procedures for carrying out group-based statistical comparisons. FreeSurfer analysis tools for calculating subcortical volume and gray and white matter volume have been found to be highly reliable with both manual tracing methods and other automated analysis methods such as FSL (Morey et al., 2009).

-Insert Figure 4-

The FreeSurfer analysis pipeline was used for motion correction, removal of non-brain matter identified as dura matter or skull using a watershed/hybrid surface deformation process (Segonne, Pacheco, & Fischl, 2007), automated talairach transformation, subcortical white matter and gray matter structures (Fischl et al., 2002; Fischl et al., 2004), tessellation of the gray and white cortical boundary, automated topology defect correction (Fischl, Liu, & Dale, 2001; Segonne, et al., 2007), and surface deformation for optimal differentiation of white and gray matter and gray and cerebrospinal fluid intensity boundaries (Dale, et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Each step was carried out by the author sequentially on each participant's T1 image. All procedures were carried out through the hierarchical use of the reconstruction and manual editing scripts and with the use of the tksurfer and tkmedit editing and visualization tools.

Individual T1 images required roughly 40 hours of preprocessing before the cortical maps were produced. At which point they were manually checked by the author, slice by slice, for intensity normalization errors in the pial and white matter boundary using the tkmedit and tksurfer tools in FreeSurfer. Intensity errors occur when non-brain tissue is coded as brain tissue (e.g., cerebrospinal fluid voxels register as gray matter and therefore cause abnormal cortical surfaces) or when gray matter is coded as white matter and vice versa. Manual editing was carried out on the wm.mgz file with control points and then re-running the second and third

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phase of the reconstruction process. A total of 49 participants required manual editing of the white matter and consisted of re-running the second and third phase of the reconstruction process due to movement artifacts and cortical surface errors. After reconstruction, the 49 brains' white matter and pial boundaries were checked for intensity normalization and smooth reconstruction.

Alignment. Care was taken to align each participants head in the scanner head coil using during image acquisition in order to minimize image alignment problems by faculty of the University of Texas Health and Science Center at San Antonio. In order to ensure alignment, each participant's head was aligned using a red laser, securely packed with foam, and a thin piece of non-stick tape is place over the forehead to prevent movement. After the scan, AC-PC alignment was carried out using DISPLAY in the lab of Dr. Steven R. Pliszka at the University of Texas Health and Science Center at San Antonio. In order to align the brain and minimize spatial distortions, each brain was oriented by its anterior commissure (AC) and posterior commissure (PC) manually in AFNI. The anterior and posterior commissures are in the center of the brain and serve as central anatomical landmarks from which to spatially normalize the brain. During the AC-PC alignment procedure, the superior boundary and the posterior boundary of the anterior commissure was manually located in the axial, sagittal, and coronal view, and marked (Figure 5). Next, the inferior boundary of the posterior commissure was identified in the axial, sagittal, and coronal view and marked. Lastly, two locations were identified in the sagittal view and marked, while angular deviation (head alignment) is continuously checked. Once the angular deviation of the AC-PC and sagittal markers are correct, the image is rotated along the $x - y - z$ axis, using the five markers and aligned consistently among all participants.

-Insert Figure 5-

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Neuroanatomical Regions of Interest

All regions of interest (ROI) in the FreeSurfer suite (34 cortical ROIs) were developed using an automated labeling system based on gyral regions of the Desikan-Killiany Atlas (Desikan et al., 2006). These ROI's were found to be highly reliable when compared to 40 manually segmented brains: interclass correlation coefficient = 0.835 and an average distance error of less than 1mm (Desikan, et al., 2006). The following ROI served as the dependent variables in this study given their empirical association to ADHD pathophysiology.

-Insert Figure 6-

Inferior Parietal Gyrus. The inferior parietal gyrus features the inferior parietal gyrus and the angular gyrus and were defined inferior to the superior parietal gyrus (Figure 6). The anterior and posterior boundaries were the supramarginal gyrus and the lateral occipital gyrus. The medial and lateral boundaries were the superior parietal gyrus and the middle temporal gyrus (Desikan, et al., 2006).

Superior Parietal Gyrus. The anterior and posterior boundaries of the superior parietal cortex were defined as the precentral gyrus and lateral occipital cortex. The medial and lateral boundaries of the superior parietal cortex were the precuneus and/or cuneus cortex and the inferior parietal cortex (Desikan, et al., 2006).

Precuneus Gyrus. The anterior boundary of the precuneus was defined as the posterior extent of the paracentral lobule and the posterior boundary of the precuneus was the lingual gyrus. The medial and lateral boundaries were the parietal-occipital fissure and the superior parietal gyrus (Desikan, et al., 2006).

Anterior Cingulate Cortex. The anterior boundary of the anterior cingulate cortex was the posterior margin of the cingulate sulcus (inferior to the superior frontal sulcus), and the posterior

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boundary was the genu of the corpus callosum. The superior-lateral boundary was defined as the superior frontal gyrus, and the inferior-lateral boundary was the medial aspect of the orbitofrontal gyrus (Desikan, et al., 2006).

Orbitofrontal Cortex. The orbitofrontal cortex was divided into the lateral and medial division. The posterior boundary of the lateral division was defined as the anterior aspect of the lateral orbitofrontal gyrus (where it appears to join with the frontomarginal sulcus), and the posterior boundary was the posterior aspect of the lateral orbital gyrus. The medial and lateral boundaries were defined as the midpoint of the olfactory sulcus and the lateral aspect of the lateral orbital sulcus and/or the circular insular sulcus (Desikan, et al., 2006). The medial division of the anterior boundary of the medial division of the orbitofrontal cortex served as the anterior boundary of the medial orbital gyrus, and the posterior boundary served as the posterior boundary of the medial orbital gyrus rectus. The medial and lateral boundaries were defined as the cingulate cortex and the medial aspect of the superior frontal gyrus (Desikan, et al., 2006).

Superior Frontal Gyrus. The superior frontal gyrus served as the anterior boundary of the superior frontal sulcus and the posterior boundary was defined as the paracentral sulcus. The medial and lateral boundaries of the superior frontal gyrus served as the medial boundary of the frontal lobe and superior frontal sulcus (Desikan, et al., 2006).

Middle Frontal Gyrus. The middle frontal gyrus was subdivided into two divisions, the rostral division and the caudal division. The rostral division was defined as the anterior boundary of the superior frontal gyrus and the posterior boundary was defined as the posterior portion of the middle frontal gyrus. The medial and lateral boundaries were marked by the superior and inferior frontal sulci (Desikan, et al., 2006). The caudal division served as the anterior boundary of the middle frontal gyrus and the inferior boundary was defined as the posterior boundary of

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the precentral gyrus. The medial and lateral boundaries were marked as the superior frontal gyrus and the inferior frontal sulcus (Desikan, et al., 2006).

Frontal Pole. The anterior and posterior boundaries of the frontal pole were the superior frontal gyrus and the posterior boundary of the middle frontal (Desikan, et al., 2006).

Statistical Analyses

Analysis of Variance (ANOVA) were run in order to ensure there were no statistically significant group differences with respect to age, general conceptual ability (DAS-GCA), or total brain volume between the ADHD-C and typically developing control participants. Furthermore, a 2 (group) X 2 (measure) MANOVA was used to determine if ADHD-C and control groups do not differ with respect to academic achievement (reading) in order to rule out potential learning disability. Next, 2 (group) X 1 (measure) Analysis of Covariance (ANCOVA) will be run to determine if groups differ on any of the regions of interest with age, total brain volume, and/or DAS-GCA held constant, depending on the results of the prior analysis. Next, the ADHD group will be subdivided by their medication status yielding two groups: Treated and Not-Treated with psychostimulant medications. A 3 (group) X 1 (measure) Analysis of Covariance (ANCOVA) will be used to determine if any of the groups differ on any of the regions of interest. Fisher Least Significant Difference tests were used for testing post-hoc analysis. Statistical analyses will be run using the FreeSurfer Qdec (Query, Design, Estimate, and Contrast) single-binary application with a false discovery rate threshold of *q=.05* and statistical corrections for multiple comparisons and Statistical Package for the Social Sciences/Predictive Analytics Software (SPSS, Version 18). The Qdec file will designate all ADHD and control subjects and respective cortical thickness and surface measurements and then be used for General Linear Model analysis

of group differences. Lastly, all subjects will be used in a linear regression model to predict the

amount of variance in executive functioning measures that is explained by cortical thickness.

CHAPTER 4: RESULTS

ADHD and Control - Participant Demographic Variables

The first set of analyses was used to determine if ADHD and Control participants differed with respect to age, intellectual ability, and reading ability. Separate analysis of variance (ANOVA) procedures found statistically significant differences between ADHD and Control participants in intellectual ability [F 1, 46 = 6.742, p = .013], but no differences in age [F 1, 46 = 1.069, p = .307], reading ability [F 1, 46 = 3.137, p = .083]. ADHD participants demonstrated significantly lower intellectual ability (DAS-GCA) compared to control participants, though performance was still in the average range (ADHD DAS-GCA; Mean = 103.66, SD = 12.73). Intellectual ability has been found to moderate cortical thickness measurements (Shaw, et al., 2006b), thus, intellectual ability was used as a covariate in cortical thickness analyses (see below). Groups did not differ in gender based on Pearson's chi-square analysis ($\chi2$ (1) = .279, p = .597). Participant group means, standard deviations, and *p*-values are shown in Table 2.

-Insert Table 2-

ADHD and Control – Neuropsychological Variables

ADHD and Control participant means, standard deviations, and statistical *p*-values for parent and teacher behavioral measures as well as response interference measures are presented in Table 2. A 2 (group) by 2 (measure) MANCOVA with DAS-GCA controlled was used to determine if groups differed on response inhibition (i.e., D-KEFS Color-Word and Interference subtests). There were no statistically significant group differences on response inhibition (Wilks' Λ = .960, F 2, 30 = .633, p = .538, $\eta2$ = .040). These findings are presented in Figure 7.

-Insert Figure 7-

A MANOVA revealed statistically significant group differences on parent reported behavioral symptoms. ADHD participants were rated as having significantly more behavioral symptoms compared to Control participants according to parent reports (Wilks' $\Lambda = .283$, F 3, 31 = 26.194, $p = .000$, $\eta2 = .717$). Follow-up analyses found significant differences on parent reports: CGI-R/I Parent Report [F 1, 34 = 75.802, $p = .000$], BASC-2 PRS (Hyperactivity [F 1, 34 = 49.123, $p = .000$] and BASC-2 PRS Attention Problems [F 1, 34 = 75.001, $p = .000$]. An ANOVA revealed significant differences between ADHD and Control groups on teacher reported behavioral symptoms: CGI-R/I Teacher Report [F 1, 45 = 15.500, $p = .000$]. Parent and teacher reports (BASC-2 and Conners' CGI-R/I) are presented in Figure 8.

<center>*-Insert Figure 8-*</center>

ADHD and Control - Cortical Thickness

Analysis of the differences between the ADHD and Control groups was carried out with Analysis of Covariance (ANCOVA) with DAS-GCA used as a covariate. Bonferroni corrections were used to correct for multiple comparisons and false discovery rate (FDR = .05) methods were also used to control for multiple spatial comparisons in cortical thickness in both hemispheres. FDR estimates the proportion of Type 1 errors and corrects for errors in all regions reaching statistical significance (Storey, 2002). ADHD and Control groups means and standard deviations for cortical thickness measures are presented above in Table 4.

Anterior Cingulate Cortex. Hypothesis 1a was confirmed. There was a statistically significant difference in cortical thickness between the ADHD and Control participants in the right rostral anterior cingulate [F 2, 47 = 6.481, $p = .014$, $\eta2 = .128$]. There were no significant differences in any of the other regions: Left Caudal Anterior Cingulate [F 2, 47 = .014, $p = .905$, $\eta2 = .000$]; Left Rostral Anterior Cingulate [F 2, 47 = 2.783, $p = .102$, $\eta2 = .059$]; Right Caudal

<center>51</center>

Anterior Cingulate [F 2, 47 = .006, p = .939, η2 = .000]. Figure 11 shows the inflated surface and

regions of cortical thinning in the medial view of the right rostral anterior cingulate cortex.

Figure 12 shows the pial surface and regions of cortical thinning in the medial view of the right

rostral anterior cingulate cortex.

      Frontal Cortex. Hypothesis 1b was not confirmed. There were no statistically significant

group differences between ADHD and Control participants in any of the frontal and prefrontal

regions: Left Caudal Middle Frontal [F 2, 47 = 1.924, p = .172, η2 = .042]; Left Lateral Orbital

Frontal [F 2, 47 = .016, p = .901, η2 = .000]; Left Medial Orbital Frontal [F 2, 47 = .330, p =

.568, η2 = .007]; Left Superior Frontal [F 2, 47 = .017, p = .896, η2 = .000]; Right Caudal

Middle Frontal [F 2, 47 = .037, p = .849, η2 = .001]; Right Lateral Orbital Frontal [F 2, 47 =

.209, p = .650, η2 = .005]; Right Medial Orbital Frontal [F 2, 47 = .428, p = .516, η2 = .010];

Right Superior Frontal [F 2, 47 = .075, p = .786, η2 = .002].

      Parietal Cortex. Hypothesis 1c was not confirmed. There were no statistically significant

group differences between ADHD and Control participants in any of the parietal cortex regions:

Left Cuneus [F 2, 47 = .012, p = .913, η2 = .000]; Left Inferior Parietal [F 2, 47 = .977, p = .328,

η2 = .022]; Left Precuneus [F 2, 47 = .103, p = .750, η2 = .002]; Left Superior Parietal [F 2, 47 =

2.260, p = .140, η2 = .049]; Right Cuneus [F 2, 47 = .384, p = .539, η2 = .009]; Right Inferior

Parietal [F 2, 47 = .013, p = .908, η2 = .000]; Right Precuneus [F 2, 47 = .614, p = .437, η2 =

.014]; Right Superior Parietal [F 2, 47 = 2.969, p = .092, η2 = .063].

-Insert Figure 11-

-Insert Figure 12-

Total Brain Volume

Overall brain volume between ADHD and Control groups was analyzed with a 2 (group) by 1 (measure) ANOVA. No significant difference emerged between ADHD and Control [F 1, 46 = .292, p = .591]. Overall brain volume for ADHD Treated, ADHD Not-Treated, and Control was analyzed with a 3 (group) by 1 (measure) ANOVA and was not significant [F 2, 47 = .322, p = .727]. Means and standard deviations for total brain volume are shown in Tables 3 and 4.

-Insert Table 4-

ADHD Treated, ADHD Not-Treated, and Control Participant Demographic Variables

To evaluate the possible effect of medication history, the ADHD group was divided into two groups, ADHD Treated with medications and ADHD Not-Treated with medications, based on whether or not the child was being treated with psychostimulant medication at the time of the study. A series of ANOVAs found statistically significant differences between ADHD Treated, ADHD Not-Treated, and Control participants in intellectual ability [F 2, 46 = 3.902, p = .028] and reading ability [F 2, 46 = 6.074, p = .005]. Intellectual ability has been found to moderate cortical thickness measurements and so DAS-GCA was controlled for in cortical thickness analyses (Shaw, et al., 2006b). Follow-up ANOVAs found statistically significant group differences in intellectual ability between ADHD Not-Treated and Control (p = .009), and word reading ability between ADHD Not-Treated and Control (p = .003) with the ADHD Not-Treated group scoring significantly below the Control group. No group differences emerged between ADHD Treated versus Controls or ADHD Treated versus ADHD Not-Treated on any of the demographic variables. The groups did not differ in gender based on Pearson's chi-square analysis ($\chi 2$ (2) = .665, p = .717).ADHD Treated, Not-Treated, and control participants' group means, standard deviations, and *p*-values are shown in Table 3.

-Insert Table 3-

ADHD Treated, ADHD Not-Treated, and Control – Neuropsychological Variables

A 3 (group) by 2 (measure) MANCOVA with DAS-GCA as the covariate was used to determine if groups differed on response inhibition (D-KEFS Color-Word and Interference subtests). There were no statistically significant group differences on response inhibition (Wilks' $\Lambda = .862$, F 4, 58 = 1.119, $p = .356$, $\eta2 = .072$). ADHD Treated, ADHD Not-Treated, and Control participants' performance on each of the response inhibition measures is presented in Figure 9.

-Insert Figure 9-

ANOVAs with Fisher Least Significant Difference (LSD) post-hoc pairwise comparison analyses revealed statistically significant group differences on CGI-R/I Parent Report between ADHD Treated and Control ($p = .001$) and ADHD Not-Treated and Control ($p = .003$). No group differences were found between the ADHD Treated and ADHD Not-Treated groups on CGI-R/I ($p = .742$). There were also significant group differences on CGI-R/I Teacher Report between ADHD Treated and Control ($p = .000$), ADHD Not-Treated and Control ($p = .000$), but no differences between ADHD Treated and ADHD Not-Treated ($p = .868$). Differences emerged on the BASC-2 PRS Attention report between ADHD Treated and Control ($p = .000$), ADHD Not-Treated and Control ($p = .000$), but no differences between the ADHD groups ($p = .491$). There were also significant group differences on BASC-2 PRS Hyperactivity scores between ADHD Treated and Controls ($p = .000$) and ADHD Not-Treated and Controls ($p = .000$), but no differences between the ADHD groups ($p = .495$). Parent and teacher reports for each group are presented in Figure 10.

