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A preliminary exploration of the relationship between gray and white matter neurometabolites, neuropsychological function, and functional impairment in young adults with attention-deficit hyperactivity disorder

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A PRELIMINARY EXPLORATION OF THE RELATIONSHIP BETWEEN GRAY AND WHITE MATTER NEUROMETABOLITES, NEUROPSYCHOLOGICAL FUNCTION, AND FUNCTIONAL IMPAIRMENT IN YOUNG ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDER

by

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ABSTRACT

Attention Deficit Hyperactivity Disorder (ADHD) has gained acceptance as a neurobiological disorder, supported by a growing body of literature that documents differences in brain structure and function in individuals diagnosed with ADHD. There is growing interest in exploring patterns of neurometabolite concentrations through the methods of proton spectroscopy (^{1}H-MRS). Previous studies have employed single voxel techniques, examining neurometabolite concentrations in small, localized regions of brain tissue. This study is the first to employ Spectroscopic Imaging (SI), which allows for acquisition of neurometabolite spectra from a larger sample of brain tissue, in the cerebral cortex of individuals diagnosed with ADHD. Nine adolescents and young adults diagnosed ADHD and twelve control participants were enrolled in the study. Similar to previous findings, the ADHD group demonstrated significant reductions in gray matter volumes of brain regions relevant for sustained attention, inhibition, and working memory. Additionally, performance on measures of visual-spatial problem solving, academic achievement, and cognitive flexibility/response inhibition was more impaired than controls. Preliminary analyses of the SI neurometabolite data revealed few significant results, but several trends were noted, including some sex-related differences

in neurometabolite concentrations. As anticipated, different patterns of correlations between neurometabolite concentrations and performance on measures of attention were discovered for the ADHD group in comparison to controls. The present study also sought to extend the literature on ADHD by providing a preliminary exploration of neurometabolite concentrations in late adolescence in the context of functional impairment in young adulthood. Although many individuals report symptom remediation when they enter adulthood, functional outcomes indicate that the impact of the disorder is far reaching, impacting aspects of quality of life, academic achievement, employment, relationships, and engagement in risk behaviors. Difficulties in collection of follow-up data limited the findings regarding functional outcome and neurological correlates. Implications and ideas for future research involving ^{1}H-MRS techniques and ADHD are discussed. Overall, the study highlights trends and patterns indicative of a unique neurometabolic profile of individuals with ADHD, suggesting that additional longitudinal research is necessary to advance our understanding of this developmental disorder.

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INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most widely studied disorders in the field of neuropsychology. Individuals diagnosed with ADHD manifest behaviors of inattention, hyperactivity, and impulsivity that may cause severe deficits in academic and psychosocial functioning (Barkley, 2006). ADHD is now considered a "neurobiological condition," with evidence supporting a role in etiology for genetics, environment, and neuroanatomy (Halperin, Marks, & Schulz, 2008). Although the term "neurobiological" is quite broad, historically, research in the ADHD field tends to be encapsulated into specific areas of interest. These areas include neuropsychological test performance, neuroanatomy, epidemiological evaluations of disease prevalence, genetic factors, and studies of functional outcomes in academic performance and adulthood. There is growing overlap between research on neuroanatomical correlates and neuropsychological test performance, particularly given the rise in functional neuroimaging techniques. However, most studies of neuroanatomy focus on structural brain differences.

More recently, there is interest in the role of neurometabolite concentrations in ADHD, studied through proton magnetic resonance spectroscopy (^{1}H-MRS). ^{1}H-MRS allows for in-vivo investigation of metabolic processes occurring in brain tissue. Within the handful of available publications, the majority investigate neurometabolites through single-voxel methods, which allow for analysis of a small, temporally located voxel of brain tissue. Because studies select different regions of interest, single voxel-based findings are frequently inconsistent between studies. Additionally, studies of gross neuroanatomy in ADHD populations find differences in multiple brain areas and whole

brain volume, rather than implicating one specific brain region. Spectroscopic imaging (SI), a technique which captures neurometabolite concentrations in multiple voxels spread out across a slab of brain tissue, may be a more appropriate technique for examining ADHD-related metabolic differences.

This study is the first to employ SI to examine differences in neurometabolite concentrations in gray and white matter in a sample of young adults diagnosed with ADHD. After determining whether global differences in neurometabolite concentrations exist between adolescents diagnosed with ADHD and healthy controls, additional analyses were conducted to determine whether neurometabolite concentrations correlate with markers of neuropsychological function in late adolescence and brain morphology. There was also interest in exploring the relationship between neurometabolite concentrations in late adolescence and functional impairment in early adulthood. By combining data on neuroanatomical correlates, neuropsychological test performance, and functional impairment of individuals with ADHD, it was hoped that new relationships between brain chemistry and the behavioral manifestation of ADHD will emerge.

Before proceeding to the specific aims and methods of this project, the following introduction is provided to orient the reader to the current state of relevant ADHD research. First, a discussion of diagnostic issues, prevalence rates, and developmental course is provided. Additionally, information about persistence of ADHD in young adulthood and functional impairment related to an ADHD diagnosis will be explored. Following this is a brief overview of the anatomical literature, ending with a thorough examination of the state of ADHD spectroscopy research.

Diagnosis, Prevalence, and Developmental Course

As specified by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR; APA, 2000), ADHD is a disorder characterized by symptoms of persistent inattention and hyperactivity, occurring across multiple settings and causing significant impairment for the individual. Three subtypes are specified in the current diagnostic system: Predominantly Inattentive Type, Predominantly Hyperactive-Impulsive Type, and Combined Type. Examples of inattentive behaviors include being easily distracted by extraneous stimuli, making careless errors on schoolwork, having difficulty sustaining attention (especially on non-preferred activities), avoiding tasks that require mental effort, losing things, and forgetting steps or instructions. Hyperactive-impulsive symptomatology is characterized by behaviors such as fidgeting, talking excessively, acting as if "driven by a motor," impatience, and interrupting or intruding on others. Study methodology makes it difficult to compare results across studies based on differences in selection of subtype. Some studies screen for Predominantly Inattentive Type or Predominantly Hyperactive-Impulsive Type (i.e., Courvoisie, Hooper, Fine, Kwock & Castillo, 2004), while the majority select individuals diagnosed with Combined Type (i.e., Batty et al., 2010; Carrey, MacMaster, Gaudet & Schmidt, 2007; Depue et al., 2010; Shaw et al., 2006). Occasionally, studies will sample for all three subtypes and consider them separately in analyses. The more common practice, particularly in studies of neuroimaging which tend to have smaller sample sizes, is to lump all subtypes together (i.e., Yang, Wu, Dung & Ko, 2010) or to ignore subtype diagnosis information (i.e., Colla, Ende, Alm, Deuschle, Heuser, & Kronenberg, 2007). The sample sub-type diagnostic characteristics should be evaluated when determining generalizability of the

findings. When considering differential diagnoses, the manual suggests that developmental level of the child be taken into consideration (APA, 2000). Specific guidelines are not provided for the clinician, which becomes problematic when considering how the DSM handles the diagnosis of older adolescent and adult patients (Barkley, 2010).