-Insert Figure 10-

ADHD Treated, ADHD Not-Treated, and Control: Effects of Long-Term Psychostimulant

Treatment on Cortical Thickness

Analysis of group differences between ADHD Treated, ADHD Not-Treated, and Control were carried out with Analysis of Covariance (ANCOVA) with DAS-GCA used as a covariate. Means and standard deviations for ADHD Treated, ADHD Not-Treated, and Control groups are presented in Table 5.

Anterior Cingulate Cortex. Hypotheses 2b and 2c were not confirmed in regions of the anterior cingulate cortex. Hypothesis 2a was confirmed. There was a statistically significant difference in cortical thickness between the ADHD Treated, ADHD Not-Treated, and Control participants in the Right Rostral Anterior Cingulate [F 3, 47 = 3.416, p = .042, η2 = .137]. Fisher Least Significant Difference (LSD) post-hoc analyses found differences between ADHD Treated and Control (p = .043) and between ADHD Not-Treated and Control (p = .017), but no differences were observed between the ADHD groups (p = .513). Thus, no effect of medication treatment was found for estimates of cortical thickness. There were no significant differences in any of the other regions in the anterior cingulate cortex: Left Caudal Anterior Cingulate [F 3, 47 = .108, p = .898, η2 = .005]; Left Rostral Anterior Cingulate [F 3, 47 = 2.072, p = .138, η2 = .088]; Right Caudal Anterior Cingulate [F 3, 47 = .048, p = .953, η2 = .002].

Frontal Cortex. Hypotheses 2a, 2b, and 2c were not confirmed for regions in the prefrontal cortex. There were no statistically significant group differences between ADHD Treated, ADHD Not-Treated, and Control participants in any of the frontal and prefrontal regions: Left Caudal Middle Frontal [F 3, 47 = 1.118, p = .336, η2 = .049]; Left Lateral Orbital Frontal [F 3, 47 = .367, p = .695, η2 = .017]; Left Medial Orbital Frontal [F 3, 47 = .239, p = .788, η2 = .011]; Left Superior Frontal [F 3, 47 = 1.302, p = .283, η2 = .057]; Right Caudal

Middle Frontal [F 3, 47 = .243, p = .785, η2 = .011]; Right Lateral Orbital Frontal [F 3, 47 = .109, p = .897, η2 = .005]; Right Medial Orbital Frontal [F 3, 47 = .209, p = .812, η2 = .010]; Right Superior Frontal [F 2, 47 = 1.467, p = .242, η2 = .064].

Parietal Cortex. Hypotheses 2a, 2b, and 2c were not confirmed for regions in the prefrontal cortex. There were no statistically significant group differences between ADHD Treated, ADHD Not-Treated, and Control participants in any of the parietal cortex regions: Left Cuneus [F 3, 47 = 1.358 p = .268, η2 = .059]; Left Inferior Parietal [F 3, 47 = .480, p = .622, η2 = .022]; Left Precuneus [F 3, 47 = .124, p = .884, η2 = .006]; Left Superior Parietal [F 3, 47 = 1.357, p = .268, η2 = .059]; Right Cuneus [F 3, 47 = 2.165, p = .127, η2 = .091]; Right Inferior Parietal [F 3, 47 = .461, p = .634, η2 = .021]; Right Precuneus [F 3, 47 = .970, p = .387, η2 = .043]; Right Superior Parietal [F 3, 47 = 1.639, p = .206, η2 = .071].

-Insert Table 5-

Relative Contribution of Cortical Thickness to Response Inhibition and Parent and Teacher Reported Symptoms of ADHD

Linear regression models were used to determine the relationship between cortical thickness of the rostral anterior cingulate cortex and behavioral and executive functioning measures. Past studies found IQ to influence cortical thickness (Shaw, et al., 2006b), and so IQ was considered before running regression models. IQ did not explain a significant amount of the variance in cortical thickness in the right rostral ACC ($R2$ = .038, F 1, 45 = 1.575, p = .192) and so was not entered into the regression models. Thus, each model included one predictor variable (neuropsychological or parent/teacher report) and one dependent variable (e.g., right rostral ACC thickness). The results of these regressions indicate that for this sample, a significant amount of the variance in BASC-2 Hyperactivity ($\Delta R2$ = .374, F 1, 34 = 19.726, p < .000), BASC-2

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Attention ($\Delta R2 = .396$, F 1, 34 = 21.595, $p < .000$), and CGI-R/I Parent Report ($\Delta R2 = .334$, F 1, 34 = 16.563, $p < .000$) was explained by right rostral ACC cortex thickness. This suggests that nearly 37.4% of the variance in BASC-2 Hyperactivity, 39.6% of the variance in and BASC-2 Attention, and around 33.4% of the variance in CGI-R/I Parent Reported levels of ADHD symptoms can be accounted for by of the right rostral anterior cingulate cortex thickness.

Linear regression analyses were not significant for CGI-R/I Teacher Report, D-KEFS Color-Word or D-KEFS Inhibition performance. Regression results including standardized beta coefficients, F statistics, p values, and $\Delta R2$ are presented for the right rostral anterior cingulate cortex in Table 6. Figures 13 – 18 show scatterplots with linear representations of the relationship between each behavioral and/or neuropsychological measure and right rostral anterior cingulate cortex thickness measurements.

-Insert Table 6-

-Insert Figure 13-

-Insert Figure 14-

-Insert Figure 15-

-Insert Figure 16-

-Insert Figure 17-

-Insert Figure 18

CHAPTER 5: DISCUSSION

Previous research has found that children with ADHD have reduced gray and white matter volume in numerous brain regions (Valera, et al., 2007). Symptoms of ADHD have been found to be related to structural abnormalities as well as brain functional abnormalities (e.g., widespread activation patterns that are considered inefficient compared to activation patterns of typically-developing children without ADHD) (Durston, et al., 2004; Sheridan, et al., 2007). It is unclear whether volumetric abnormalities are a product of reduced cortical surface area or cortical thickness and if reductions are related to symptoms or severity of ADHD. Current research in neuroimaging of ADHD is inconclusive due to the use of highly comorbid samples (e.g., including children with multiple disorders), small sample sizes, and not accounting for past medication history which may alter brain development (see Table 1).

Thus, one aim of the current study was to assess cortical thickness in a carefully diagnosed group of children with ADHD-Combined Type who were free from comorbid disorders. A second purpose was to determine if past medication history was related to possible differences in cortical thickness measures. In addition to the study of long-term psychostimulant effects on cortical thickness, the study sought to evaluate the relationship between cortical thickness estimates and response inhibition, and parent and teacher reported symptoms of ADHD. In sum, this study was the first to assess the relationship between cortical thickness, medication history, and implications for response inhibition and behavioral symptoms of ADHD.

Results from the current study include significant cortical thinning of the right rostral ACC but non-significant thinning in any region of the prefrontal cortex (PFC) or parietal cortex. It was also found that medication history did not affect cortical thickness measures. Treated and Not-Treated ADHD groups had reduced cortical thinning in the right rostral ACC with the

Treated group ($p = .043$) only slightly different from controls compared to the Not-Treated

ADHD group ($p = .017$). Lastly, right rostral ACC thickness predicted a significant amount of

the variance in parent and teacher reported symptoms of ADHD. No such relationship emerged

between cortical thickness and response inhibition neuropsychological measures.

ADHD-C and the Cortex

  Anterior Cingulate Cortex. Hypothesis 1a of this study postulated that children with

ADHD would have significant cortical thinning of the ACC compared to controls. This

hypothesis was confirmed. Children with ADHD had significant cortical thinning in the right

rostral ACC compared to typically developing children without ADHD.

  There have been several regions of the cortex implicated in ADHD symptoms. Perhaps

the most consistent findings include abnormalities of the anterior cingulate cortex (ACC).

Numerous studies in ADHD reported dysfunction in response inhibition, attention, motor

control, and continuous monitoring of behavior as well as volumetric reductions of the ACC

(Bush, et al., 1999; Bush et al., 2008; Makris, et al., 2007; Makris, et al., 2010; Pliszka, et al.,

2006). No differences in this study were observed in the bilateral caudal ACC or in the left

rostral ACC. In addition, past work suggests the ACC and related networks play a key role in

many of the underlying behavioral impairments in ADHD including response inhibition (e.g., via

related motor inhibition networks), feedback-based decision making and error detection, and

vigilance (Botvinick, Cohen, & Carter, 2004; Bush, et al., 1999). Thus, it is hypothesized that

reductions in the number of neuronal cell bodies (e.g., reduced cortical thickness) of the right

rostral ACC may be related to, or at least influence, the behavioral deficits in ADHD. This would

lend support to specific findings of hypoactivation of the ACC during a Go/No-Go inhibition

task (Pliszka, et al., 2006) and a stop signal reaction time task (e.g. response inhibition)

(McAlonan et al., 2009). The current study is the first to report significant cortical thinning in the right ACC in children with ADHD-C.

Findings for reduced cortical thickness in the right but not the left ACC were not altogether surprising. Right-hemisphere volumetric reductions and functional impairments, particularly within the frontal lobes is a common finding in the neuroimaging literature (Valera, et al., 2007). Right-hemispheric disruptions may be specific to ADHD given the importance of the right-hemisphere for arousal (e.g., and efficiency of information processing (e.g., the efficiency and accuracy with which one can organize and manipulate information) (Posner & Petersen, 1990; Sergeant, Oosterlaan, & van der Meere, 1999; Sturm & Willmes, 2001).

Prefrontal Cortex. Hypothesis 1b of this study postulated that children with ADHD would have significant cortical thinning in the prefrontal cortex compared to controls. This hypothesis was not confirmed in any PFC region of interest. No differences between groups in the prefrontal cortex was unexpected given the many studies that have reported prefrontal-striatal volumetric reductions (Valera, et al., 2007), and theories implicating executive functions (EF) and prefrontal cortex (PFC) dysfunctions in ADHD (Barkley, 1997). It is clear that EF's are important for disorders of attention and disruptive behavior disorders (Willcutt, et al., 2005), though they may be best used to specify an EF endophenotype of ADHD and are not necessary or specific to an ADHD diagnosis (Nigg, et al., 2004). Thus, it may be that in children with ADHD and EF deficits, the PFC is likely disrupted. In the current study, children with ADHD did not differ from Controls on two response inhibition measures (e.g., D-KEFS Color-Word and Interference subtests; ADHD Color-Word Mean = 90, Control Color-Word = 97, ADHD Interference = 103, Control Interference = 103; see Table 2). Because there were no differences in either response inhibition measure, it could be that this ADHD group did not, on average,

exhibit impairments in PFC functioning. This might explain the non-significant differences between groups in PFC cortical thickness measures. This hypothesis is speculative, however, and would require further study. Such theories and research regarding EF's and the PFC are supported and appear to be under investigation (Halperin & Schulz, 2006; Nigg, et al., 2004; Nigg, et al., 2005). Another possibility for the non-significant findings in the PFC in this study could be due to controlling for intellectual functioning (IQ), which has been found to be related to cortical thickness (Shaw, et al., 2006b). By controlling for IQ, the current study's results may be more reliable and less prone to Type 1 statistical error (α) than studies that did not control for IQ.

Parietal Cortex. Hypothesis 1c of this study postulated that children with ADHD would have significant cortical thinning in parietal cortex regions of interest compared to controls. This hypothesis was not confirmed. The parietal lobe has received less attention compared to the ACC or PFC but due to its connections with the PFC and association with posterior attention networks is becoming an important structure for those studying ADHD.

The parietal lobe and associated posterior circuitry, influence attention by signaling the midbrain (substantia nigra) and thalamus to change the attentional focus from one stimulus to another stimulus and so is important for the study of attention and ADHD (Posner & Raichle, 1994). Research on humans and monkeys with posterior network lesions reported slowed covert orienting (e.g., changing one's field of attention by physically moving the eyes or head) and were found to be slow in returning attention to previously attended stimuli (Petersen, Robinson, & Currie, 1989; Posner, 1988; Posner & Cohen, 1984). Children with ADHD have shown reduced functional connectivity between the precuneus of the parietal lobe and regions of the ACC (Castellanos, et al., 2008) as well as associations between parietal cortex thinning and

impairments in alerting (Westlye, Grydeland, Walhovd, & Fjell, 2011). Only a handful of studies have looked at structural abnormalities in the parietal lobe in ADHD. Recently, some have reported cortical thinning and volumetric reductions in the bilateral parietal cortex (in addition to cortical thinning in the frontal, temporal, and occipital lobes) (Wolosin, Richardson, Hennessey, Denckla, & Mostofsky, 2009) and parietal-occipital cortex (Narr et al., 2009) in children with ADHD. Results remained statistically significant even after controlling for IQ according to Narr et al., (2009).

One fundamental difference between the analysis in the current study and that of Narr et al., (2009) was that the current study used hypothesis driven regions of interest analysis, rather than whole-brain analysis. Whole brain analysis is more prone to Type 1 error given the hundreds of thousands of *t*-tests that it requires, compared to the a priori analysis of specified and empirically derived regions of interest. In addition, Wolosin et al., (2009) did not control for IQ in their analysis of cortical thickness or overall brain volume, despite assaying IQ for exclusionary purposes (e.g., participants with IQ < 80 were excluded). Findings of non-significant differences in any of the parietal cortex regions in the current study may be due to using IQ as a covariate. Lastly, longitudinal research found that normalized cortical thickness trajectories (e.g., cortical development that may initially lag but later catches up to what is typical) in the right parietal cortex predicted better outcomes in children with ADHD (Shaw, et al., 2006). Thus, it may be that more severe forms of ADHD (e.g., greater symptom severity, comorbid diagnoses such as oppositional defiant disorder, or samples gathered in clinical settings) are characterized by superior parietal cortex abnormalities that do not correct with normal development. Thus, the non-significant differences in parietal cortex thickness in the

current study may be due to the use of a community sample that was free from psychiatric comorbidities.

Effects of Long-term Psychostimulant Medication on Brain Cortical Thickness

One of the central questions regarding the use of psychostimulant treatment in ADHD has been its effect on the developing brain. Longitudinal studies have found that methylphenidate treatment was associated with significant height and weight reductions in children with ADHD (Swanson, Elliott, et al., 2007; Swanson, et al., 2006). It was therefore hypothesized that if long-term psychostimulant treatment was associated with changes in bodily height and weight, the same might also be true for brain structures. Indeed, studies have found brain volumetric differences in children with ADHD who were chronically-treated with psychostimulants compared to those who had no history of treatment (Bledsoe, et al., 2009; Semrud-Clikeman, et al., 2006; Shaw, et al., 2009).

Hypotheses of the current study postulated cortical thickness would be moderated by psychostimulant medication history. Specifically, hypothesis 2a postulated that the Treated ADHD group would have reduced cortical thinning compared to the Not-Treated ADHD group, hypothesis 2b that the Treated ADHD group would have similar cortical thickness as the Control group, and hypothesis 2c that the Not-Treated ADHD group would demonstrate cortical thinning compared to the Control group.

Hypothesis 2a was not confirmed: there were no significant differences in right rostral ACC thickness (or in any cortical region of interest, see Table 5) between the ADHD groups ($p =$ .513). This finding was unexpected and suggests that in this sample, long-term psychostimulant medication history does not significantly affect cortical thickness measures. Hypothesis 2b and 2c, however, were partially confirmed in that both the Treated ($p = .043$) and Not-Treated

ADHD ($p = .017$) groups demonstrated significant cortical thinning, compared to controls, in the right rostral anterior cingulate cortex (ACC).

One explanation for these non-significant findings might be explained by methodological differences in measuring cortical thickness (e.g., grey matter density) compared to gross anatomical volume (e.g., measuring grey matter and white matter together). For example, Castellanos et al., (2002) found children with ADHD who were treated with pschostimulants differed in white matter (WM) volume but not grey matter (GM) volume compared to children with ADHD who had not been treated with medications. Difference in WM density or volume was not measured in this this study and so could not be compared in the Treated and Not-Treated ADHD groups. GM and WM have different developmental trajectories. GM following an inverted "U" developmental course (e.g., different cortical regions peaking at different times with synaptogenesis occurring with development) and WM tending to increase linearly throughout childhood and young adulthood (Giedd et al., 1999). It may be that the measurements in this study are affected by attempting to measure GM only, which is developing quite rapidly in children aged 11 (i.e., children in this study) and decreases via neuronal pruning around the same time, compared to white matter which is developing at a more predictable rate. Studies on the effects of long-term psychostimulant treatment that are able to measure WM integrity or functional connectivity such as diffusion tensor imaging (DTI) are needed to understand how/if medication affects WM and GM differently.