Reported prevalence rates range from 3-7% in school-age children (APA, 2000), although more recent prevalence studies suggest that rates may be as high as 9.2% in the general population (Ramtekkar et al., 2010). When the DSM-IV criteria are employed, prevalence rates in studies conducted outside of the United States reveal remarkably similar statistics, suggesting that this diagnosis is not culturally bound (Faraone, Sergeant, Gillberg, & Biederman, 2003). Heritability of ADHD has been well established through twin studies (Faraone et al., 2005). The disorder is thought to occur more commonly in males (APA, 2000). Some research indicates that this gender imbalance may be driven by the tendency of males to display concurrent disruptive or oppositional behaviors, making them more likely to be targeted for assessment by teachers or parents (Spencer, Biederman, & Mick, 2007). Population studies imply that females are more likely to exhibit inattentive symptoms, and therefore, may be underdiagnosed and undertreated (Spencer et al., 2007; Ramtekkar et al., 2010). Given the sex-based prevalence rates, early studies, particularly those exploring neuroanatomical correlates, failed to include female participants. More recently, studies have expanded their inclusionary criteria to include females, but females continue to be under-represented in studies of ADHD.

The DSM-IV stipulates that in order for a diagnosis of ADHD to be made, symptoms must be present prior to 7 years of age (APA, 2000). Individuals failing to meet this criterion may be classified as ADHD-Not Otherwise Specified category (APA, 2000). The age of onset criteria has come under attack by key researchers in the field. In a critical editorial, Barkley (2010) speaks to the arbitrary nature of the age 7 designation, originally set forth in DSM-III. Little evidence exists that patients presenting with symptoms prior to age 7 differ from those with symptom onset occurring later in life (Polanczyk, Caspi, Houts, Kollins, Rohde & Moffitt, 2010). Additionally, verifying this diagnostic criterion presents problems when parent-report is not available.

Given the longitudinal nature of the present study, research on ADHD in adult populations is particularly relevant. Research suggests that a significant number of children "outgrow" their diagnosis when they enter adulthood. Following a cohort of males diagnosed with ADHD for ten years, one study reported that although 65% of the original sample no longer met criteria for full diagnosis, 78% of the subjects showed persistent sub-syndromatic symptoms of inattention or hyperactivity (Biederman, Petty, Evans, Small, & Faraone, 2010). DSM-IV-TR recommends that adults who demonstrate sub-threshold symptoms be labeled "In Partial Remission." The current criteria fail to take into account the shifting nature of attentional demands in adulthood.

Many of the current DSM symptoms are specific to the classroom environment, and may not speak directly to the type of inattentive/hyperactive behaviors exhibited by adults. Surveying the available literature, Spencer et al. (2007) propose a developmental trajectory of symptom decline, with hyperactive symptoms remitting rapidly in adolescence. Attention recovery is less pronounced, and inattentive symptoms are often

predominant in adult ADHD samples. A recent review of studies compiled the most frequently cited problem behaviors for adults diagnosed with ADHD (Goodman, 2009). Adult inattention was characterized by difficulties with task completion, poor time management, distractibility, and forgetfulness. Adult hyperactivity was hallmarked by subjective feelings of restlessness, choosing active jobs over "desk" jobs, or working multiple jobs, while impulsivity typically involved interrupting others mid-conversation or when they are working, making impulsive, frequent job changes, and exhibiting low frustration tolerance (Goodman, 2009). Although many adults with ADHD report fewer specific deficits than children, their deficits may have a more immediate and profound impact on functioning (i.e., changes in job, loss of relationships, etc.)

Using DSM-IV diagnostic criteria, a recent study showed a shift in the prevalence rates of ADHD in the general population, with children under 12 showing the highest rates (11.7%), followed by adolescents (9.7%), and then young adults (6.4%) (Ramtekkar et al. 2010). Although previously, statistics such as these have been used to illustrate the attenuation of ADHD-related problems with age, the authors of this paper suggest that the statistics are in fact an artifact of the current diagnostic criteria. In their study, young adults with a history of ADHD continued to display more ADHD-like symptoms than their never-diagnosed peers. Ramtekkar et al. (2010) suggest that a lower symptom count may be appropriate for older patients, placing more emphasis on whether core deficits are interfering with current function (Ramtekkar et al., 2010). A review of the proposed criteria for DSM-V indicates that the number of symptoms required for diagnosis has been reduced from 6 per category to 4 for individuals age 17 or older. This shows

progress, although it fails to speak to the possibility that the available criteria descriptions also require some revision.

Individuals diagnosed with ADHD have several options available for treatment, although the most common is psychopharmacological. Children and adolescents are typically prescribed psychostimulants, such as amphetamine (i.e., Adderall) or methylphenidate (i.e., Ritalin, Concerta), which reduce symptoms in approximately 65-85% of the impacted population (Halperin et al., 2008). Adults may be prescribed these medications or a variety of anti-depressant medications which also appear to aid in remediating attention problems. Given that some parents and individuals are uncomfortable employing pharmacological treatments, other options include behavioral/psychosocial therapies and accommodations in the classroom that may help students with ADHD excel academically.

Neuropsychological Deficits and Behavioral Correlates

Although the primary symptoms accounted for at diagnosis include inattention, hyperactivity, and impulsivity, depending on subtype, other classes of cognitive and behavioral deficits may be indicative of or related to a diagnosis of ADHD. Critics argue that the current diagnostic system is atheoretical and inadequate, failing to account for the wide variety of ADHD-relevant neuropsychological deficits (Barkley, 1997). Moving beyond the description-based classification of DSM, Barkley (1997) proposes that the core deficit of ADHD is response inhibition. This deficit precedes difficulties in the areas of working memory, affect regulation, internalization of speech, and synthesis of ideas, and subsequently, planned/organized action. Despite this proposal, other researchers have suggested that most studies incorporating only one measure of attention fail to accurately

classify individuals diagnosed with ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Substantial overlap frequently exists between control and clinical samples performance on measures of attention, suggesting heterogeneity may be more prevalent in ADHD than previously theorized. A recent study indicates that individuals diagnosed with ADHD may fall into four distinct categories, each demonstrating a different area of weakness in attention management (Fair, Bathula, Nikolas, & Nigg, 2012). The proposed system suggests that individuals may be classified based on the following skill deficits: increased response variability, reduced working memory span and inhibition, inaccurate temporal processing speed, and weak signal detection suggestive of altered arousal. Interestingly, the researchers found similar patterns of performance variability in their typically developing sample (Fair et al., 2012). Based on this recent line of research, it is possible that the diagnostic system for ADHD may change substantially in the next decade to account for the heterogeneity in neuropsychological profiles that is frequently reported.

Barkley (2006) classifies the available ADHD research into easily understandable categories of deficits. As would be expected, ADHD is characterized by neuropsychological deficits on tests of sustained attention. Behaviorally, this inattentiveness is demonstrated through inconsistency in speed of response and low accuracy scores (i.e., Barkley, 2006; Vaurio, Simmonds & Mostofsky, 2009). Under the category of general cognition, Barkley reports that children and adolescents with ADHD demonstrate deficits in verbal working memory, time management, planning, error recognition, and verbal problem solving. Poor inhibitory control has also been demonstrated behaviorally (Batty et al., 2010). These skill sets fall under the broad

umbrella term of executive function, which has been described as an individual's ability to respond to a novel problem through the use of decision making, planning, purposeful action, and effective performance (Lezak, Howieson & Loring, 2004). Interestingly, although many researchers hypothesize that ADHD is a disorder of executive dysfunction (i.e., Barkley, 1997), research on other specific executive function skills such as creating novel responses, learning rules, and shifting sets are less conclusive, with ADHD participants frequently performing at the same level as healthy controls (i.e., Barkley, 2006). A recent meta-analysis of executive function in ADHD youth found that deficits in this set of skills is "neither necessary nor sufficient" to qualify an individual for a diagnosis (Willcutt, Doyle, Nigg, Faraone & Pennington, 2005).