The findings may also be due to an interaction of the number of years children receive psychostimulant treatment, their age at study intake, and the age at which children began psychostimulant treatment for ADHD. For example, using a longitudinal design, Shaw et al., (2009) found children with ADHD who were not treated with psychostimulant medication had

rapid cortical thinning of the right motor frontal motor cortex, left middle/inferior frontal gyrus, and the right parietal-occipital cortex. They found that the rate of cortical thinning was significantly greater than what is expected for children of the same age. In their sample, children with ADHD who were treated with psychostimulants had a more similar cortical developmental trajectory to controls compared to the not-treated ADHD group. The mean age of the ADHD group in the current study was 11.71 (SD = 1.80) whereas mean age of the ADHD group in the initial scan of Shaw et al. (2009) group was 12.5 years (SD = 2.1) and the follow-up scan mean age was 16.4 (SD = 2.4). This is significant given those with ADHD have been found to have delays in global cortical thickness by as much as 3 years (normal peak cortical thickness is 7.5 years for typically developing children whereas it is 10.5 for those with ADHD) (Shaw, et al., 2007). Thus non-significant findings for medication history in the current study may be partly due to the sample's generally short history of medication use (Mean 2.4 years, SD= .4) as well as their younger age (and therefore greater brain developmental variability).

One study, using fMRI found hypofunctioning of the ACC and left ventrolateral prefrontal cortex during a Stop Signal Task (e.g, inhibition of dominant response, see Logan, Cowan, and Davis (1984) for specific details of the Stop Signal Task) (Pliszka, et al., 2006). They found no differences in neural response between children with ADHD who received long-term treatment with medications and those with ADHD who had never taken medications. They concluded that those with ADHD do not activate the same regions of the brain during inhibition tasks as controls, regardless of medication treatment history. This finding of non-significant differences in treated and not-treated children with ADHD in the ACC is similar to findings in the current study. Taken together, findings suggest that difficulties detecting mistakes, in

monitoring and adjusting behavior in ADHD might be related to functional and structural abnormalities of the ACC.

Brain and Behavior

Structural MRI is not yet sensitive enough or suited for clinical diagnostic purposes; we are unable to tell much about behavior from an MRI scan unless gross anatomical lesions or anomalies are present. Exceptions include detectable cysts, lesions, and other clear atrophy of tissue or edema. While MRI techniques provide information about the volume of a brain structure/region, they do not imply, by themselves, information about the functioning of the structure/region or implications for behavior. There are many reasons for this. A surplus of cerebral white matter may indicate stronger neural connections/integrity between brain structures and regions, or may indicate a lack of synaptic pruning and less efficient neural pathways such as in Autism (Courchesne, et al., 2001). The same is true for gray matter; thinning of the cortical mantle may predict disease such as Alzhiemer's Disease (Kuperberg, et al., 2003), whereas thickening of cortical gray matter has been observed in adolescents with (Brieber, et al., 2007). Thus, it is difficult to predict the functional importance of gray or white matter volumes/thicknesses without also including behavioral measurements. It is for this reason that most structural neuroimaging studies attempt to connect volumetric measurement with behavioral outcome measures (e.g., correlating brain matter volumes with test performance, behavioral ratings, or symptom severity).

The current study used regression models to determine the amount of variance in cortical thickness that could be accounted for by an executive function measure (e.g., response inhibition) and parent and teacher reported levels of attention and hyperactivity problems (e.g., BASC-2 Hyperactivity and Attention Parent Reports and Conners' Global Index

Restless/Impulsive Parent and Teacher Reports). In general, the models found BASC-2 Hyperactivity and Attention measures from parent reports predicted 37% and 39% of the variance in right rostral ACC, respectively. In addition, the CGI-R/I parent report also predicted a significant amount of variance in cortical thickness (e.g., 33%). CGI-R/I teacher reports, however, predicted only 7% of the variance in right rostral ACC thickness.

These findings suggest a brain-behavior relationship between right rostral ACC thickness and symptoms of hyperactivity and impulsivity. Specifically, the data, suggest that, for most behavioral reports, a .010 millimeter decrease in cortical thickness is associated with 10 point increase (e.g., more behavioral problems/symptoms) in the parent and teacher reported levels of ADHD symptoms. As previously stated, cortical thinning appears to be present in many brain regions in ADHD (Narr, et al., 2009), and associated with worse clinical outcomes (Shaw, et al., 2006). This is the first study to find cortical thinning of the right rostral ACC and a specific relationship between cortical thinning and symptoms of hyperactivity and impulsivity, but not response inhibition performance, in ADHD. The lack of a relationship between cortical thickness and response inhibition performance is likely explained by the non-significant group differences on both D-KEFS response inhibition measures. Thus, because regression analyses are based on non-equal variances (Cohen, Cohen, West, & Aiken, 2002), it is not surprising that no relationship was found between cortical thickness and response inhibition measures.

Findings may provide evidence for the development of neuroimaging endophenotypes for ADHD. Neuroimaging endophentoypes provide ways of developing measurable markers within brain structures or brain functioning that relate to or predict genetic susceptibility or risk (Glahn, Thompson, & Blangero, 2007). For example, neurological endophenotypes can be used to index genetic risk or vulnerability, help identify behavior-specific quantitative trait loci (QTLs), and

provide specific ways improving signal to noise by quantifying action-specific genetic function

(Gottesman & Gould, 2003). Findings of significant cortical thinning of the right rostral ACC in

ADHD provide new insights into the neural underpinnings of behavioral regulation problems in

ADHD, and impulsivity in general, which are likely moderated by specific dopaminergic gene

(e.g., DRD4 and DAT) polymorphisms (Congdon, Lesch, & Canli, 2008). Furthermore,

continued study and development of neuroimaging endophenotypes may provide avenues of

extending research on ADHD into animal models which will allow for a deeper understanding of

the neuroscience and neurobiology of ADHD(Gottesman & Gould, 2003), which might also

catalyze research and development of psychostimulant medications for ADHD and disruptive

behavior disorders.

Clinical Implications

Children with ADHD in this study had significant thinning in the ACC which was related

to parent and teacher reported levels of behavioral severity. Other studies have found similar

functional (Durston, 2003; Tian et al., 2006) and structural (Seidman et al., 2006; Semrud-

Clikeman, et al., 2006) abnormalities in ADHD. There are several clinical implications that can

be drawn from these findings.

One suggestion is that behavioral interventions that target ACC activation are likely to

help with symptoms of ADHD including hyperactivity and impulsivity. Past work in children

with Reading Disorder has shown that behavioral remediation strategies can improve functional

activation of the ACC, which predicted improvements in reading ability (Temple et al., 2003).

Behavioral interventions such as Attention Training (ATT) (Posner & Raichle, 1994) which

activate the alerting, orienting, and executive control networks with a cued reaction time and

flanker task (Attention Network Test; see Fan, McCandliss, Sommer, Raz, & Posner (2002) may

provide reliable ways of improving attentional deficits and tracking improvement over time. Improvements in attention in school-aged children after exposure to five days of ATT training have been demonstrated in randomized controlled clinical trials (Rueda et al., 2004). These studies support brain plasticity and changes to underlying neural circuitry following environmental exposures including behavioral remediation for attention problems in ADHD.

Brain Plasticity and Psychostimulant Medication. There is also evidence that children with ADHD who receive long-term treated with psychostimulants perform better on executive functioning and academic measures than children with ADHD who have never taken medications (Semrud-Clikeman, et al., 2008). In this study, EF and academic testing was done after medication washout which suggests the beneficial effects of medication may be retained even after discontinuing medication treatment. These results are clinically important and may be interpreted in light of the current study. Specifically, the current study found ACC thickness was more similar (though not statistically significant, hypothesis 2b and 2c, see above) to controls in those in the Treated ADHD group which suggests psychostimulants may normalize brain development in ADHD thus allowing for improvements in learning and behavior. The inverse may also be true, that psychostimulants lower the threshold for learning thereby allowing for changes in brain connectivity in the ACC. Because neither of these studies was longitudinal, it is unknown if the beneficial effects of medication would remain weeks, months, or years after discontinuing.

Executive Functioning and ADHD. Findings suggest executive functioning impairments (e.g., as assessed by response inhibition) may not be specific to ADHD. This is important given that clinical assessment and differential diagnosis of ADHD often includes executive functioning (e.g., EF) tests (Barkley, 2005). Research suggests as many as half of children with ADHD may

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not qualify for EF impairments when measured by response inhibition tests (Biederman et al., 2004; Nigg, et al., 2005). This has prompted work on the development and investigation of a neuropsychological "executive deficit type" of ADHD in DSM-V (Nigg, et al., 2005). Such work is critically important for understanding the behavioral heterogeneity of ADHD, multiple pathways to symptoms, and for the development of symptom-specific treatments for ADHD. Despite being one of the most commonly studied EFs in ADHD (Willcutt, et al., 2005), the role of response inhibition needs further clarification and should not weigh heavily into clinical diagnostic decisions when assessing for ADHD. Comprehensive neuropsychological assessments, encompassing a wide-range of behavioral, psychological, social, and cognitive functions are recommended over brief assessments that focus on EFs.

Multimodal Assessment of ADHD Symptoms. Parent reported symptoms of ADHD (e.g., BASC-2 and CGI-R/I Parent Report Forms) in the current study better differentiated children with ADHD than teacher reports (e.g., CGI-R/I Teacher Report Forms). Research has shown inter-rater reliability between parent and teacher reported symptoms of ADHD can be quite low (Wolraich et al., 2004). This highlights the importance of multi-informant and multi-setting assessment of ADHD symptoms. DSM-IV criteria for ADHD state that impairment must be present in more than one setting, and failing to consider both parent and teacher reports may increase Type 1 (e.g., diagnosing ADHD when a child does not meet all criteria) or Type 2 error (e.g., not diagnosing ADHD when a child that meets all criteria) when making clinical diagnostic decisions. There may also be important differences in symptom severity and symptom presentation in home versus school settings which should be clearly understood and discussed before developing treatment interventions.

Limitations of the Current Study

The current study was limited in sample size, particularly when the ADHD group was subdivided into Treated (n = 18) and Not-Treated (n = 14) with psychostimulant medications. In addition, there were only 15 typically-developing controls. This limited the statistical power somewhat, though the overall sample size of 47 is relatively common in the neuroimaging literature (see Table 1) due to inherent costs and time required for MRI methods. Partial eta squared effect sizes for the comparison of group differences in right rostral ACC (e.g., $\eta^2 = .128$) suggested the MANOVA had adequate power and was not necessarily affected by sample size.

The result of non-significant differences on response inhibition has important implications, especially when viewed as a measure of EF. Response inhibition alone is not considered a robust measurement of EF. There are many neuropsychological tests thought to measure EF, including working memory, planning, sustained attention, cognitive flexibility, all of which have been found to be impaired skills in ADHD (Willcutt, et al., 2005). The current study used the response inhibition measures from a previous study on neuropsychological outcomes and effects of chronic medication (Semrud-Clikeman, et al., 2008). Thus, this study was limited in its depth of assessing neuropsychological functioning by only including measures of response inhibition. However, it was hypothesis driven and response inhibition was deliberately chosen as an outcome measure based on its importance and relationship to ADHD (Barkley, 1997; Willcutt, et al., 2005).

The study findings and conclusions could have been improved by *simultaneously* using functional MRI methods and structural MRI methods. While correlations between cortical thickness and behavioral measures generally imply a functional but not causal relationship, fMRI methods allow for direct and in-vivo testing of brain and behavior relationships. Past fMRI work

in ADHD suggest hypofunctioning of the ACC during the Counting Stroop Task (i.e., a measure of response inhibition specially designed for fMRI) (Bush, et al., 1999) and a Stop Signal Task (i.e. requires inhibition of dominant and automatic response to stimuli) (Pliszka, et al., 2006). These studies suggest inhibition is impaired in ADHD and is related to abnormal activation of the ACC. Findings from the current study suggest a functional relationship between right rostral ACC thickness and parent ratings of hyperactivity and impulsivity, though more work is needed on the overlap between structural thickness measures and functional/activation outcomes. For example, by combining structural MRI and fMRI methods we might be able to determine if thicker of cortical gray matter is related to better functional activation (or more abnormal activation). No study to date has attempted to measure such relationships simultaneously in ADHD.

Future Research Directions

Research on DSM-IV ADHD Subtypes. Future studies may wish to investigate potential structural brain differences between DSM-IV ADHD subtypes. The current study utilized a sample of children with ADHD-Combined Type and did not look at children with ADHD-Predominantly Inattentive or ADHD-Hyperactive Impulsive. Because DSM-IV subtypes differ in their behavioral profiles, the underlying neural structures and functioning may also be different. Neuropsychological research is equivocal and it is unclear if or how subtypes differ, beyond observable behavioral differences (Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2005; Huang-Pollock, Mikami, Pfiffner, & McBurnett, 2007; Huang-Pollock, et al., 2005; Nigg, Blaskey, Huang-Pollock, & Rappley, 2002; Nigg, Tannock, & Rohde, 2010). In addition, ADHD subtypes show poor temporal stability (i.e., a child diagnosed with ADHD-PI at age seven may experience the hyperactive or combined subtype at age 10 or 15) (Lahey, Pelham, Loney, Lee, &

Willcutt, 2005). As can be seen in Table 1, however, the majority of MRI research on ADHD has used mixed samples or focused on samples of ADHD-C. Thus, continued investigations of ADHD subtypes or symptom dimensions would provide important information on the potential changes in neural circuitry that accompany changes in symptoms.

Larger Sample Sizes. Continued investigations into the brain-behavior relationships of ADHD would benefit from larger sample sizes of ADHD and Control groups. Greater sample sizes would provide greater statistical power and would likely improve the group variance that is required to detect differences in relatively small cortical brain regions with low variance (e.g., low variability in cortical thickness across subjects). The developmental trajectories of brain white and grey matter can vary greatly between developmental cohorts (Giedd, et al., 1999), thus, it will be important to attempt to control variables that may account for brain structural and functional differences, such as age or IQ. In addition, studies that wish to investigate the effects of medication will benefit from larger samples with less variance in age. Thus, studies that investigate the effects of psychostimulant medication may benefit from the use of cross-sectional designs that will help account for developmental differences in response to medication.

The ACC and ADHD Symptoms. The ACC has been shown to be involved in many cognitive processes and behaviors including error detection (Carter et al., 1998), monitoring conflict (Botvinick, et al., 2004) and response inhibition (Bush, et al., 1999), yet this is the first study to find a relationship among the ACC measures and parent and teacher reported levels of hyperactivity and impulsivity. It is unlikely that the ACC modulates these behaviors in isolation; it is one structure in a complex network that is involved in the execution of complex behaviors (Bush, et al., 2000). Findings from the current study suggest that the ACC may be involved in specific externalizing symptoms (e.g., hyperactivity, impulsivity, restlessness) of ADHD. Future

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research should consider the ACC when studying externalizing symptoms and behaviors that have traditionally been explained by prefrontal-striatal and cerebellar network dysfunctions.

ACC dysfunction has been implicated in numerous psychiatric and neurological conditions including Obsessive Compulsive Disorder, Schizophrenia, Post-Traumatic Stress Disorder, Stuttering, ADHD, and Bipolar Disorder (Bouras, Kovari, Hof, Riederer, & Giannakopoulos, 2001; Chang, Erickson, Ambrose, Hasegawa-Johnson, & Ludlow, 2008; Riffkin et al., 2005; Yamasue et al., 2003; Yucel et al., 2002). Future research is needed in order to either differentiate the ACCs involvement in these distinct disorders or to understand common symptoms or behaviors among these disorders that might be explained by ACC dysfunction. Findings from such a study might provide insights into the multiple roles of the ACC and behavior and also might inform treatment interventions that had not been considered previously.

Cortical Thickness and Behavioral Implications. Lastly, studies that combine multiple methods (e.g., neuropsychological, structural MRI, and fMRI) will provide the most information regarding brain-behavior relationships in ADHD as well as aid in the development treatment interventions. Connecting structural MRI with neuropsychological variables (one of the methods in this study) is not a new technique and is generally correlational in nature. The relation between cortical thickness (e.g., an estimate of the density of neurons in a cortical region) and neuropsychological functioning (e.g., the efficiency or accuracy with which one is able to complete a behavioral or cognitive task) is unknown at this time. It is unclear whether cortical *thickness* or *thinness* is better for different functions and for different locations in the brain, given differences in brain developmental trajectories. Thus, longitudinal studies linking brain structure and neuropsychological functioning are one way of addressing these research questions. Studies

linking structural MRI with fMRI may also provide important information regarding the underlying functioning of an anatomical region.

If research can demonstrate that MRI or fMRI is sensitive enough to detect improvements or changes in brain functioning then they may be considered useful for developing and measuring treatment outcomes. Given that fMRI has been able to detect functional brain changes (e.g., improvements) in remediated readers (Shaywitz et al., 2003; Temple, et al., 2003), future research should consider using neuroimaging techniques to develop or assess the efficacy of treatments for ADHD. For example, if ACC thinning is a biomarker for symptoms of hyperactivity, inattention, and impulsivity, then thickening of the ACC with behavioral treatment targeted at these symptoms may indicate behavioral improvements. Such research would extend our understanding of brain-behavior relationships in ADHD and cultivate novel ways to development new treatment interventions and also assess their effectiveness.

APPENDIX

Figure 1. Axial MR Image of the Caudate, Putamen, Globus Pallidus, and Thalamus.
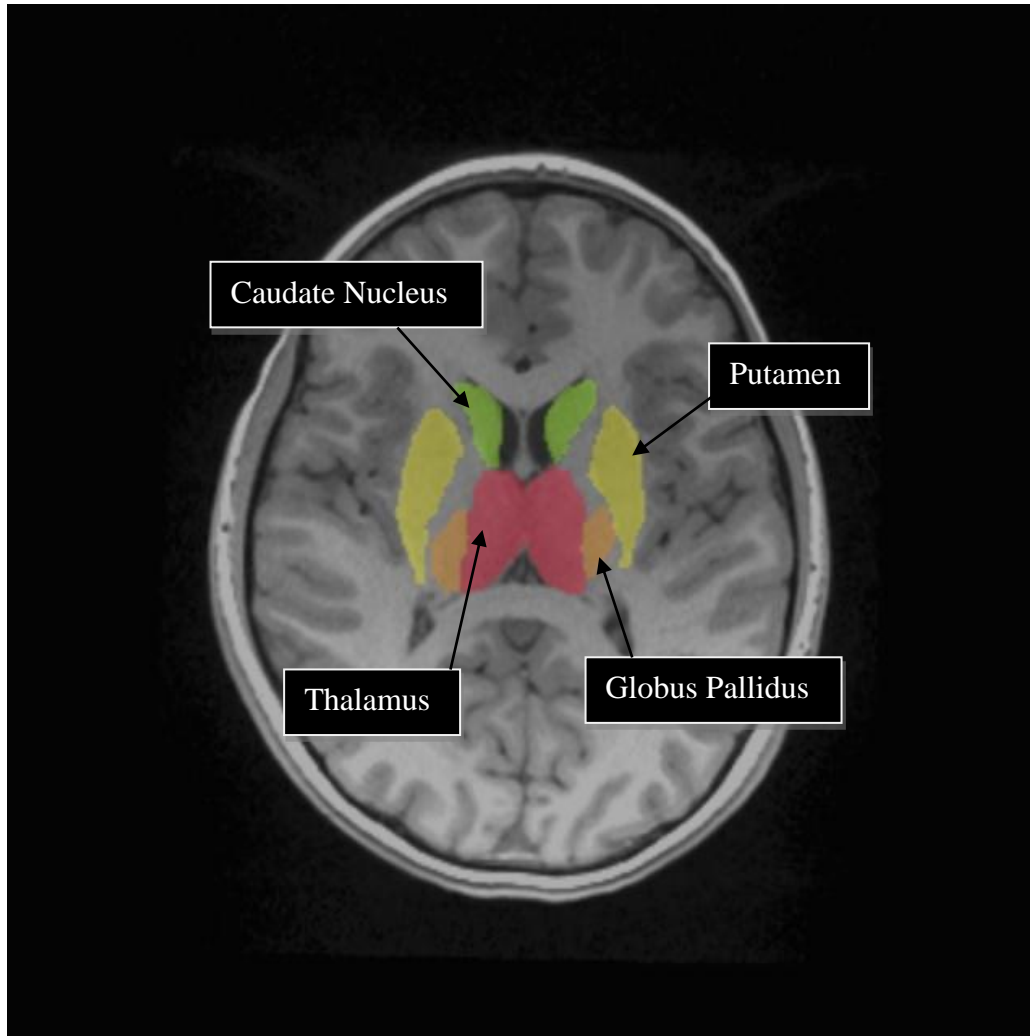
Note. Depiction of subcortical structures implicated in ADHD. For interpretation of the

references to color in this and all other figures, the reader is referred to the electronic version of

this dissertation.

Figure 2. Mid-Sagittal Image Depicting the Lobules of the Cerebellar Vermis
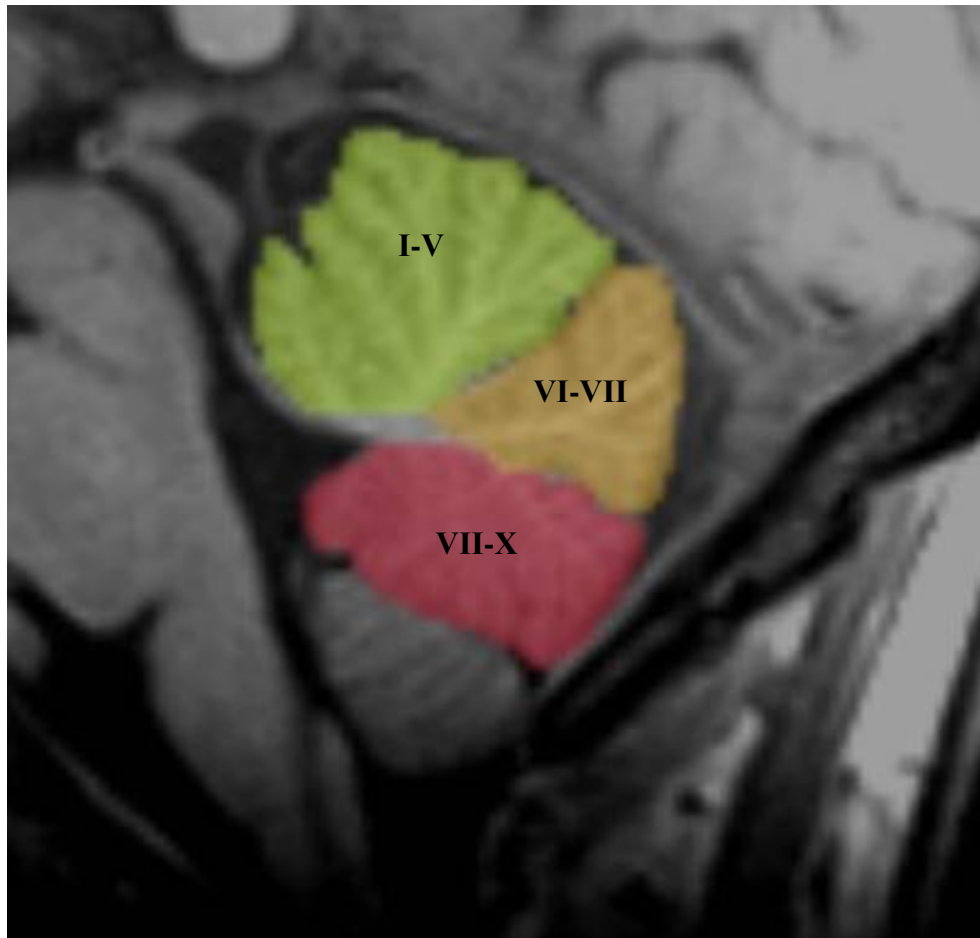
Note. I-V = Lobules I-V of the Anterior Vermis; VI-VII = Lobules VI-VII of the Posterior

Superior Vermis; VII-X = Lobules VII-X of the Posterior Inferior Vermis.

Figure 3. Surface-Based Morphometry of the Cortex
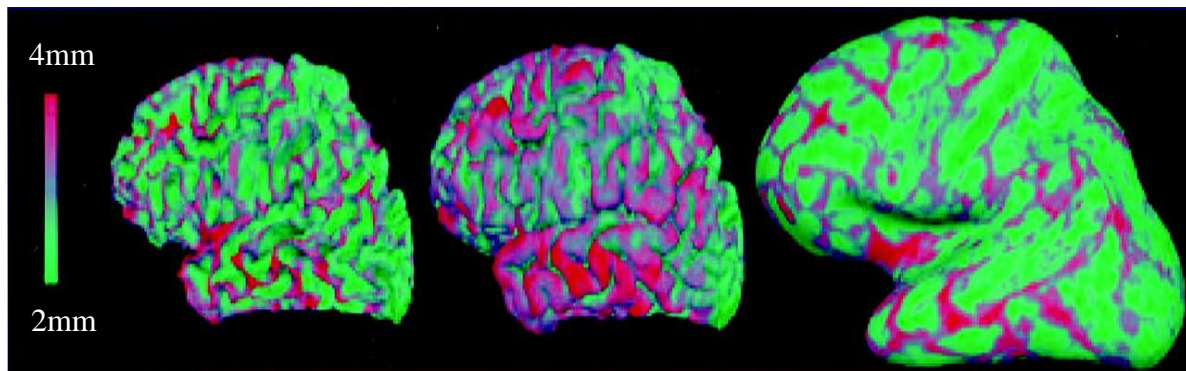
Note. Depiction of cortical thickness in human cerebral cortex. At far left, sulci are colored in green (lighter) and gyri are colored in red (darker). Image in the center is slightly inflated and reveals more of the cortex area. The image at far right is even further inflated and shows nearly all of the deep sulci. This type of imaging allows for a more detailed understanding of cortical thickness, cortical area, and gyral and sulcal formation. Image from: Fischl and Dale (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images, *PNAS, 97*(20), 11050-11055. Artwork used with the expressed permission of Dr. Bruce Fischl.

Figure 4. Cortical thickness map.
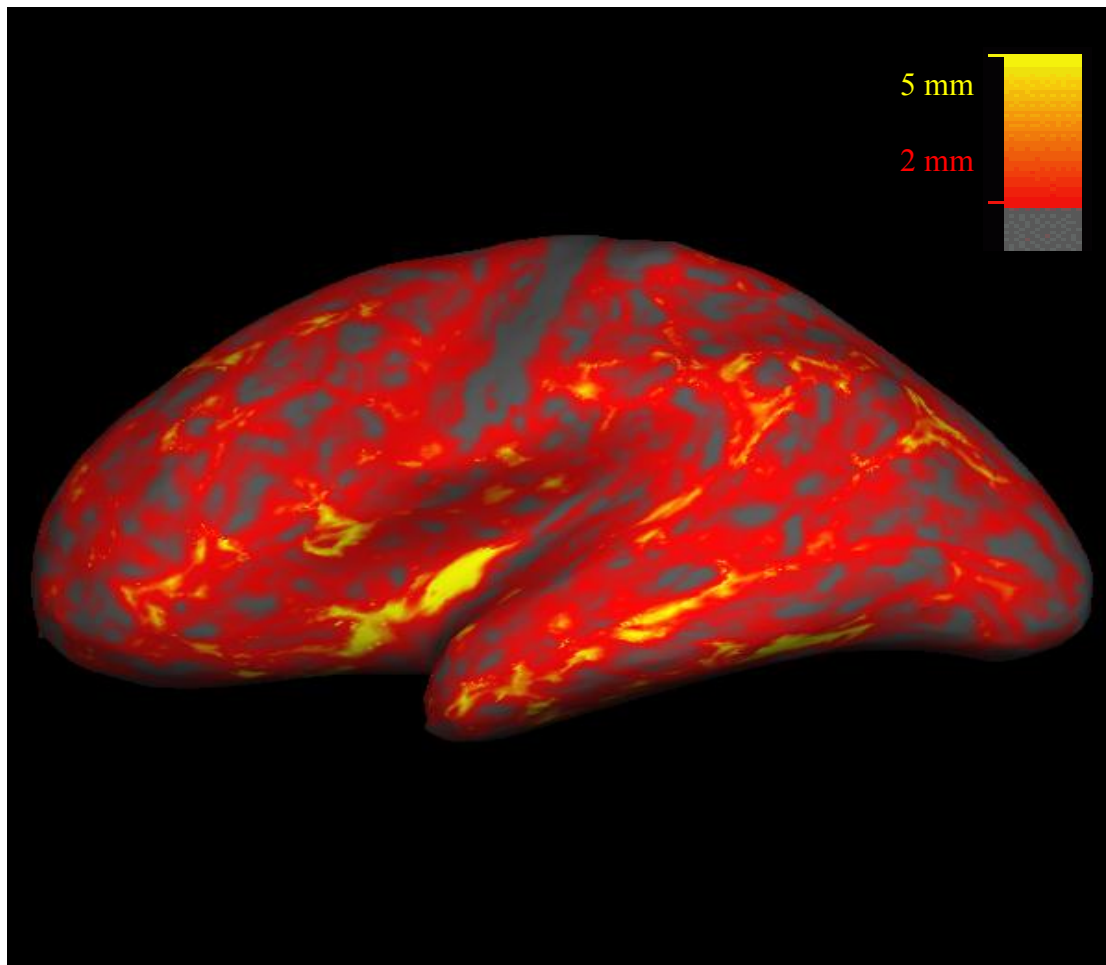
Note. Cortical thickness map shows relative thickness measurement across the cortex. Lighter colors indicate thicker cortical regions and darker colors indicate thinner cortical regions.

Figure 5. AC-PC alignment in the sagittal view. Crosshairs converge on the posterior boundary of the anterior commissure.
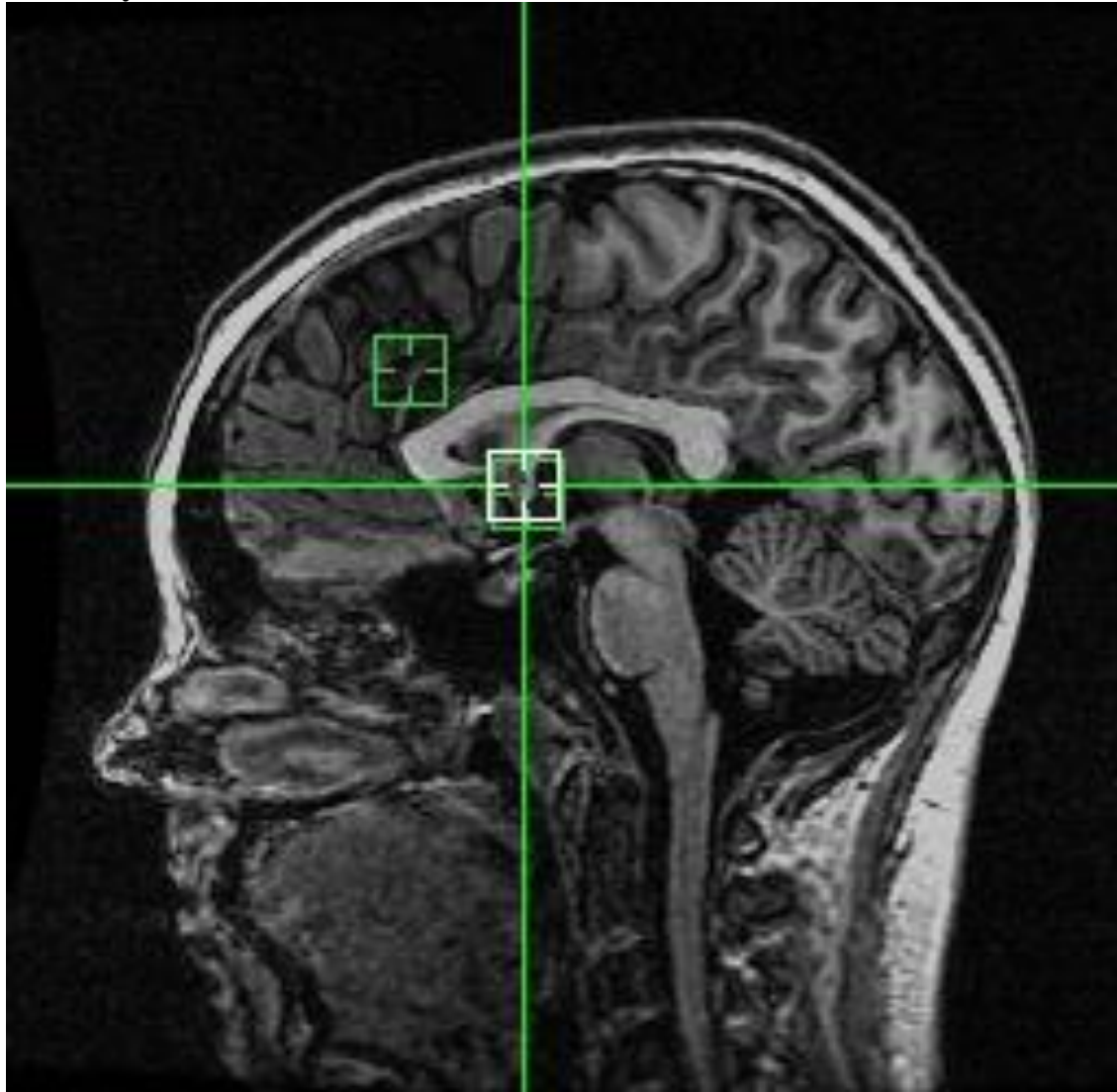
Note. Mid-sagittal T1 image showing the identification of the superior anterior commissure

(white box) and inferior-posterior edge of the anterior commissure.