Additional deficits are reported in the areas of language, visuo-spatial abilities, and motor coordination. With regard to language development, some studies find that children with ADHD demonstrate a delay in language initiation and a delay in the internalization of speech (Barkley, 2006). Other hallmark language characteristics of ADHD samples include excessive conversational speech, decreased verbal fluency, and depressed listening comprehension abilities (Barkley, 2006).

Deficits in visual-spatial abilities and motor coordination are also reported, although they are difficult to separate from problems with attention. Likely related to problems with spatial attention, research shows that children with ADHD may demonstrate deficits in visual processing and visual orientation (Boles, Adair & Joubert, 2009). Some studies find delays in motor coordination, often characterized by poor handwriting quality (Barkley, 2006). Fine motor coordination requires attention to detail. Qualitatively, when children with ADHD are observed completing written tasks, they

frequently rush through the motions making careless errors despite cues to slow down. Whereas some children with motor coordination deficits have a physical limitation which impacts their ability to hold or manipulate writing utensils, children with ADHD may be functioning with a mismatch between the speed of their thought and their motor speed.

Given the wide range of individual neuropsychological deficits, there is an interest in determining whether global intellectual deficits may also be associated with a diagnosis of ADHD. Studies frequently include a measure of general intellectual function when batteries of neuropsychological tests are administered. Findings with regard to intelligence vary significantly from study to study. The most common finding is that ADHD participants demonstrate a significantly lower IQ than controls (i.e., Batty et al., 2010; Shaw et al., 2006). Although the differences are often statistically significant, it should be noted that the ADHD groups consistently fall in the average range of intelligence, suggesting that this difference may not be clinically meaningful. Some neuroimaging studies show comparable intelligence to controls, with both groups scoring above the population mean (i.e., Seidman, et al., 2006; Yeo et al., 2003). Sample size in these studies tends to be small, and may reflect errors in sampling rather than population characteristics.

Taken as a whole, findings in the area of neuropsychological test performance suggest that individuals with ADHD exhibit inconsistent patterns of performance, with deficits found across cognitive domains. Although initially proposed as a disorder of impaired behavioral inhibition leading to executive function deficits, the actual deficits appear to be more widespread and may speak to a more general level of impairment in this population (Halperin et al., 2008).

Functional Outcomes

Academic and Career Outcomes

The neuropsychological deficits associated with a diagnosis of ADHD can lead to functional impairment in several important life domains. For children, the impact of ADHD is often examined in the academic realm. Academic outcomes in primary school and high school are particularly salient and concerning, given the subsequent impact they have on career opportunities and success. School-aged children and adolescents with ADHD are more likely to require special education services (Barkley, 2006; Biederman et al., 2010) and academic tutoring (Barkley, et al., 2006). When compared to non-ADHD peers, children and adolescents with ADHD are more likely to be retained due to failing grades and are less likely to graduate from high school (Barkley, 1997; Barkley et al., 2006; Biederman et al., 2010). Adolescents with ADHD who graduate show deficits in global school performance when compared to their peers. One study found that at the time of graduation, a cohort of hyperactive youth had a lower mean grade point average during their senior year and achieved lower class rankings than unaffected peers (Barkley et al., 2006).

Undiagnosed adolescents exhibiting symptoms of inattention and hyperactivity may also be at risk for academic problems. One study reported that adolescents with sub-threshold ADHD (i.e., not meeting full DSM-IV-TR criteria) were more likely to be grade-retained than their peers who carried an ADHD diagnosis (Bussing, Mason, Bell, Porter & Garvan, 2010). The authors speak to the difficulty inherent in this finding. Adolescents who are not diagnosed will not qualify for services at school, but their attention problems may affect their functional academic outcomes.

Problems in academic achievement may lead to functional problems in adulthood. Young adults with ADHD are less likely to seek higher education, and thus are commonly reported to have lower salaries (i.e., Able, Johnston, Adler & Swindle, 2007; Barkley, 2006). Hyperactive young adults received significantly poorer ratings of job performance from employers and were more likely to be fired from their jobs (Barkley, 2006). Providing a parallel to the study of undiagnosed adolescents (Bussing et al., 2010), Able et al. (2007) found that undiagnosed adults, who never sought treatment for ADHD but met symptom criteria, were less educated, less employed, and less wealthy than a sample of control adults with no reported attention problems. Even in high-IQ, highly educated individuals diagnosed with ADHD, functional impairments are found (Antshel, Faraone, Maglione, Doyle, Fried, Seidman & Biederman, 2009). When compared to a sample of healthy controls matched for intelligence, high-IQ adults with ADHD reported more problems in their work environment and lower salaries.

Risk Behaviors

Given that impulsivity is a hallmark symptom of ADHD, engagement in high-risk behaviors is often examined as a potentially negative functional outcome in this population. In childhood and adolescence, delinquent behaviors are particularly concerning. Behavioral problems at school lead to higher rates of suspension and expulsion in ADHD samples (Biederman et al., 2010). Outside of the academic realm, adolescents with childhood ADHD were more likely to become involved in the juvenile justice system (Bussing et al., 2010). Legal problems become indicative of high-risk behavior in adulthood. Males who exhibited persistent symptoms of ADHD in young adulthood were more at risk for being arrested and convicted of a crime (Biederman et

al., 2010). When compared to non-diagnosed controls, adults with ADHD were twice as likely to have been arrested and had other legal difficulties, such as more moving traffic violations (Biederman et al., 2006).

ADHD samples demonstrate some increased risk for accident-related injuries, possibly related to impulsive tendencies. Barkley (2006) reported that individuals with ADHD are more prone to accidental injuries. As a result, increased utilization of health care services and increased health-related expenditures for families with an ADHD individual are also commonly reported. Some studies of children and adolescents fail to explore the topic of risky sexual behavior. However, studies of young adults with ADHD shed some light on this subject. When compared to a community sample of non-diagnosed individuals, hyperactive young adults were more likely to initiate sexual relationships at a younger age, become parents at a younger age, and receive treatment for sexually transmitted diseases (Barkley et al., 2006). Sex initiation at a younger age is reported in other studies with less selective ADHD samples (Biederman et al., 2010).

Substance use is another risk behavior that is often associated with ADHD. Some studies find increased prevalence for recreational drug use, use of psychoactive substances, alcohol use, and increased addiction to tobacco products (i.e., Biederman et al., 2006; Biederman et al., 2010; Wilens, 2004). When ADHD is assessed in adolescent and adult populations seeking treatment for substance use disorders, higher prevalence rates of persistent, childhood-onset ADHD are reported than would be expected in a community-based sample (see review by Wilens, 2004). Frequently, it is the presence of a comorbid ODD diagnosis that predicts substance abuse in individuals with ADHD. In a study of at-risk youth, increased risk for cannabis use and alcohol use was only

associated with ODD and not with ADHD (Bussing et al., 2010). One study reported similar rates of current alcohol use between the ADHD adult participants and controls, but the ADHD cohort had higher lifetime rates of substance abuse (Seidman et al., 2006). High-IQ may be protective against certain impulsive, risky behaviors that are commonly associated with a diagnosis of ADHD. Despite the evidence that high-IQ ADHD individuals experience some degree of disorder-related impairment, this cohort exhibited lower rates of cigarette use and substance abuse than estimates of use in the general population (Antshel et al., 2009).