Figure 6. Desikan-Killiany Atlas; Desikan et al. (2006).

Figure 7. ADHD and Control Parent and Teacher Reports

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; BASC-2 Hyperactivity = Behavioral Assessment Scale for Children 2nd Edition Hyperactivity Scale T-Score; BASC-2 Attention = Behavioral Assessment Scale for Children 2nd Edition Attention Scale T-Score; CGI-R/I Parent = Conners' Global Index – Restless Impulsive Parent Ratings Scale T-Score; CGI-R/I Teacher = Conners' Global Index – Restless Impulsive Teacher Ratings Scale T-Score.

Figure 8. ADHD and Control on Response Inhibition Measures

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; D-KEFS Color-Word = Delis-Kaplan

Executive Function System Color-Word Inhibition Subtest (Standard score); D-KEFS

Interference = Delis-Kaplan Executive Function System Interference Subtest (Standard score).

Figure 9. ADHD-Treated, ADHD-Not Treated, and Control on Response Inhibition Measures

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; D-KEFS Color-Word = Delis-Kaplan

Executive Function System Color-Word Inhibition Subtest (Standard score); D-KEFS

Interference = Delis-Kaplan Executive Function System Interference Subtest (Standard score).

Figure 10. ADHD-Treated, ADHD-Not Treated, and Control Parent and Teacher Reports

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; BASC-2 Hyperactivity = Behavioral Assessment Scale for Children 2nd Edition Hyperactivity Scale T-Score; BASC-2 Attention = Behavioral Assessment Scale for Children 2nd Edition Attention Scale T-Score; CGI-R/I Parent = Conners' Global Index – Restless Impulsive Parent Ratings Scale T-Score; CGI-R/I Teacher = Conners' Global Index – Restless Impulsive Teacher Ratings Scale T-Score.

Figure 11. Right Rostral Anterior Cingulate Cortex. Significant Differences Between ADHD and Control Groups.
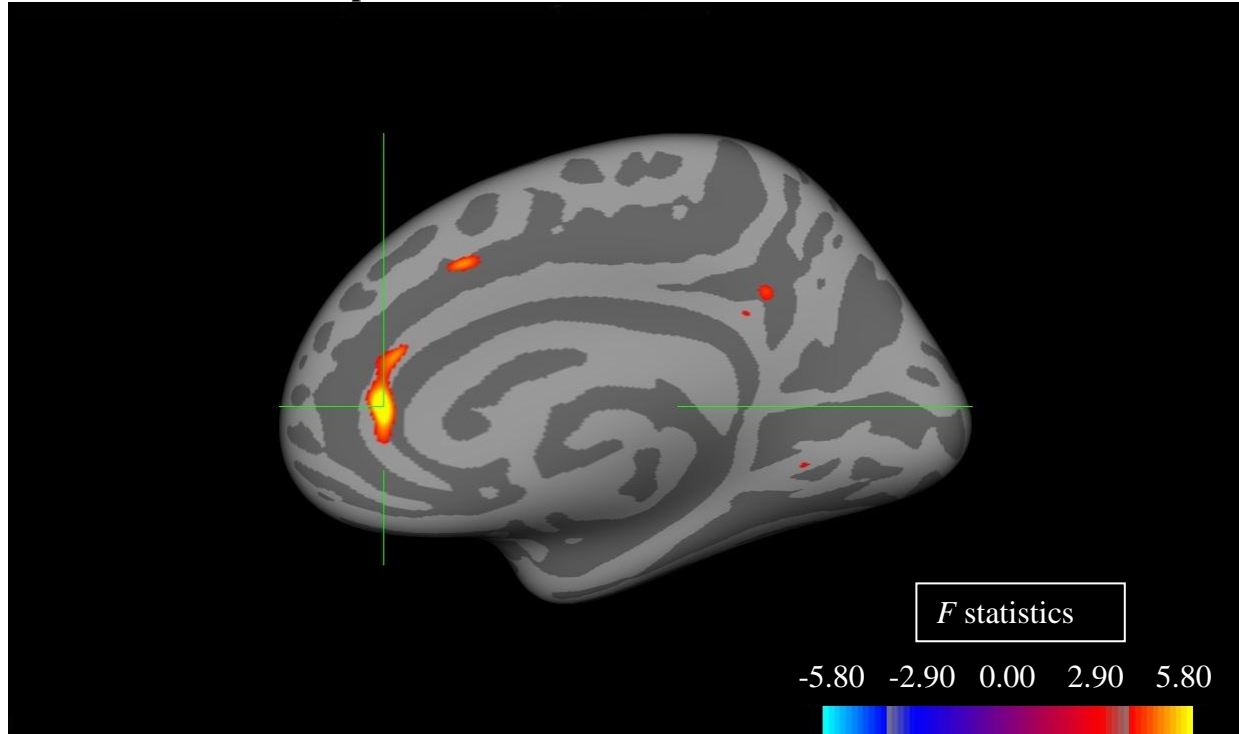
Note. Color maps indicate significant F statistics. Significant thinning of the right rostral anterior cingulate cortex is indicated by the high number of significant vertices that had F statistics greater than 5. Lighter colors indicate higher F values.

Figure 12. Pial Surface Showing Right Rostral Anterior Cingulate Cortex - Significant Differences Between ADHD and Control Groups.
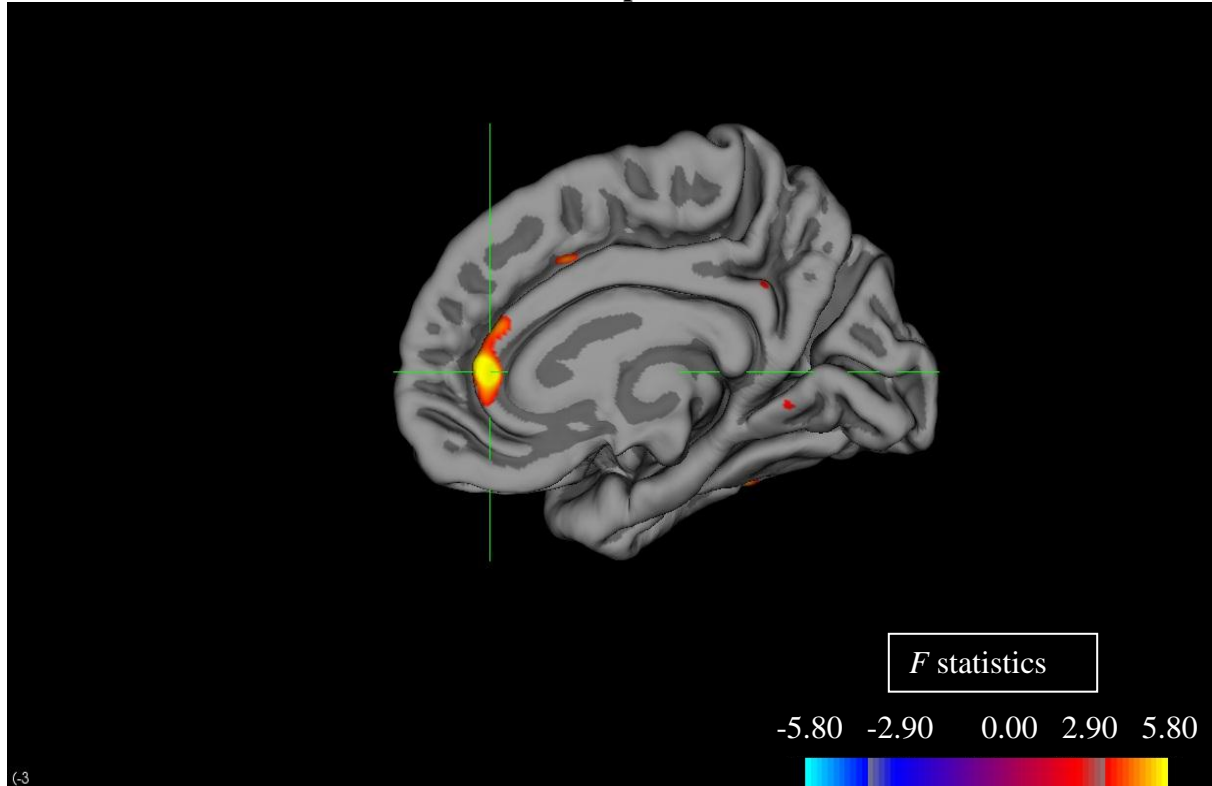
Note. Color maps indicate significant *F* statistics. Significant thinning of the right rostral anterior cingulate cortex is indicated by the high number of significant vertices that had *F* statistics greater than 5. Lighter colors indicate higher *F* values.

Figure 13. BASC-II Hyperactivity and Anterior Cingulate Cortex Thickness

R2 Linear = 0.374

BASC-II Hyperactivity T-Scores

Right Anterior Cingulate Cortex Thickness
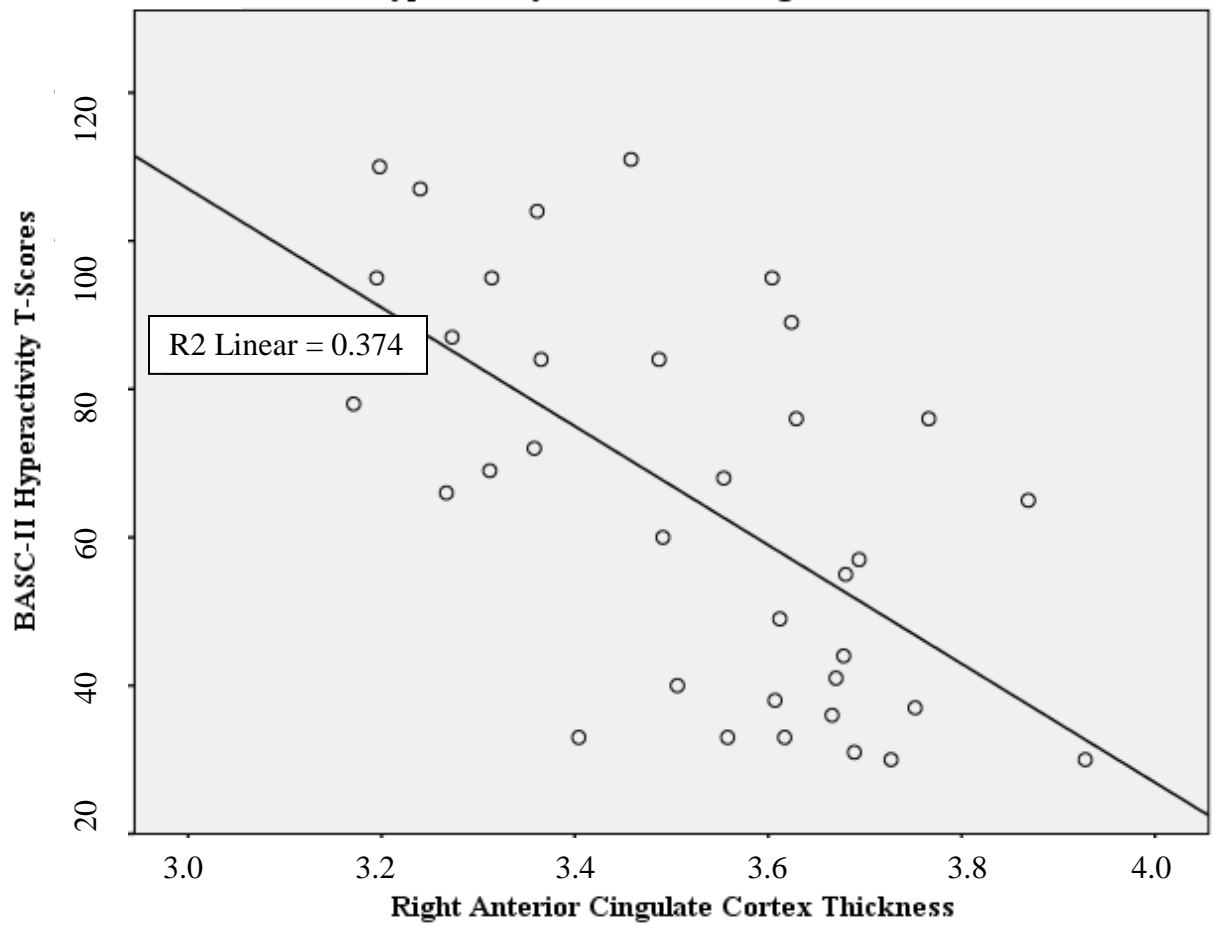
Figure 14. BASC-II Attention and Anterior Cingulate Cortex Thickness

R2 Linear = 0.396
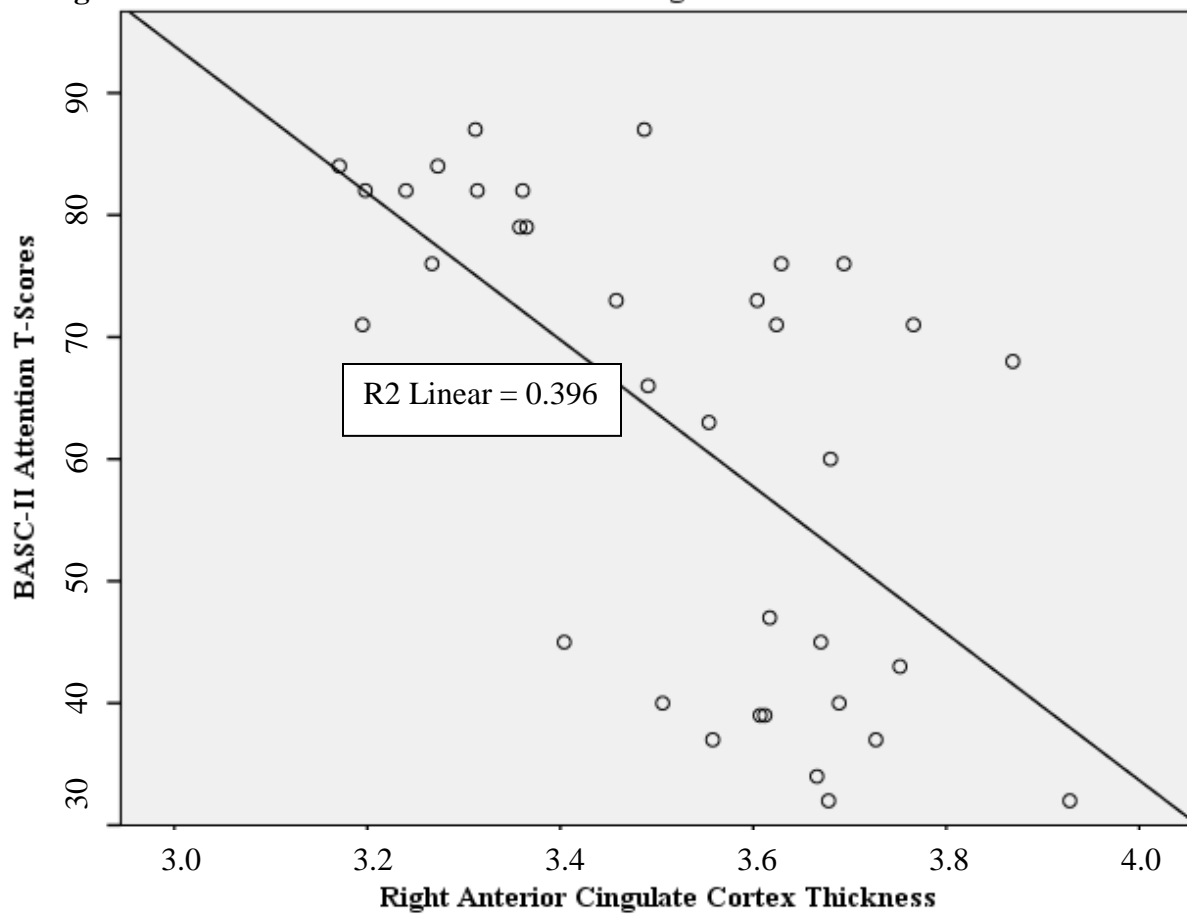
Figure 15. Conners' Global Index - Restless/Impulsive Composite Parent Report and Anterior Cingulate Cortex Thickness
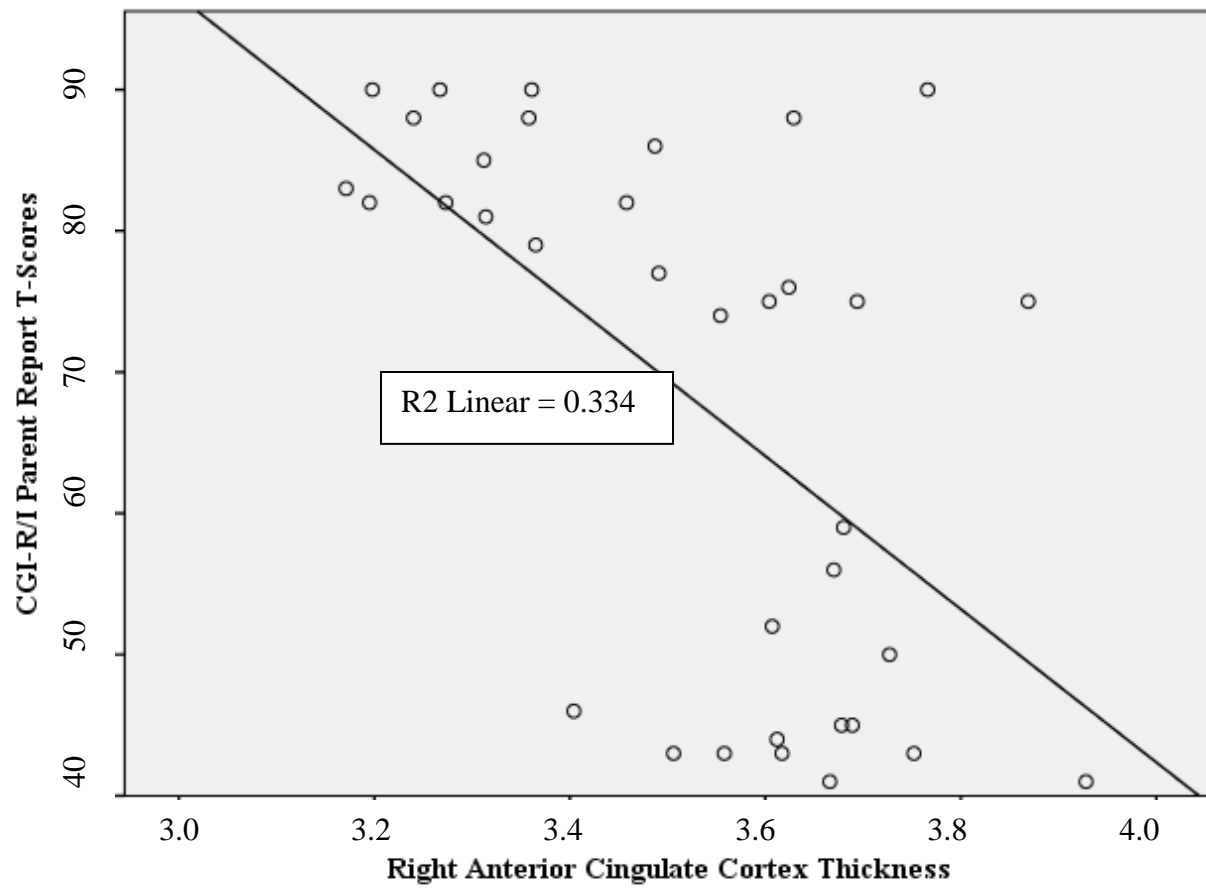
Figure 16. Conners' Global Index - Restless/Impulsive Composite Teacher Report and Anterior Cingulate Cortex Thickness
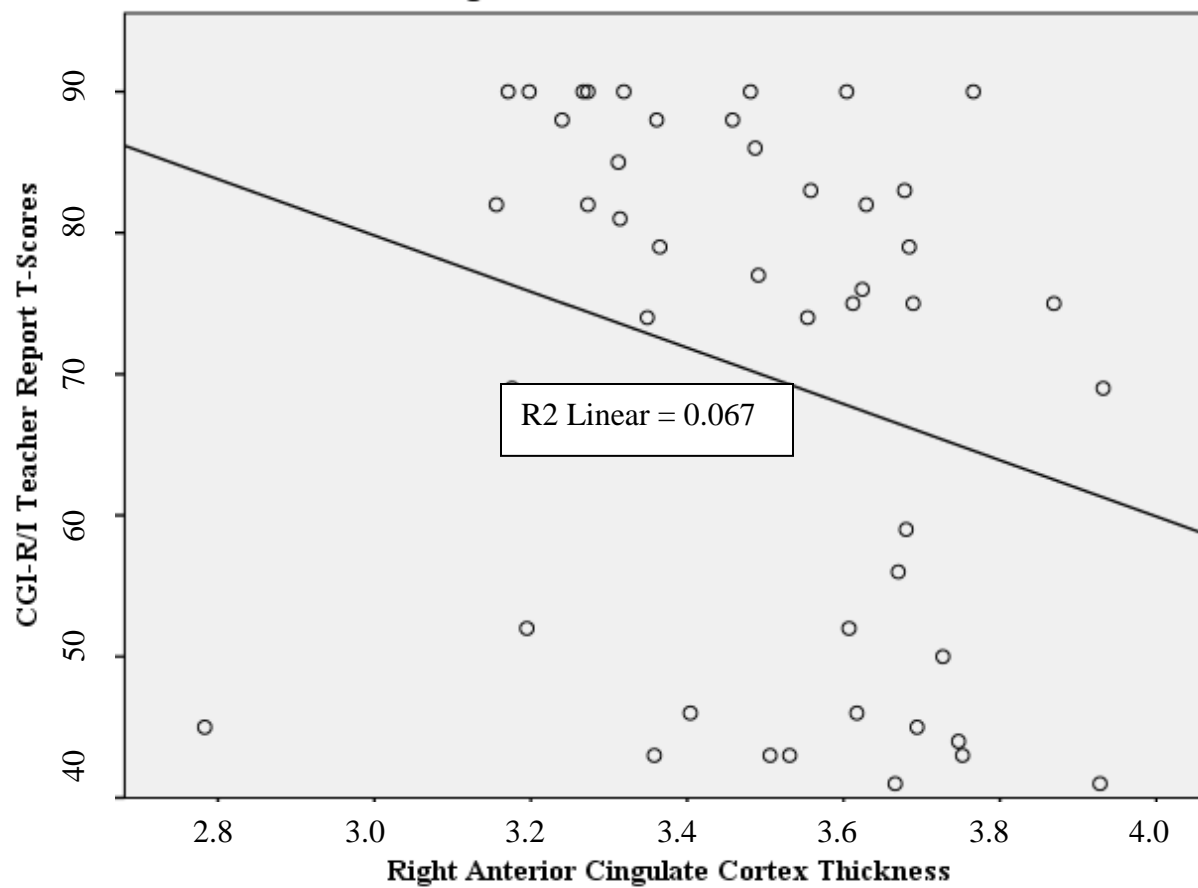
Figure 17. D-KEFS Color-Word Performance and Anterior Cingulate Cortex Thickness
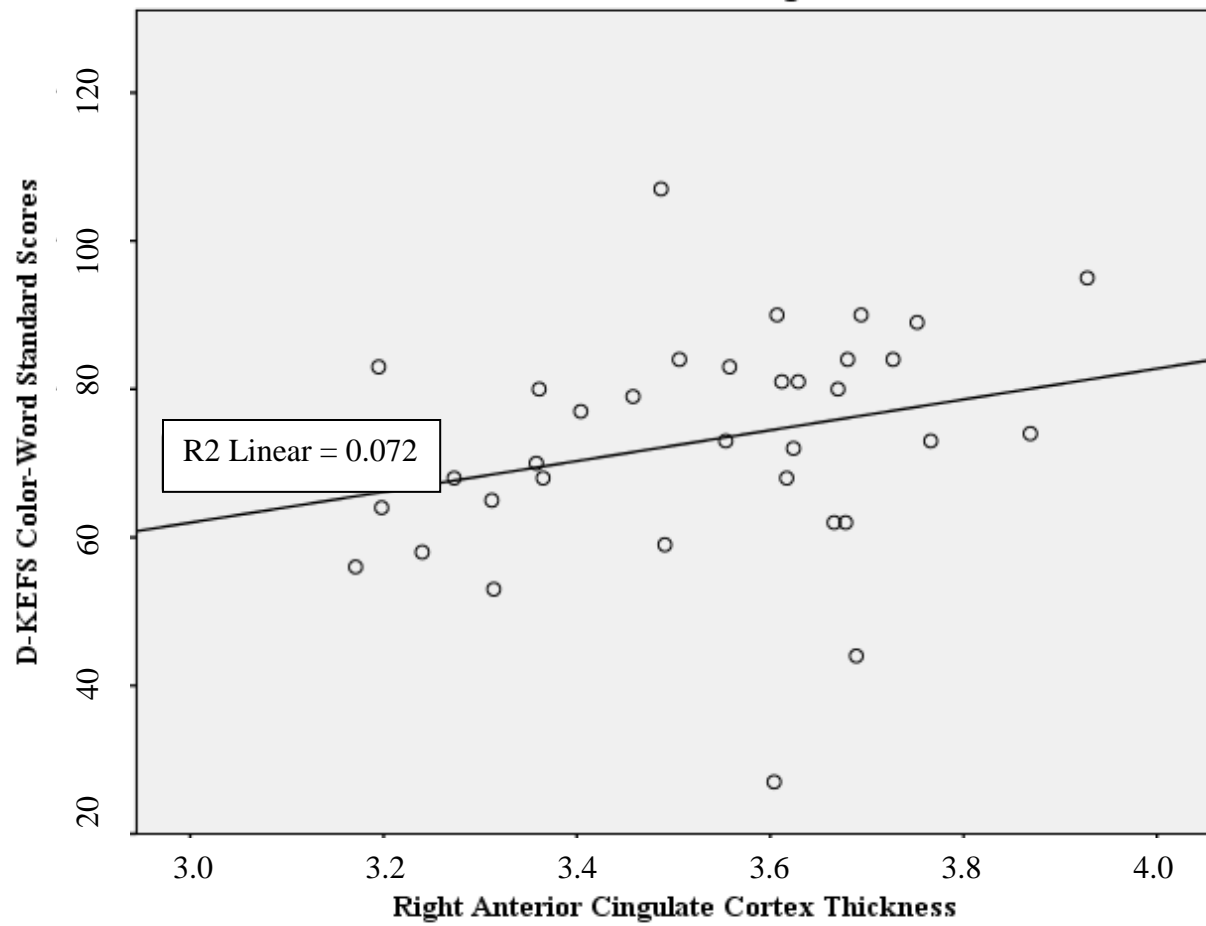
Figure 18. D-KEFS Interference Performance and Anterior Cingulate Cortex Thickness

R2 Linear = 8.447e5
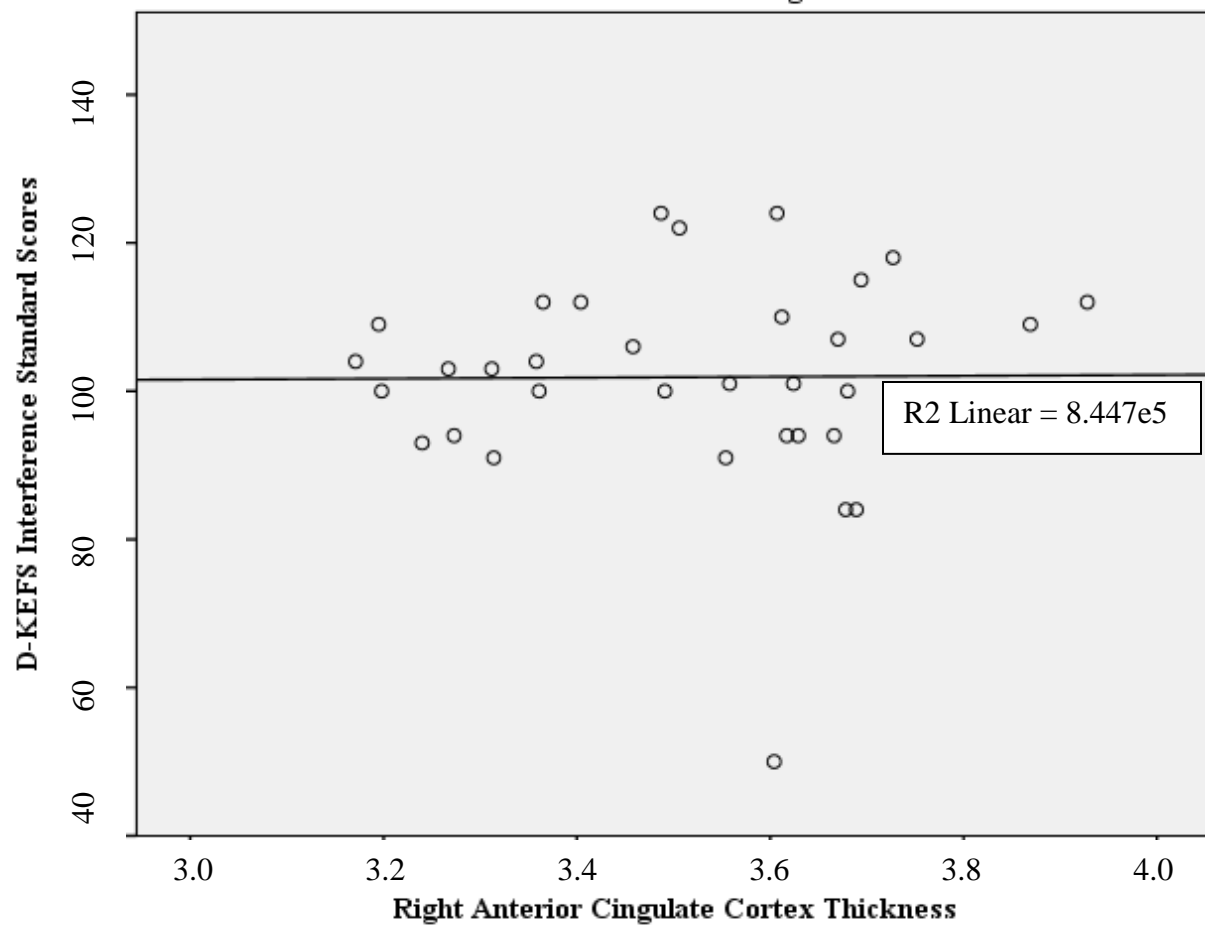
Table 1. Volumetric Studies of ADHD

Study	Sample	Age	Comorbidity	Main Finding
Ashtari et al., 2005	18 ADHD-C, 15 Controls	8.94	ODD, Math LD, Enuresis, Adjustment disorder	Decreased fractional anisotropy in right striatal, right cerebral peduncle, left middle cerebellar peduncle, left cerebellum, and left parieto-occipital areas.
Aylward et al., 1996	10 ADHD, 10 Controls, 16 ADHD + TS	11.26	TS	Smaller left globus pallidus in ADHD. No difference between ADHD+Tourette.
Baumgardner et al., 1996	16 TS, 21 TS + ADHD, 13 ADHD, 27 Controls	11.3	TS	Body of corpus callosum smaller in ADHD.
Berquin et al., 1998	46 ADHD, 47 Controls	11.7	CD, ODD, LD, Anxiety Disorder	Smaller posterior inferior volume of vermis in ADHD.
Bledsoe et al., 2009	14 ADHD-C w/ no treatment, 18 ADHD-C w/ history of treatment, 15	11.5	None	Smaller posterior inferior area of vermis in treatment naïve ADHD-C. No structural differences between chronically treated ADHD and Controls.

Table 1 (cont.)

	controls			
Bussing et al., 2002	7 ADHD + CD, 5 ADHD, 19 Controls	10	7 ADHD + CD	Caudate and cerebral volume of ADHD and ADHD+CD not statistically different from Controls. Reduced volume of posterior inferior vermis in ADHD. Reduced volume of caudate in treated children with ADHD.
Castellanos et al., 1994	50 ADHD, 48 Controls	12.3	8 CD, 21 ODD, 13 Reading or Math LD	Smaller right caudate in ADHD compared to controls.
Castellanos et al., 1996	57 ADHD, 55 Controls	11.7	CD, ODD, LD, Anxiety Disorder	Smaller cerebral volume, caudate, and globus pallidus in children with ADHD.
Castellanos et al., 2001	50 ADHD, 50 Controls (female sample)	9.7	Anxiety, MDD, RD	Smaller total brain and posterior-inferior vermis volume in girls with ADHD compared to controls.
Castellanos et al., 2002	152 ADHD, 139 Controls	10.5	?	Longitudinal study found smaller total cerebral, subcortical, and cerebellar volumes in children with ADHD. Caudate volumes initially smaller in ADHD but control volumes decreased

Table 1 (cont.)

				with age and after 10 years no differences between ADHD and control caudate volumes were found.
Durston et al., 2004	30 ADHD, 30 discordant siblings of children with ADHD, 30 Controls	12.1	ODD, CD, motor and tic disorder	ADHD and unaffected siblings evinced significant reductions in right prefrontal gray matter and left occipital gray and white matter. Right cerebellum reduced by nearly 5% in ADHD but not siblings.
Filipek et al., 1997	15 ADHD, 15 Controls	12.4	No	Smaller left caudate body and head, reductions in right anterior superior white matter, parietal-occipital white matter in ADHD. Differences observed between positive responders to medication; negative responders had smaller white matter in posterior regions.
Giedd et al., 1994	18 ADHD, 18 Controls	11.9	CD (2/18) and ODD (16/18)	Body of corupus callosum (rostral) smaller in ADHD. Observed correlation between size of corpus callosum and symptoms of hyperactivity.
Hesslinger et al., 2002	8 ADHD, 17 Controls	31.4	?	Smaller orbitofrontal volume in subjects with ADHD.