Social Problems and Quality of Life

Although deficits in social skills and social competence are not a core component of the ADHD diagnostic criteria, they are associated features. It is likely that inattention, hyperactivity, and impulsivity may cause problems for diagnosed individuals in their social relationships (Nijmeijer, Minderaa, Buitelaar, Mulligan, Hartman & Hoekstra, 2008). In their review of the literature on social behavior in ADHD individuals, Nijmeijer et al. (2008) report that children with ADHD-Hyperactive/Impulsive type may approach peers in a disruptive, aggressive, or hyperactive manner which can result in rejection and isolation. Children with ADHD-Inattentive type are more subdued in their approach to social interactions, but slow response time, passivity, and anxiety may impact the way they are viewed by others (Nijmeijer et al., 2008). As a result, studies often report less satisfaction in social relationships and increased isolation (see review by Nijmeijer et al., 2008). Hyperactive young adults were more likely to report problems in social relationships, including having fewer close friendships and problems maintaining friendships over time (Barkley et al., 2006). Adult studies show higher rates of self-

reported marital discord, marital separation and divorce, and parenting difficulties in ADHD populations (Halperin et al., 2008).

Given the extensive functional impairments that an individual with ADHD may face, it is not surprising that overall quality of life is impacted. Across samples, adolescents with ADHD (Bussing et al., 2010), ADHD adults (Antshel et al., 2009), and even undiagnosed adults (Able et al., 2007) report lower ratings of life satisfaction. Even if the course of symptoms remits completely or becomes less intense over time, quality of life may be affected. In an internationally distributed consensus statement on the status of ADHD, Barkley (2002) commented that "ADHD is not a benign disorder."

Interestingly, despite the extensive amounts of literature on outcomes in adulthood, most longitudinal ADHD studies explore the transition from childhood to adolescence. Adult research is primarily retrospective. Studies may explore how current diagnosis impacts current functioning, but fail to provide a better understanding of what childhood factors might predict success or difficulty for an individual as they enter later stages of life.

Neuroimaging and ADHD

In a historical account of ADHD, Barkley (2006) relays that the first time the disorder received attention in the United States was in the early 20th century following an epidemic of encephalitis in 1917 to 1918. At this time, an increasing number of children survived the disease due to medical advancements but, as a result, had behavioral sequelae that included problems with attention, inhibition, impulsivity, and delinquency. Although this epidemic occurred prior to the development of our own behavioral diagnostic system, it was one of the first indicators that behaviors associated with ADHD

could result from damage to the brain (Barkley, 2006). As more instances of this behavioral pattern surfaced and the diagnostic system was elaborated, interest grew in uncovering the neurological etiology of the disorder. Given limitations in the available imaging tools, neuropsychological and psychophysiological test data was initially the only avenue available for exploration of brain function (Barkley 2006). The 1990s witnessed an evolution in the study of ADHD, with a rapid increase in the number of studies exploring structural brain differences in ADHD individuals. As technology advances, function and development are also being addressed via imaging paradigms.

Currently there are several different modalities which allow for in vivo exploration of the human brain. This review of neuroanatomy as it relates to ADHD will focus on results obtained from magnetic resonance imaging (MRI) scans, highlighting correlational analyses (when available) that tie the structural findings back to neuropsychological data and functional outcomes. A brief overview of the basic principles of MR technology is provided to orient the reader. During an MRI, a strong magnetic field is applied to an area of interest, such as the human head. Protons found on hydrogen atoms in the living tissue align themselves with the magnetic field (Kurth & Bigler, 2008). A radio frequency pulse is then applied, and the hydrogen atoms absorb energy from the pulse altering their spin. When the radio pulse ends, the protons return to their original orientation, in line with the magnetic field, releasing a small amount of energy which is detected by the MR coil (Kurth & Bigler, 2008). Given that different tissues are composed of different densities of hydrogen atoms, the intensity of energy released from various tissues helps to distinguish different areas of the brain (Kurth & Bigler, 2008). One method of analyzing structural images is with a method called voxel-

based morphometry (VBM), a process which normalizes and spatially smooths gray matter areas allowing for comparison across subjects (Ashburner & Fuston, 2000). More recently, research methods employ automated segmentation software, such as FreeSurfer of Afni, which uses a combination of volume-based and surface-based analysis to segment individual brains according to a template and provides data about gray matter and white matter volumes, as well as gray matter surface area and thickness.

Structural Findings with ADHD Samples

Publications on anatomy and structure in ADHD populations are numerous. Given variability in sample size, age of subjects studied, sub-type diagnoses, and regions of interest, findings are not always consistent across studies. The following section will summarize the available findings, covering differences reported in whole brain volumes, frontal structures, sub-cortical structures, the temporal lobe, and the cerebellum.

Before transitioning the discussion to the role of individual brain structures in ADHD, one of the most consistent conclusions drawn from neuroimaging studies is with regard to whole brain volume. Group differences are often detected between ADHD samples and controls, with ADHD participants exhibiting smaller mean whole brain volume in childhood and adolescence (i.e., Batty et al., 2010; Hill et al., 2003), that persists into adulthood (i.e., Castellanos et al., 2002). Additional whole brain analyses in adolescent and adult samples reveal that ADHD individuals tend to have lower gray matter in all four lobes (Batty et al., 2010; Biederman et al., 2007; Seidman et al., 2006).

Data from whole brain studies shed an interesting light on the presented neurocognitive deficits. Given that global reductions in intelligence and neuropsychological functioning are frequently reported, one might suspect that multiple

structural areas of the brain are impacted. Castellanos et al. (2002) conducted a longitudinal and cross-sectional study of brain development in a large sample of ADHD participants and healthy controls, with subjects undergoing between one and four MRI scans over time. ADHD participants were found to have globally smaller cerebral and cerebellar volumes. Although children with ADHD start at a lower total brain volume, longitudinal data from this study suggests that their growth curves run parallel to controls for all regions except the caudate. Overall, the authors argue that neural deficits are not primarily frontal in nature, but affect the whole brain (Castellanos et al., 2002).

Although whole brain differences are frequently reported, conflicting evidence does exist. Depue et al. (2010) found no differences in whole brain volume in a young adult sample of combined-type ADHD individuals. This study did an extensive pre-study screening to ensure that participants did not qualify for additional psychiatric diagnoses, and only one sub-type of ADHD was included. Further research on neurological differences may reveal differing patterns of whole brain presentation among ADHD sub-types or among individuals with comorbid diagnoses.

Despite the assertion that whole brain differences exist, researchers often focus their search for neuranatomical differences in ADHD samples to areas such as the prefrontal cortex and frontostriatal circuits, brain areas involved in the orchestration of executive function and attention. Some studies find smaller total volume of the prefrontal cortex (i.e., Biederman et al., 2007; Castellanos et al., 2002). Frontal gray matter volume has been found to be negatively associated with symptoms of ADHD; as gray matter volume decreases, symptoms severity of ADHD increases (Castellanos et al., 2002). Other studies find more specific differences, such as smaller right dorsolateral frontal

volumes (Hill et al., 2003) or total dorsolateral frontal volumes (Monuteaux et al., 2008). In an adult sample, the most pronounced volumetric differences were found in the left superior frontal gyrus (in their chosen analysis system, this region accounted for approximately 60% of the dorsolateral prefrontal cortex) and right anterior cingulate cortex (Seidman et al., 2006). Anterior cingulate reductions have been found in other samples (i.e., Biederman et al., 2007). Authors highlight that these results are particularly interesting, given that their ADHD sample was remarkably similar to the controls on measures of intelligence and had similar rates of comorbid disorders (Seidman et al., 2006). Structural differences in prefrontal circuitry in conjunction with normal performance on executive function/neuropsychological measures could imply that by the time individuals with ADHD reach adulthood, they have neurologically compensated for volumetric deficits in the specified prefrontal areas. An additional study of adults found reduced volumes in the orbitofrontal cortex (Hesslinger, Tebartz van Elst, Thiel, Haegele, Hennig & Ebert, 2002), an area typically thought to assist in the sensory integration of stimuli related to reward and punishment as well as decision making and planning.