Table 1 (cont.)

	(adult study)			
Hill et al., 2003	23 ADHD, 24 Controls	9.35	ODD	Smaller total brain, prefrontal, anterior vermis and posterior inferior vermis, corpus callosum area, and splenium in children with ADHD. No differences observed inferior prefrontal, caudate, or posterior superior vermis in ADHD.
Hynd et al., 1990	10 ADHD, 10 Dyslexic, 10 Controls	9	Yes, 7/10 ADHD met criteria for another DSM-III disorder.	Right greater than left width of anterior frontal brain region compared to controls. Study based on 1 axial brain slice.
Hynd et al., 1991	7 ADHD, 10 Controls	9	Yes	Smaller corpus callosum in children with ADHD.
Hynd et al., 1993	11 ADHD, 11 Controls	11	?	Wider right caudate compared to left in ADHD, opposite for control children.
Kates et al., 2002	13 ADHD, 13 TS, 13 Controls	9.4	ODD, Specific Phobia	Reductions in frontal gray and white matter volume in children with ADHD.
Lyoo et al., 1996	76 ADHD, 48 Controls	12	CD, Dyslexia	Smaller splenium and isthsmus of corpus callosum in children with ADHD. Greater posterior lateral ventricles in children with ADHD.

Table 1 (cont.)

Mackie et al., 2007	36 ADHD, 36 Controls	10	?	Smaller posterior superior volume in children with ADHD-C. Reductions in posterior inferior regions of the vermis across time related to worse clinical outcomes.
Makris et al., 2007	24 ADHD, 18 Controls	38.0	ANX, MDD, LD, Substance abuse	Thinning of the inferior parietal lobe, dorsolateral prefrontal cortex, and anterior cingulate cortex in adults with ADHD. Thinning took place primarily in the right hemisphere.
Mataro et al., 1997	11 ADHD, 19 Controls	14.6	?	Larger right caudate in children with ADHD. Larger caudate associated with impairments in attention and symptom severity per Conners'.
Mostofsky et al., 1998	12 ADHD, 23 Controls	11.3	None	Smaller posterior inferior area in children with ADHD.
Mostofsky et al., 2002	12 ADHD, 12 Controls	10.1	ODD and Simple Phobia	Smaller frontal gray and white matter volume in children with ADHD. Majority of the reduction was observed in right frontal lobe.
Overmeyer et al., 2001	18 ICD-10 Hyperkinetic, 16 Controls	10.4	CD, ODD, Dyslexia	Smaller right gray matter volume in superior frontal gyrus and right posterior cingulate, and basal ganglia,

Table 1 (cont.)

				emphasized reductions in right globus pallidus and putamen.
Pineda et al., 2002	15 ADHD-C, 15 ADHD-PI, 15 Controls	?	CD	No differences in caudate volume in ADHD vs. control children. Overall, groups had larger left caudate volumes compared to right.
Qiu et al., 2009	47 ADHD, 66 Controls	10.5	ODD and Specific Phobia	Boys with ADHD had smaller basal ganglia volumes than girls with ADHD or controls. Specifically, reductions were observed in the head and body of the caudate, anterior putamen, left anterior globus pallidus, and right ventral putamen. No differences between ADHD subtypes.
Semrud-Clikeman et al., 1994	15 ADHD, 15 Controls	10	None	Smaller posterior corpus callosum smaller in ADHD compared to controls. No difference observed in sample of ADHD + stimulant medicated.
Semrud-Clikeman et al., 2000	10 ADD/H, 11 Controls	12.9	None	Smaller left caudate head volume and smaller volume of right frontal lobe in children with ADD.
Semrud-Clikeman et		12.5	3 ADHD + ODD	Smaller right ACC in treatment naïve children with ADHD vs. chronically

Table 1 (cont.)

al., 2006				treated ADHD and controls. Smaller bilateral caudate volume in ADHD group vs. controls.
Shaw et al., 2006	163 ADHD, 166 Controls	8.9	?	Children with ADHD in the worse outcome group showed cortical thinning in the left medial prefrontal cortex. Right parietal normalization in children with ADHD was associated with better clinical outcome.
Sowell et al., 2003	27 ADHD, 46 Controls	12	?	Reductions bilaterally in inferior dorsolateral prefrontal cortex, bilaterally in lateral anterior and midtemporal cortex. Greater volume in inferior parietal gray matter in ADHD.
Wellington et al., 2006	12 ADHD-C, 12 Controls	15	Depression, LD	Reversed asymmetry of the putamen in ADHD-C. Smaller left than right putamen in ADHD, opposite for controls.
Wolosin et al., 2007	21 ADHD, 35 Controls	10.8	8 ODD, 4 Simple Phobia	Smaller cerebral volume and total cortical volume by 8% in children with ADHD. Decreased cortical surface area by 7% and significant decrease in cortical folding in children with ADHD

Table 1 (cont.)

Yeo et al., 2003	23 ADHD, 24 Controls	9.47	ODD	Smaller right dorsolateral prefrontal cortex in children with ADHD.

Table 2. ADHD and Control Participant Demographic and Neuropsychological Variables

	Group		
Measure	**ADHD (n = 32)**	**Control (n = 15)**	*p* **Value**
Gender	**21m/11f**	**11m/4f**	.597
Age (Years)	11.71 (1.80)	11.11 (2.01)	.307
WIAT-II Word Reading	101.53 (10.18)	107.20 (10.35)	.083
DAS-GCA	103.65 (12.73)	113.86 (12.21)	**.013**
BASC-2 Hyperactivity	64.62 (24.58)	36.53 (6.91)	**<.000**
BASC-2 Attention	62.17 (11.05)	39.47 (7.26)	**<.000**
CGI-R/I Parent	79.62 (12.27)	46.73 (5.82)	**<.000**
CGI-R/I Teacher	76.06 (16.03)	55.80 (14.87)	**<.000**
D-KEFS Color-Word	90.82 (15.59)	97.08 (14.92)	.478
D-KEFS Interference	103.61 (28.33)	103.91 (13.57)	.781

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; WIAT-II Word Reading = Wechsler Individual Achievement Test 2nd Edition Word Reading Subtest – Standard Score; DAS-GCA = Differential Ability Scales General Conceptual Ability; BASC-2 Hyperactivity = Behavioral Assessment Scale for Children 2nd Edition Hyperactivity Scale T-Score; BASC-2 Attention = Behavioral Assessment Scale for Children 2nd Edition Attention Scale T-Score; CGI-R/I Parent = Conners' Global Index – Restless Impulsive Parent Ratings Scale T-Score; CGI-R/I Teacher = Conners' Global Index – Restless Impulsive Teacher Ratings Scale T-Score. D-KEFS Color-Word = Delis-Kaplan Executive Function System Color-Word Inhibition Subtest (Standard score); D-KEFS Interference = Delis-Kaplan Executive Function System Interference Subtest (Standard score).

Table 3. ADHD-Treated with Medication, ADHD-Not Treated with Medication, and Control Participant Demographic and Neuropsychological Variables

	Groups			
Measure	**ADHD-Treated**	**ADHD-Not Treated**	**Control**	***p* Value**
n	18	14	15	
Gender	11m/7f	10m/4f	11m/4f	.717
Age (Years)	11.48 (1.52)	12.02 (2.13)	11.11 (2.01)	.428
DAS-GCA	105.67 (14.10)	101.07 (10.66)	113.87 (12.21)	**.028**
WIAT-II Word Reading	105.83 (10.39)	96.00 (6.86)	107.20 (10.34)	**.005**
BASC-2 Hyperactivity	77.00 (17.21)	81.92 (22.93)	37.33 (7.16)	**<.000**
BASC-2 Attention	72.11 (12.32)	75.25 (12.05)	40.50 (7.76)	**<.000**
CGI-R/I Parent	79.00 (12.84)	79.75 (12.07)	46.75 (6.05)	**<.000**
CGI-R/I Teacher	76.88 (15.72)	75.00 (16.96)	56.07 (15.39)	**.001**
D-KEFS Color-Word	85.70 (16.85)	95.08 (13.70)	97.08 (14.92)	.235
D-KEFS Interference	95.63 (27.78)	110.91 (27.95)	103.92 (13.57)	.252

Note. ADHD = Attention-Deficit/Hyperactivity Disorder; WIAT-II Word Reading = Wechsler

Individual Achievement Test 2nd Edition Word Reading Subtest – Standard Score; DAS-GCA =

Differential Ability Scales General Conceptual Ability; BASC-2 Hyperactivity = Behavioral

Assessment Scale for Children 2nd Edition Hyperactivity Scale T-Score; BASC-2 Attention =

Behavioral Assessment Scale for Children 2nd Edition Attention Scale T-Score; CGI-R/I Parent

= Conners' Global Index – Restless Impulsive Parent Ratings Scale T-Score; CGI-R/I Teacher =

Conners' Global Index – Restless Impulsive Teacher Ratings Scale T-Score. D-KEFS Color-

Word = Delis-Kaplan Executive Function System Color-Word Inhibition Subtest (Standard

Table 3 (cont.)

score); D-KEFS Interference = Delis-Kaplan Executive Function System Interference Subtest

(Standard score).

Table 4. ADHD and Control Participant Brain Volume and Cortical Thickness Measurements (mm)

	ADHD (n = 32)		Control (n = 15)		
	Mean	**SD**	**Mean**	**SD**	***p*-value**
n	32		15		
Total Brain Volume (mm^3)	132.25	14.37	129.87	13.23	.591
Left Frontal Cortex					
Caudal Middle Frontal	2.99	.124	2.94	.165	.172
Lateral Orbitofrontal	3.15	.175	3.15	.160	.901
Medial Orbitofrontal	2.97	.294	2.99	.243	.568
Superior Frontal	3.35	.136	3.33	.195	.896
Right Frontal Cortex					
Caudal Middle Frontal	2.96	.142	2.94	.173	.849
Lateral Orbitofrontal	3.19	.171	3.25	.242	.650
Medial Orbitofrontal	3.08	.274	3.02	.193	.516
Superior Frontal	3.31	.153	3.30	.197	.768
Left Parietal Cortex					
Superior Parietal	2.60	.097	2.54	.122	.140
Inferior Parietal	3.01	.126	2.97	.107	.328
Precuneus	2.88	.113	2.86	.155	.750
Cuneus	2.24	.169	2.22	.141	.913
Right Parietal Cortex					
Superior Parietal	2.62	.114	2.55	.145	.092
Inferior Parietal	3.08	.140	3.05	.161	.908
Precuneus	2.89	.136	2.85	.154	.437
Cuneus	2.31	.154	2.34	.159	.539
Left Anterior Cingulate Cortex					
Rostral ACC	3.37	.353	3.49	.207	.102
Caudal ACC	3.03	.362	2.98	.228	.905

Table 4 (cont.)

Right Anterior Cingulate Cortex					
Rostral ACC	3.43	.235	3.63	.172	**.014**
Caudal ACC	2.98	.282	3.01	2.89	.939

Note. Regions of interest.

Table 5. ADHD-Treated with Medication, ADHD-Not Treated with Medication, and Control Participant Brain Volume and Cortical Thickness Measurements (mm)

	ADHD-Treated		ADHD-Not Treated		Control		*p-value*
n	18		14		15		
	Mean	SD	Mean	SD	Mean	SD	
Total Brain Volume (mm^3)	131.53	16.04	133.17	13.91	129.87	13.23	.322
Left Frontal Cortex							
Caudal Middle Frontal	3.01	.142	2.98	.103	2.94	.165	.336
Lateral Orbitofrontal	3.17	.192	3.13	.155	3.15	.160	.695
Medial Orbitofrontal	2.98	.341	2.95	.235	3.00	.243	.788
Superior Frontal	3.39	.128	3.31	.136	3.33	.195	.283
Right Frontal Cortex							
Caudal Middle Frontal	2.98	.170	2.94	.109	2.94	.173	.785
Lateral Orbitofrontal	3.20	.191	3.19	.148	3.26	.242	.897
Medial Orbitofrontal	3.08	.310	3.08	.232	3.02	.193	.812
Superior Frontal	3.35	.157	3.25	.130	3.30	.197	.242
Left Parietal Cortex							
Superior Parietal	2.61	.107	2.58	.085	2.54	.122	.268
Inferior Parietal	3.01	.133	3.02	.121	2.97	.107	.622
Precuneus	2.89	.103	2.88	.129	2.86	.155	.884
Cuneus	2.28	.175	2.20	.160	2.22	.141	.268
Right Parietal Cortex							

Table 5 (cont.)

Superior Parietal	2.63	.112	2.61	.118	2.55	.145	.206
Inferior Parietal	3.10	.161	3.06	.110	3.05	.161	.634
Precuneus	2.91	.142	2.86	.125	2.85	.154	.387
Cuneus	2.35	.158	2.25	.128	2.34	.159	.127
Left Anterior Cingulate Cortex							
Rostral ACC	3.31	.433	3.46	.196	3.49	.207	.138
Caudal ACC	3.05	.380	3.01	.353	2.98	.228	.898
Right Anterior Cingulate Cortex							
Rostral ACC	3.45	.233	3.40	.242	3.63	.172	**.042**
Caudal ACC	3.00	.304	2.95	.260	3.01	2.89	.953

*Note. Regions of interest.

Table 6. Regression Analyses for ADHD and Control Rostral Anterior Cingulate Cortex Thickness

Variable	$\Delta R2$	β(std)	B(unstd)	F	p-Value
BASC-2 Attention	.396	-.629	-.007	21.595	.000
BASC-2 Hyperactivity	.374	-.612	-.005	19.726	.000
CGI-R/I Parent	.334	-.578	-.006	16.563	.000
CGI-R/I Teacher	.067	-.258	-.003	3.144	.083
D-KEFS Color-Word	.072	.268	.003	2.469	.126
D-KEFS Interference	.000	.009	.000	.003	.958

Note. Group membership (ADHD and Control) and DAS-GCA (an estimate of IQ) were

included as covariates in the regression models. BASC-2 Hyperactivity = Behavioral Assessment

Scale for Children 2nd Edition Hyperactivity Scale T-Score; BASC-2 Attention = Behavioral

Assessment Scale for Children 2nd Edition Attention Scale T-Score; CGI-R/I Parent = Conners'

Global Index – Restless Impulsive Parent Ratings Scale; CGI-R/I Teacher = Conners' Global

Index – Restless Impulsive Teacher Ratings Scale. D-KEFS Color-Word = Delis-Kaplan

Executive Function System, Color-Word Subtest; D-KEFS Interference = Delis-Kaplan

Executive Function System, Interference Subtest. D-KEFS Color-Word = Delis-Kaplan

Executive Function System Color-Word Inhibition Subtest (Standard score); D-KEFS

Interference = Delis-Kaplan Executive Function System Interference Subtest (Standard score).

CURRICULUM VITAE

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PERSONAL

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EDUCATION AND TRAINING

2012	Internship	University of Washington School of Medicine & Seattle Children's Hospital - General Child Track
2012	Ph.D. (exp.)	Michigan State University Major: Clinical Psychology Cognate: Neuropsychology and Neuroimaging Dissertation: *"Cortical Thickness and Morphology in Children with ADHD-Combined Subtype: Effects of Medication Treatment and Implications for Neuropsychological Functioning and Behavior"*
2008	M.A.	Michigan State University Major: Clinical Psychology Cognate: Neuropsychology and Neuroimaging Thesis: "*A Neuropsychological Investigation of Treated vs. Treatment Naïve Children with Attention Deficit/Hyperactivity Disorder – Combined Type*"
2005	B.S.	Portland State University (Cum Laude) Major: Psychology Minor: Biology Senior Project: *"An fMRI Study of Attention- Deficit/Hyperactivity Disorder in Adolescent Girls: Effects of Stimulant Medication on Working Memory"* (Data collected and analyzed at the University of California, Berkeley, 2004*).*
2004		University of California, Berkeley, Research Opportunity Program Scholarship. fMRI project on ADHD. *(Advisor: Stephen Hinshaw, Ph.D.)*

2002-04	Oregon Health and Science University – Doernbecher Children's Hospital, Research assistant, Department of Anesthesiology and Pediatric Pain.

HONORS AND AWARDS

Joseph Becker Research Award, University of Washington School of Medicine, Clinical Psychology Internship Program
Blue Cross Blue Shield of Michigan Student Award Grant, 2011 ($3,500)
Fellowship, Latin American School for Education, Cognitive, and Neural Sciences, University of Chile, March 2011 (Fully funded)
College of Social Science Dean's Fellowship, Michigan State University, *FreeSurfer Surfaced-Based Cortical Mapping Workshop*– Harvard University/Massachusetts General Hospital, 2009 ($1,200)
Graduate Fellowship, Michigan State University, 2008 ($3,500)
Phi Kappa Phi, National Honor Society, 2005
University of California, Berkeley, Research Opportunity Program Scholarship, 2004, Advisor, Stephen Hinshaw, Ph.D. (Fully funded)
President's Award for Outstanding Community Engagement, Portland State University, 2004
Undergraduate Dean's List, Portland State University, 2001-2005
Darren Ulven Memorial Scholarship, 2001 ($1,000)

RESEARCH EXPERIENCE

Assistant Director – Consortium for Neurodevelopmental Study, Michigan State University, East Lansing, Michigan, August 2006 – 2011. Supervisor: Margaret Semrud-Clikeman, Ph.D.
(Professor of Psychology and Psychiatry; Director, CNS Lab)

Research Assistant – Scholarship at the University of California, Berkeley, Berkeley, California, 2004.
Department of Psychology. Supervisor: Stephen Hinshaw, Ph.D. (Chair, Department of Psychology, UC Berkeley)

Research Assistant – Portland Oregon Veterans Affairs Medical Center, Portland Oregon, August 2002-June 2005. Supervisor: Mark Garzotto M.D. (Professor of Surgery/Urology; Chief Urologic Oncology)

Research Assistant – Oregon Health and Sciences University, Doernbecher Children's Hospital, Portland, Oregon, June 2002 – May 2004. Supervisor: Jeffrey Koh M.D. (Chief, Division of Pediatric Anesthesiology; Director, Pediatric Pain Management Center)

PEER REVIEWER

Guest Reviewer, Archives of Clinical Neuropsychology
Guest Reviewer, Journal of Attention Disorders
Guest Reviewer, Biological Psychiatry

CLINICAL EXPERIENCE

Current Training – University of Washington, School of Medicine and Seattle Children's Hospital Clinical Psychology Internship

-Completing clinical rotations in Consultation/Liaison Service in the Department of Psychiatry, Inpatient Psychiatric Unit, and Outpatient Psychiatry Clinic, and Neuropsychological Service.

Graduate Training – Intervention Experience

-Michigan State University Psychological Clinic, East Lansing, Michigan, 2007-2010.
- Clinton County Regional Education Services Agency, St. Johns, Michigan, 2007.
- Maple Hill Head Start, Lansing, Michigan, 2008.

Graduate Training – Neuropsychological Assessment Experience

-Clinician, Michigan State University Psychological Clinic, East Lansing, Michigan, 2007-2010.
-Assistant Director, Consortium for Neurodevelopmental Study, Michigan State University, 2007-2011.

Additional Clinical Training

-Diversity and Multicultural Workshop, Michigan State University, March 2010; Frederick Leong, Ph.D.; Department of Psychology, Michigan State University

-Dialectical Behavior Therapy Workshop, Attended March 2009; Randy Wolbert, Ph.D., Behavioral Tech, LLC.

-Personality Assessment Inventory (PAI) and Inventory of Interpersonal Problems (IIP) Workshop, Attended September 2009; Christopher J. Hopwood, Ph.D., Department of Psychology, Michigan State University, East Lansing, MI.

-Empirically Supported Behavioral Treatment for Oppositional Children: Helping the Noncompliant Child: Family-Based Treatment for Oppositional Behavior, September, 2007, Nick Long, Ph.D., Michigan State University, East Lansing, MI.

TEACHING

2010 Instructor. Michigan State University, East Lansing, Michigan. Child and Family Psychopathology, 424, Section 101. Summer 2010.

2010 Teaching Assistant. Michigan State University, East Lansing, Michigan. Cognitive and Neuropsychological Assessment, 852, Section 101 (Graduate level). Fall 2010.

2009 Instructor. Michigan State University, East Lansing, Michigan. Cognitive Psychology, 200, Section 101. Summer 2009.

2008 Instructor. Michigan State University, East Lansing, Michigan. Child and Family Psychopathology, 424, Section 101. Summer 2008.

2007 Instructor. Michigan State University, East Lansing, Michigan. Child and Family Psychopathology, 424, Section 730. Summer 2007.

PROFESSIONAL AFFILIATIONS

Student Member, National Academy of Neuropsychology (NAN)
Student Member, Children and Adults with ADHD (CHADD)
Student Member, International Neuropsychological Society (INS)
Student Affiliate, American Psychological Association (APA)

GRANTS

Neurodevelopmental and Behavioral Indicators Of Pediatric Brain Tumors (In process).

Blue Cross Blue Shield of Michigan Student Award Grant (2010). Project entitled, *"Cortical Thickness and Morphology in Children with ADHD-Combined Subtype: Effects of Medication Treatment and Implications for Neuropsychological Functioning and Behavior",* $3,500.

PEER-REVIEWED PUBLICATIONS

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. (2011). Neuroanatomical and Neuropsychological Correlates of the Cerebellum in Children with Attention-Deficit/Hyperactivity Disorder Combined-Type. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*(6), 593-601.

Fine, J., Semrud-Clikeman, M., Bledsoe, J., & Musielak, K. (In press). A critical review of the NLD literature as a developmental disorder. *Child Neuropsychology.*

Semrud-Clikeman, M. & Bledsoe, J. (2011). Updates on Attention-Deficit/Hyperactivity Disorder and Learning Disorders. *Current Psychiatry Reports.*

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. (2010). Response Inhibition and Academic Abilities in Typically Developing Children with Attention-Deficit-Hyperactivity Disorder-Combined Subtype. *Archives of Clinical Neuropsychology, 25*(7), 671-679.

Bledsoe, J., Semrud-Clikeman, & M., Pliszka, S.R. (2009). An MRI Study of the Cerebellar Vermis in Chronically-Treated and Treatment-Naïve Children with ADHD-Combined Type. *Biological Psychiatry*, *65,* 620-624.

Garzotto, M., Park, Y., Mongoue-Tchokote, S., Bledsoe, J., Peters, L., Blank, B., Austin, D., Beer, T., Motomi, M. (2005). Recursive Partitioning for Risk Stratification in Men Undergoing Repeat Prostate Biopsies. *Journal of Cancer*, 104, 9, 1911-7.

Garzotto, M., Mongoue-Tchokote, S., Bledsoe, J., Parra, O., Peters, L., Park, Y., Beers, T. M., & Mori, M. (2004) Predictors of prostate cancer in men undergoing serial prostate biopsies: Results from 371 patients. *American Society of Clinical Oncology, 23, 402.*

PUBLICATIONS IN PROGRESS

Bledsoe, J. Semrud-Clikeman, M. (Submitted). Brain Cortical Thickness in Children with Attention-Deficit/Hyperactivity Disorder Combined Subtype: Effects of Psychostimulant Medication Treatment and Implications for Neuropsychological Functioning and Behavior. *Archives of General Psychiatry.*

Semrud-Clikeman, M., Pliszka, S.R., Bledsoe, J., & Lancaster, J. (Submitted). Volumetric MRI differences in treatment naïve and chronically treated children with ADHD-Combined Type. *Biological Psychiatry*.

Semrud-Clikeman, M., Fine, J.G., Zhu, D., Bledsoe, J. (Submitted). Functional neuroimaging differences in mental rotation in graduate students. *Neuropsychology*.

BOOK CHAPTERS

Semrud-Clikeman, Bledsoe, J., & Vroman, L. (in press). Rehabilitation and school re-entry in traumatic brain injury. Applied Neuropsychology.

Semrud-Clikeman, M. & Bledsoe, J. (in press). Neuropsychological and Neuroimaging Aspects of Developmental Language Disorders.

Semrud-Clikeman, M, Bledsoe, J., & Vroman, L. (In press). Medical, School, and Family Systems in Neurorehabilitation. In. C.A. Noggle & R.S. Dean with M.T. Barisa (Eds.). Neuropsychological Rehabilitation. New York: Springer Publishing Company.

Semrud-Clikeman, M. & Bledsoe, J. (2011). Neuroscience and Ethnicity. (In press).

Semrud-Clikeman, M., & Bledsoe, J. (2011). Traumatic Brain Injury in Children and Adolescents. In A. Davis (Ed.). Handbook of Pediatric Neuropsychology. New York: Springer Publishing Company.

Semrud-Clikeman, M., Fine, J.G., & Bledsoe, J. (2009). Neuroimaging in Women. In E. Fletcher-Janzen & C. Reynolds (Eds.), The Neuropsychology of Women. New York: Kluwer.

Semrud-Clikeman, M., Bledsoe, J. (In press). Medical, school, and family systems in neurorehabilitiation. C. Noggle & R. Ball (Eds.). Contemporary Neuropsychology. New York: Springer.

Semrud-Clikeman, M., Teeter Ellison, P.A., & Bledsoe, J. (In Press); Traumatic Brain Injury in Children and Adolescents. In M. Semrud-Clikeman & P.A. Teeter Ellison (Eds.) Child Neuropsychology. New York: Springer Science.

Semrud-Clikeman, M. & Bledsoe, J. (In press). Neuropsychological and Neuroimaging Aspects of Developmental Language Disorders. Handbook of Neuropsychology and Language.

CONFERENCE PRESENTATIONS

Semrud-Clikeman, M., Fine, J., & Bledsoe, J. (2011). Differences in Social Perception in Children with NLD and Asperger Disorder. Poster presented at the National Academy of Neuropsychology, Marco Island, Florida.

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. Brain Cortical Morphology and Reading Ability in Children with Reading Disorder. Poster presented at the Latin American School for Education, Cognitive, and Neural Science. San Pedro de Atacama, Chile. March, 2011.

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. Neuropsychological Correlates of Cerebellar Vermis Morphology in Children with ADHD-Combined Type. Poster to be presented at the American Psychological Association Meeting (APA). August, 2010. San Diego, CA.

Semrud-Clikeman, M, Fine, J.G., Bledsoe, J., Vronman, L, and Hasson, R. (2010, August). *Aberrant structural MRI findings in children with nonverbal learning disabilities.* American Psychological Association Annual Meeting, San Diego, CA.

Semrud-Clikeman, M, Fine, J.G., Bledsoe, J., Vronman, L., Zhu, D., Pham, A., Schlang, K. (2010, August). *Functional neuroimaging differences in mental rotation in graduate students.* American

Psychological Association Annual Meeting, San Diego, CA.

Fine, J.G., Semrud-Clikeman, M., Bledsoe, J., Vroman, L., Zhu, D., Pham, A. and Schlang, K. (2010,
August). *Gender differences in functional neuroimaging in visual and verbal comparison tasks.*
American Psychological Association Annual Meeting, San Diego, CA.

Fine, J.G., Semrud-Clikeman, M, Bledsoe, J. & Hasson, R (2010, August). *Meta-analysis of the NVLD*
empirical literature: Scientific rigor of extant research. American Psychological Association
Annual Meeting, San Diego, CA.

Semrud-Clikeman, M., Fine, J., Bledsoe, J., Vroman, L., Crow, S. Asperger's Disorder versus
Nonverbal Learning Disabilities: A Diagnostic Conundrum. Poster to be presented a the
National Academy of Neuropsychology Conference, October 2010, Vancouver, British
Columbia.

Semrud-Clikeman, M., Fine, J., Bledsoe, J., Vroman, L., Zhu, D., Pham, A., & Schlang, K.
Functional neuroimaging differences in mental rotation in graduate students. Poster
presented at the American Psychological Association Meeting (APA). August, 2010.
California.

Bledsoe, J., Semrud-Clikeman, M., & Pliszka, S.R. *Cerebellar Area in Chronically-Treated and*
Treatment-Naïve Children with ADHD-C. Poster presented at the National Academy of
Neuropsychology, (NAN). October, 2008. New York.

Bledsoe, J., Semrud-Clikeman, M., Pliszka, S.R. *Response Interference and Academic Ability in*
Children with Attention-Deficit/Hyperactivity Disorder – Combined Type. Poster
presented at the National Academy of Neuropsychology (NAN). October, 2008. New
York.

Semrud-Clikeman, M., Goldenring Fine, J., Zhu, D., & Bledsoe, J. *Differential Activation to*
Emotions in Video Vignettes vs. Photos. Poster presented at the National Academy of
Neuropsychology (NAN). October, 2008. New York.

Semrud-Clikeman, M., Goldenring Fine, J., Zhu, D., & Bledsoe, J. *Differential Activation to*
Positive and Negative Emotions to Photos and Videos. Poster presented at the National
Academy of Neuropsychology (NAN). October, 2008. New York.

Goldenring Fine, J., Semrud-Clikeman, M., Zhu, D., & Bledsoe, J.*Gender Differences in BOLD*
Activation to Happy and Sad Photos and Video Vignettes. Poster presented at the
National Academy of Neuropsychology (NAN). October, 2008. New York.

Bledsoe, J., Semrud-Clikeman, M., Pliszka, S.R. *An MRI Study of the Cerebellar Vermis in Chronically Treated and Treatment Naïve Children with Attention-Deficit/Hyperactivity Disorder.* Poster presented at the American Psychological Association Meeting (APA), August, 2008. Boston, Massachusetts.

Fine, J.G., Semrud-Clikeman, M., Zhu, D., Ogg., J.A., Bledsoe, J. (2008). *Gender Differences in Activation of Happy and Sad Video Vignettes*. Poster presented at the annual meeting of the International Neuropsychological Society, February, 2008. Waikoloa, Hawaii.

Fine, J.G., Semrud-Clikeman, M., Zhu, D., Bledsoe, J. (2008). *Greater Differential Activation to Emotions in Video Vignettes vs. Photos*. Poster presented at the annual meeting of the International Neuropsychological Society, February, 2008. Waikoloa, Hawaii.

Fine, J.G., Semrud-Clikeman, Zhu, D., Bledsoe, J. (2008). *Gender Differences in Activation to Happy and Sad Human Faces.* Annual meeting of the International Neuropsychological Society, February 2008, Waikoloa, Hawaii.

Semrud-Clikeman, M., Fine, J.G., Zhu, D., Ogg, J. A., Bledsoe, J. (2008). *Asymmetric activation to happy and sad video vignettes.* Annual meeting of the International Neuropsychological Society, February 2008, Waikoloa, Hawaii.

Semrud-Clikeman, M., Fine, J.G., Zhu, D., Bledsoe, J. (2008). *Asymmetric activation to happy and sad photos.* Annual meeting of the International Neuropsychological Society, February 2008, Waikoloa, Hawaii.

Semrud-Clikeman, M., Fine, J.G., Bledsoe, J. (2008). *Meta-analysis of empirical research in assessment and diagnosis of NVLD.* Annual meeting of the International Neuropsychological Society, February 2008, Waikoloa, Hawaii.

Bledsoe, J., Semrud-Clikeman, M., Pliszka, S.R. *Academic and Executive Functioning in Treated vs. Treatment Naïve Adolescents with Attention Deficit/Hyperactivity Disorder – Combined Type.* Poster presented at the Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), International Conference, November, 2007. Washington, D.C.

Bledsoe, J., Semrud-Clikeman, M., Pliszka, S.R. *Effects of Stimulant Medication on Attention and Concentration in Treated vs. Treatment Naïve Adolescents with Attention Deficit/Hyperactivity Disorder – Combined Type.* Poster presented at the American Psychological Association Conference, August, 2007. San Francisco, CA.

Bledsoe, J., Sheridan, M., Hinshaw, S.P. *An fMRI study of attention-deficit/hyperactivity disorder in adolescent girls: effects of stimulant medication on working memory*. Poster presented at the Western Psychological Association Annual Meeting, April, 2005. Portland, OR.

Garzotto M, Collins L, Park Y, Mongoue-Tchokote S, Bledsoe J, Peters L, Blank BH, Beer TM, Mori M. *PSA Doubling Time for the Prediction of Aggressive Prostate Cancer on Repeat Prostate Biopsy*. Poster presented at the 2005 American Society for Clinical Oncology, Prostate Cancer Symposium.

Garzotto M, Collins L, Park Y, Mongoue-Tchokote S, Bledsoe J, Peters L, Blank BH, Beer TM, Mori M. *PSA Doubling Time for the Prediction of Aggressive Prostate Cancer on Repeat Prostate Biopsy*. Poster presented at the 2004 American Urological Association Annual Meeting.

Bledsoe, J. *Domestic Violence and Attention Deficit Hyperactivity Disorder*. Presented at Tri-County Batterer Intervention Project Network Meeting. Portland, OR. July 2002.

Legg, E, Bledsoe J, Garzotto M: *The morbidity of transurethral prostatectomy: a contemporary series*. Poster presented at the Northwest Urological Society Meeting. Portland, OR December 7-8, 2002.

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Bledsoe, J. C., Semrud-Clikeman, M., & Pliszka, S. R. (In Press). Neuroanatomical and Neuropsychological Correlates of the Cerebellum in Children with Attention-Deficit/Hyperactivity Disorder - Combined Type. *Journal of the American Academy of Child & Adolescent Psychiatry*.

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