Few studies focus on structural areas thought to be relevant for inhibitory control, a key deficit for individuals diagnosed with ADHD. One group found that children with combined type ADHD had thinner bilateral cortex in the pars opercularis, a small section of the inferior frontal gyrus frequently associated with inhibitory control (Batty et al., 2010). A study of young adults diagnosed with combined-type ADHD also found reduced grey matter volume in the right inferior frontal gyrus, which predicted poor performance on measures of processing speed, response inhibition, and response variability (Depue et al., 2010). In a post-hoc analysis of the three components of the

right inferior frontal gyrus, grey matter volumetric differences between ADHD and controls were driven by the pars triangularis, while the pars opercularis and pars orbitalis only trended towards significance. The relationship demonstrated between size of the right inferior frontal gyrus and behavioral performance was not found for control participants (Depue et al., 2010). This study failed to find volumetric differences in additional prefrontal structures between participants with combined-type ADHD and controls. When discussing their failure to find differences in other frontal regions of interest, the authors point to their stringent inclusion criteria. Given that they ruled out all other psychiatric disorders and controlled for learning abilities, their sample represents a fairly controlled group of individuals afflicted with attention deficits and no other known abnormalities (Depue et al., 2010).

Although the frontal regions have been of particular interest given the link with executive function, frontal areas do not produce behavior in isolation. The frontostriatal network is a system of pathways that connect the prefrontal cortex to subcortical areas, such as the basal ganglia. Basic structural imaging cannot directly explore these connections, thus researchers look to subcortical structures in their search for volumetric differences. The caudate nucleus is one component of the frontostriatal circuit. Originally thought to be involved only in the coordination of movement, more recent studies show that the caudate plays a role in learning and memory, especially in learning that involves reward mechanisms (Timman & Daum, 2007). Studies of children with ADHD frequently find differences in the size of the caudate nuclei between ADHD samples and controls, however the detected abnormalities tend to vary by hemisphere with some studies finding right sided abnormalities (i.e., Tremols et al., 2008), some reporting left

side reductions (i.e., Filipek, Semrud-Clikeman, Steingard, Renshaw, Kennedy & Biederman, 1997), and others showing bilateral reductions (Castellanos et al., 2002). It is proposed that by adolescence, caudate differences normalize. Therefore, in older adolescent and adult samples, differences are not reported (i.e., Castellanos et al., 2002; Seidman et al., 2006). Caudate volume has been negatively correlated with ADHD-related behavioral symptoms (Castellanos et al., 2002). Other studies of the basal ganglia find no differences in the volume of the caudate or the globus pallidus, but implicated the putamen as being smaller in ADHD participants (Sobel et al., 2010). Although the caudate and globus pallidus did not show volumetric differences in this study, inward surface deformations on all three components of the basal ganglia were found (Sobel et al., 2010). Having more inward deformations was associated significantly with ADHD symptom severity (Sobel et al., 2010).

The temporal lobe is involved in auditory processing, and as such, is integrally involved in the semantic processing of speech and language. This region is of interest given the difficulties that individuals with ADHD have with listening and language processing (Barkley, 2006). Group differences in temporal lobe volume have been reported, with ADHD participants demonstrating significantly smaller gray matter volume in the right superior temporal gyrus extending anteriorly to the medial temporal gyrus (Kobel et al., 2010). Although few studies report structural differences in the temporal lobes, negative correlations between temporal gray matter volume and symptom ratings have been reported (Castellanos et al., 2002). Additionally, differences in temporal lobe could relate back to neuropsychological deficits seen in language, particularly deficits in listening comprehension (Barkley 2006).

Abnormality of cerebellar volume in participants diagnosed with ADHD is a more consistent finding (i.e., Castellanos et al., 2002; Monuteaux et al., 2008). The cerebellum was originally hypothesized to only control coordinated and intentional movements. More recently hypotheses have broadened, and now higher order cognitive skills such as attention, language, and emotion regulation are also implicated in cerebellar function. In a healthy control sample, the cerebellum was shown to follow a u-shaped growth curve, with peak growth occurring significantly earlier in females (Tiemeier, Lenroot, Greenstein, Tran, Pierson & Giedd, 2010). Additional volumetric differences were noted between the sexes, with males having significantly larger cerebellum even after controlling for total brain volume. Although an ADHD comparison group was not included in this study, the authors hypothesized about the clinical implications of their findings. Given the protracted development and larger size of their cerebellum, males may be more susceptible to damage in this area, leading to an increase risk for developing ADHD when compared to females (Tiemeier et al., 2010).

Cortical Thickness

Structural data may implicate morphological differences between ADHD individuals and control populations, but the measure itself lacks specificity and does not provide a sensitive way to examine cortical development. By dividing brain area volumes into two sub-components, cortical thickness and cortical surface, information is revealed about how the brain changes over the life course. Cortical thickness is thought to be related to the number of cells within a column of cortical organization (Panizzon et al., 2009). Cortical thickness changes over the developmental span of humans and other animals. During early development an increase in thickness occurs, followed by a slow

tapering that suggests synaptic pruning. Cortical surface area is related to the number of columns in a given area (Panizzon et al., 2009). Surface area should expand, and the contraction seen in measures of thickness is not expected with this measure. In studies of normal development, a pattern of cortical thickness thickening and thinning is seen across studies, with lower order areas, such as the occipital cortex (involved in visual perception), developing more quickly (Shaw et al., 2008). Higher order areas that combine input from multiple sensory systems, such as the insula and anterior cingulate, show a somewhat delayed pattern of cortical change, with peak thickness being reached in middle to late adolescence (Shaw et al., 2008).

In an initial investigation of cortical thickness in ADHD, one study found that ADHD subjects had thinner mean cortical thickness than controls (Shaw et al., 2006). After adjusting for mean cortical thickness and controlling for IQ, controls were found to have thicker cortex in the following areas: superior and medial frontal gyri, bilateral cingulate region, left precentral gyrus, and the right anterior/mesial temporal cortex. Regression analyses were conducted to see if any of the cortical thickness areas would be related to current clinical outcome using the CGAS. Three variables entered the final model: thickness of the left medial prefrontal cortex, thickness of the left dorsolateral prefrontal cluster, and hyperactivity measured at baseline (Shaw et al., 2006). The pattern of cortical thinning, predominantly occurring in the prefrontal regions, fits with previously reported volumetric findings and implicates regions that are thought to be involved in attentional capacities. Frontal regions, specifically the right superior frontal gyrus, show reduced thickness in an adult sample (Almeida, Ricardo-Garcell, Prado, Barajas, Fernandez-Bouzas, Avila & Martinez, 2010). Cortical thickness values in this

region inversely correlated with severity of symptoms, such that decreased thickness was related to an increase in attentional problems.

A recent longitudinal study examined cortical thickness development in a large sample of children with ADHD and healthy controls (Shaw et al., 2007). The two groups showed a remarkably similar pattern of regional development, with primary sensory and motor areas attaining peak cortical thickness before higher-order frontal regions. However, the ADHD group reached peak cortical thickness at a later age than the controls for all regions except the primary motor cortex. Based on these findings, the authors suggest that ADHD is characterized by a delay in neural development, rather than a divergent pattern of development, as evidenced in disorders such as autism (Shaw et al., 2007). The most pronounced delay was seen in the lateral prefrontal cortex, a region consistently reported in articles that show structural differences in ADHD samples (i.e., Biederman et al., 2007; Castellanos et al., 2002). Unfortunately, the study did not include a measure of outcome, so there is no way to determine whether a relationship exists between clinical outcomes and delayed development in regional cortical thickness. Additionally, the authors have drawn some criticism for estimating developmental trajectories (Almeida et al., 2010). Although their sample was sizeable, particularly for imaging research in the area of ADHD, 40% of their sample only had one MRI. A large subset of the data presented was predicted rather than actual values (Almeida et al., 2010).

In summary, a broad range of structural abnormalities are reported in ADHD samples. It appears that not only frontal cortical regions are implicated, but also sub-cortical basal ganglia structures, portions of the temporal lobes, and the cerebellum.

These findings, when taken in conjunction with commonly reported differences in whole brain volume, support the neuropsychological field's assertion that individuals with ADHD may have deficits in a number of cognitive skills. Additionally, based on information from studies on cortical thickness, it appears that ADHD individuals follow a similar brain development trajectory when compared to healthy controls. However, their overall neural development may be somewhat delayed.

Spectroscopy and the Role of Neurometabolites

Given the disparate findings in structural research, knowledge of neurometabolite concentrations in regions of interest may provide a clearer understanding of the underlying neural abnormalities inherent in ADHD. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive method for studying neurometabolite concentrations in living tissue. Using T1-weighted images acquired during an MRI scan (immediately preceding the ^{1}H-MRS scan), a voxel (a single, localized volume), can be placed in a brain region of interest. By limiting the region of interest, the spatial resolution is reduced and sensitivity of the signal-to-noise-ratio is improved (Maudsley, 2002). In order to measure spectra in a given voxel, spatially selective radiofrequency (RF) excitation pulses are applied in three dimensions. A chemical shift will occur when the magnetic field is applied, allowing for the detection of individual metabolites. In the human brain, the most prominent signal will be that of water. In ^{1}H-MRS, the water signal must be suppressed in order to detect spectra of interest (Maudsley, 2002). ^{1}H-MRS has been applied to many clinical populations to learn more about disease progression and neuronal metabolism, including brain tumors, epilepsy, dementias, amyotrophic lateral sclerosis, and brain trauma (Maudsley, 2002).

As magnetic field size increases, the ability to detect individual neurometabolites improves. Although at least 35 metabolites have been reliably identified and studied through ^{1}H-MRS techniques (Govindaraju, Young, & Maudsley, 2000), only a small subset have been identified as relevant in studies of individuals with ADHD. Given its high concentration and well-defined spectral intensity, N-acetylaspartate (NAA) produces a particularly prominent resonance in data output from brain tissue (Maudsley, 2002). Although concentrations of NAA differ in different types of neurons, it is frequently cited as a marker of neuronal integrity, potentially reflecting cell density and metabolism (Govindaraju et al., 2000). Research on dynamic fluctuations in concentration also provide evidence for the hypothesis that NAA levels are related to neuronal dysfunction (Govindaraju et al., 2000). N-acetylaspartylglutamate (NAAG), a by-product of NAA, is structurally similar to NAA, thus the spectral resonances of these two compounds are often combined in ^{1}H-MRS analyses. NAAG is hypothesized to play a role in excitatory neurotransmission (Govindaraju et al., 2000). The combined resonance of creatine (Cr) and phosphocreative (PCr) is often used as a constant in the creation of ratios for comparison between metabolites, because it has shown stability in concentration across the lifespan and in diseases affecting neural tissue (Maudsley, 2002). Interpretation of choline's (Cho) function is complicated by its presence in multiple compounds, but it may indicate neuronal malignancy (Maudsley, 2002). Glutamate (Glu) is the most abundant amino acid found in the human brain, acting as an excitatory neurotransmitter (Govindaraju et al., 2000) in addition to playing a role in other functions such as cellular metabolism (Maudsley, 2002). Glutamine (Gln) is commonly combined with the signal from Glu (with the combined resonance labeled Glx). A precursor form of Glu, the

presence of Gln allows for storage of Glu prior to synthesis (Govindaraju et al., 2000). Myoinositol (Myo), the predominate isomer of inositol found in brain tissue, is thought to be involved in signaling and second messenger systems (Maudsley, 2002), as well potentially playing a prominent role in cell growth and gliosis (Govindaraju et al., 2000).

Research on neurometabolites in ADHD samples is sparse in comparison to the studies on structural abnormalities, but some interesting findings have been reported in the literature. In spectroscopy, predefined regions are explored via voxel placement, so researchers typically cannot draw conclusions about whole brain function. Given the specificity of this method, comparison across studies is also difficult. The most common region of interest in ADHD spectroscopy studies is the right prefrontal cortex. In a study of age and gender matched pairs between the ages of 7 and 16 years, MacMaster et al. (2003) found elevations in the concentration of Glu in the right prefrontal cortex of ADHD individuals. No differences in NAA, Cho or Cr are reported. Participants in the ADHD group were primarily combined type, although one individual qualified for a diagnosis of Predominantly Inattentive ADHD.

In a study of 15 adolescents diagnosed with ADHD (9 combined type, 6 inattentive type) and 10 control participants, voxels were placed bilaterally in the prefrontal area, which included a portion of the anterior cingulate cortex and part of the medial frontal gyrus (Yang, Wu, Dung & Ko, 2010). In the right prefrontal area, the ADHD group had significantly lower levels of Cr + phosphocreatine. Ratio analyses revealed an elevation of NAA/Cr+PCr in the right prefrontal area of the ADHD group, suggesting a right sided, frontal neurochemical alteration in this disorder.

Courvoisie et al. (2004) chose voxels in the left and right frontal lobe for their study of neurometabolites in hyperactive-type ADHD subjects. When compared to control children, the hyperactive ADHD group showed significantly higher levels of NAA, Glu, and Cho in the right frontal lobe. No differences were found for Myo. Left sided differences were less pronounced, with the hyperactive-type ADHD group showing high levels of Glu. All values were normalized using Cr concentration. It should be noted that there were differences in overall Cr, with controls peaking at a significantly higher level. Although the authors caution interpretation of results due to small sample size, they highlight that the larger right sided discrepancies support prior research which implicates right frontal region dysfunction in the disorder (Courvoisie et al., 2004). An extensive neuropsychological battery was administered to both groups; however, few differences were found. The hyperactive-type ADHD group scored lower on measures of visuomotor precision and fine-motor speed. The authors posit that these deficits may be driven by impulsive responding rather than simple sensorimotor difficulties (Courvoisie et al., 2004). Interestingly, although the neurometabolite concentrations for control participants were not significantly associated with their behavioral performance, several associations were found in the ADHD-H group. Right frontal NAA correlated with memory and learning, as well as the sensorimotor domain score. Right and left sided Myo concentrations correlated with language functioning (Courvoisie et al., 2004). This finding relates to findings in the volumetric literature, which show that correlations between neuropsychological performance and brain characteristics may vary based on group classification.

Although many studies of ADHD include only male subjects, one study of neurometabolite concentration found interesting interactions between sex and diagnosis. Seventeen ADHD participants, diagnosed with either hyperactive-impulsive type or inattentive type, and 20 controls completed several neuropsychological measures prior to undergoing an MRI (Yeo et al., 2003). ADHD participants were unmedicated for a minimum of 16 hours prior to the testing. As expected, the ADHD group performed more poorly on measures of attention. An MRS voxel was placed in the right prefrontal area. In the control sample, females had higher concentrations of NAA than males. The opposite pattern was seen in the ADHD group, with males having higher NAA concentration than females. A similar, non-significant trend was seen for Cr levels. Similar to the Courvoisie study (2004), control performance on the neuropsychological measures was not correlated with neurometabolite concentration. In the ADHD sample, however, higher Cr levels predicted poor performance on measures of attention. NAA followed a similar, non-significant trend. Additional correlations were found between right dorsolateral volume and metabolite concentrations in the chosen voxel, indicating the neurometabolite concentration increased as the size of the DLPFC increased. DLPFC volume, as with the Cr and NAA concentrations, was negatively correlated with attentional performance. Given this pattern of correlations, the authors suggest that the prefrontal area may be dysfunctional in ADHD (Yeo et al., 2003).

A study of striatal neurometabolite concentrations implicated Glu, a neurometabolite thought to modulate the release of dopamine and serotonin (MacMaster et al., 2003). No striatal differences were found in NAA, choline, or creatine (MacMaster et al., 2003). The authors hypothesize that if dopaminergic neurons are not functioning

properly, this could result in a disruption of the Glu pathway in the striatum, also leading to abnormal Glu concentrations in other regions (MacMaster et al., 2003).

Interested in exploring neurometabolite differences between various subtypes of ADHD, Ferreira et al. (2009) compared neurometabolite concentrations bilaterally in the ventromedial prefrontal cortex-thalamic-striatal regions in inattentive-type ADHD subjects, combined-type ADHD subjects, and controls. Subjects with combined-type ADHD had lower Myo/Cr ratio in the right VMPFC than controls, higher Cho/Cr ratio in the left thalamus-pulvinar than the inattentive-type ADHD group, and higher Glx/Cr ratio than both controls and inattentive-type ADHD subjects. The variations in neurometabolite concentration in the fronto-striato-thalamic region suggest problems in energy metabolism of combined-type ADHD individuals (Ferreira et al., 2009). Although the study had a relatively small sample size, the data suggests that individuals with different symptom profiles may demonstrate differences in brain chemistry.

The anterior cingulate is thought to play a role in controlling regulatory body functions (such as blood pressure and heart rate) as well as higher order cognitive functions, such as reward anticipation, emotion recognition, empathy, and decision making. Although structural differences in anterior cingulate volume are infrequently reported, the region is of interest in spectroscopy studies given its role in behavioral regulation and executive function. In a study of ADHD and comorbid bipolar disorder, researchers found elevated Glu levels in the anterior cingulate in individuals who only qualified for a diagnosis of ADHD (Moore et al., 2006). This elevation was not detected in healthy controls or ADHD individuals with comorbid bipolar disorder. In a study of neurometabolites in the right and left anterior cingulate cortex, Colla et al. (2008) found

elevated levels of Cho in adult ADHD patients when compared to a control group. Differences in CPT performance were as expected, with the ADHD group exhibiting slower reaction times. Combining the spectroscopy data with the neuropsychological test results, Cho signal was positively correlated with a measure of reaction time (hits).

Chemical shift, or spectroscopic, imaging (SI), acquires signals from multiple regions simultaneously, allowing for analysis of metabolite concentrations across a slab of brain tissue rather than a single voxel (Gadian, 1995). Only one study in the ADHD literature has employed this technique, observing neurometabolite concentration differences in a slab of cerebellar tissue. In a sample of 30 medication-free adults diagnosed with ADHD and a group of 30 healthy controls, a significant increase in Glx/Cr ratios was observed in the left cerebellar hemisphere in the ADHD participants (Perlov et al., 2010). No other metabolite differences were observed (Perlov et al., 2010).

In the only longitudinal MRS study, 13 unmedicated ADHD children and 10 healthy controls underwent a baseline scan (Carrey et al., 2007). The ADHD participants then started an eight week course of methylphenidate (MPH), a stimulant medication commonly used in the treatment of ADHD. At the end of eight weeks, all participants underwent a second scan. Behaviorally, the ADHD participants no longer met diagnostic criteria, and thus, all were considered treatment responders. Voxel placement included three locations: the right prefrontal cortex, the left striatum, and the left occipital lobe. Prior to beginning MPH treatment, ADHD-C subjects had elevated levels of Glu, Glx, and Cr in the left sided striatal voxel. No differences were found in neurometabolite concentration in the primary frontal cortex or the occipital lobe. After the eight week course of medication, striatal Cr was reduced, but differences in Glu and Glx remained

significant. These results contrast a case study publication from 2002, which showed decreases in Glx for four patients following successful medication treatment. Authors hypothesize that the increased levels of Cr may act as a neuroprotectant (Carrey et al., 2007).

The lack of longitudinal follow-up over a broader period of time speaks to a major limitation in the study of neurometabolites in ADHD populations. Additionally, mixed findings based on voxel placement location and sample characteristics make cross-study conclusions are unclear. Given that studies of anatomical structure implicate multiple brain regions in the disorder, more SI studies are necessary to determine whether patterns of neurometabolite concentration vary across a wider range of tissue. Particularly, it may be of interest to determine whether differences exist in neurometabolite concentrations in gray and white matter tissue. Despite these limitations, the preliminary research gained from spectroscopy studies speaks to the fact that neurochemistry may be implicated in the disorder.

Towards a Unified Neurobehavioral Theory of ADHD

The body of literature on ADHD is extensive and somewhat disparate. Researchers from various fields have created niche markets, studying aspects of ADHD that include clinical and psychological outcomes, neuropsychological test performance, and neurophysiology of the disorder. A more unified theory of ADHD would take all components into consideration, characterizing the disorder more comprehensively. Questions remain about the validity of our diagnostic criteria, perhaps because the etiology and neurophysiology of the disease is still unclear. A unified theory will

incorporate these different bodies of research, while also providing a clearer picture of developmental issues that relate to ADHD over the life span.

The most commonly held assumption in the field is that ADHD is a disorder of executive function deficits, characterized by neurological abnormalities in the prefrontal areas. Despite this theme in the literature, a critical review of findings implicates numerous cognitive deficits and global neurological changes, both in structure, cortical thickness, and neurometabolite concentration. Halperin et al. (2008) argue against the frontal lobe hypothesis of ADHD, presenting instead an etiological theory that links one neural pathway with the behavioral manifestations of the disorder and a separate pathway with potential for recovery.

Looking towards damage models of brain function, patients who undergo lesions or insults to their frontal brain regions typically do not show deficits in executive functioning until late adolescence or early adulthood, the time periods when these skills come “on-line” (Halperin et al., 2008). Given that some children who qualify for a diagnosis of ADHD show signs of inattention and hyperactivity at a very young age, a non-frontal neural circuit, potentially involving the non-cortical striatal region of the brain, may be responsible for these behavioral patterns (Halperin et al., 2008; Halperin & Schulz, 2006). Although non-frontal regions may be implicated in the development of ADHD, many studies do find differences between ADHD groups and controls in frontal brain regions. Rather than speaking to the involvement of the frontal circuit in the etiology of the disorder, Halperin et al. (2008) believe that these regions may play a crucial role in recovery from ADHD. Some children will show improvements in their ability to pay attention and inhibit over-active behavioral responses as they age, while

others will continue to struggle in these areas. Differences in frontal region pathways may account for these divergent outcomes, with intact frontal area circuitry allowing some adolescents and young adults to compensate for their deficits (Halperin et al., 2008).

This theory ties back to the previous discussion of changes in the developmental pattern of ADHD over the life span. Adults who continue to suffer from symptoms of ADHD more frequently present with an inattentive profile. As children turn into adolescents and then adults, they gain skills in the executive function areas of inhibition and emotion regulation. These skill sets may help suppress the motor over-activity and impulsivity. The authors recommend that this model be used to guide research on ADHD potentiation and recovery (Halperin et al., 2006).

The following study explored data from multiple domains, including neuropsychological test performance, spectroscopy, and functional impairment during the transition from adolescence to young adulthood. The study sample represents a subset of participants who participated in an earlier longitudinal study, previously published on by Hill et al. (2003) and Yeo et al. (2003).

STUDY AIMS

Aim 1: Explore the pattern of neuropsychological test performance in participants diagnosed with ADHD and healthy controls to determine whether global neurocognitive deficits exist or whether deficits are restricted to the domains of attention and executive function.

Hypothesis 1: ADHD participants will perform more poorly on measures of sustained attention, indicated by slower reaction times, more omission and commission errors, and more variable performance. Additional deficits will be identified in the domains of

working memory, visual problem solving, expressive language, and academic functioning.

Aim 2: Further the study of spectroscopy in ADHD individuals, by examining differences in concentrations of gray and white matter neurometabolites across a slab of brain tissue.

Hypothesis 1: Participants in the ADHD sample will exhibit abnormal patterns of neurometabolite concentrations in both gray and white matter tissue. Based on previous voxel-based findings, it is anticipated that ADHD participants will have a higher concentrations of Glx and Cho.

Hypothesis 2: Preliminary analyses will be performed to determine whether peak concentrations in neurometabolites vary by sex or age. Given insufficient power due to small sample size, these trends will be presented qualitatively.

Hypothesis 3: Participants in the ADHD group will demonstrate greater within-subject variability in metabolite concentrations than will control participants.

Aim 3: Explore the relationship between neurometabolite concentration and performance on measures of attention.

Hypothesis 1: In the ADHD sample, Cho concentration will be positively correlated with performance on a test of sustained attention, while Cre and NAA concentrations will be negatively correlated with test performance. Additional qualitative analyses will be run to determine if relationships exist between the neurometabolite concentrations and performance on measures of working memory and inhibition, with a similar pattern of results anticipated.

Hypothesis 2: Based on findings from previous studies (Courvoisie et al., 2004; Yeo et al., 2003), no associations will be found between neurometabolite concentration and test

performance among the control participants. Additional qualitative analyses will be run to determine if relationships exist between the neurometabolite concentrations and performance on measures of working memory and inhibition. No significant associations are anticipated for the control participants.

Aim 4: Explore the relationship between neurometabolite concentration and morphological differences in total gray matter volume.

Hypothesis 1: Based on previous findings from the initial study and more general findings in the ADHD literature, it is hypothesized that the ADHD sample will demonstrate decreased gray matter volume in several brain regions, including the right dorsolateral frontal region and the cerebellum.

Hypothesis 2: Based on findings from the previous aims (i.e., choosing metabolite concentrations that differed between groups), regression analyses will be run to determine whether morphological differences in gray matter correlate with differences in metabolite concentrations. If no significant metabolite concentration differences are detected between groups, preliminary analyses will be run to examine the relationship between brain morphology and neuropsychological test performance on measures of attention that differentiated the two groups.

Aim 5: Explore functional outcomes in the context of spectroscopy findings.

Hypothesis 1: ADHD participants will experience more functional impairments as they enter young adulthood than control participants, as evidenced by current level of education, current SES, and scores on a self-report measure of functional impairment.

Hypothesis 2: Based on findings from the previous aims (i.e., choosing metabolite concentrations that differed between groups), correlations will be run to determine

whether brain chemistry during late adolescence is related to functional impairment in young adulthood. Although the sample size of this study is too small to conduct regression analyses, it is believed that the findings will help shape regression models in larger studies of functional impairment in ADHD.

METHODS

Participants

Twelve participants with ADHD and twelve controls were recruited from a larger study of ADHD conducted from 1996 to 1997. For the initial study, ADHD participants were recruited from the UNM Health Sciences Center Child Behavior Assessment Clinic, the UNM Center for Neuropsychological Services, and through referrals from participants and staff. 52 families were contacted through letters and follow-up telephone calls for the ADHD cohort. 18 families refused to participate or did not respond to the letter and telephone call. Of the 34 remaining families who expressed interest in the study, 9 children were excluded due to presence of a learning disability, traumatic head injury, or refusal to participate upon learning more about the study. Control participants were recruited through announcements posted at the University medical center, referrals of friends from the ADHD participants, and through staff involved in the project. 28 control families initially agreed to participate in the study. Three children were excluded due to the presence of a learning disability or refusal to participate upon learning more about the study. Participants in both groups were between the ages of 7 years, 0 months and 12 years, 11 months when initially recruited.

At the time of the initial data collection, a strict screening procedure was put in place to ensure that participants in the ADHD group qualified for a diagnosis of either

ADHD-Combined Type or ADHD-Hyperactive/Impulsive Type. Children were diagnosed by a licensed psychologist or licensed psychiatrist through a semi-structured clinical interview assessing symptoms of ADHD according to the DSM-IV (APA, 1994). To corroborate the psychologist or physician's diagnosis, parent-report on a behavioral rating scale also had to indicate symptoms in the clinical range. Exclusionary criteria for the ADHD group included presence of a comorbid childhood behavioral disorder (with the exception of Oppositional Defiant Disorder) or psychiatric disorder, a learning disorder, deafness, blindness, severe language delay, cerebral palsy, history of seizures or traumatic brain injury, or pervasive developmental delay.

Control participants were required to have no history of significant behavioral or emotional problem, no evidence of learning disorders, deafness, blindness, severe language delay, cerebral palsy, history of seizures or traumatic brain injury, or pervasive developmental delay. Screening for control participants was completed via parent interview and review of a pediatric psychiatric symptom checklist. No participants were excluded based on the parent interview or the symptom checklist.

For the current study, participants from the initial study were approached to participate between 9 and 11 years after initial enrollment. 12 participants with ADHD and 12 controls successfully completed the neuropsychological battery and neuroimaging component of the study. Of the 24 individuals who completed neuroimaging, three individuals were excluded from the present analyses due to inconsistencies in the acquired scans. Two subjects had orthodontic braces which caused significant artifacts, and shimming necessary for the completion of the ^{1}H-MRS sequences could not be completed. One subject became claustrophobic during the MRI and requested that the

neuroimaging be discontinued prior to completion of all sequences. Three additional participants diagnosed with ADHD agreed to participate, but were unable to complete the neuroimaging data collection. The three participants with incomplete neuroimaging data and the three participants who did not complete MRI's at the second time point were excluded from the present analyses.

The remaining 21 participants with complete neuroimaging and neuropsychological test data ranged in age from 15 to 23 years (mean age = 18.52, *SD* =2.34). Additional demographics are provided below (Table 1). Although the ADHD group and control group were similar in age, a significant gender discrepancy existed. The ADHD sample was predominantly male (7 male participants and 2 female participants), while the control sample was split equally between the two sexes (6 male participants and 6 female participants). A measure of socioeconomic status (SES) was not administered during the second phase of data collection, so information provided during the initial study period was used to classify SES for the current reduced sample. Mean SES on the Hollingshead Four Factor Index of Social Status (Hollingshead, 1975) was similar for both groups, with the mean score falling in the social strata classification of "medium business, minor professional, technical" (Hollingshead, 1975). Mean education for the ADHD group was 11.56 years (SD = 1.33), while mean education for the control group was 12.92 (SD = 1.73). Although the difference between groups in education achievement approached significance (p = 0.065), this must be interpreted in context. The ADHD sample was slightly younger than the control group, and a higher percentage of the ADHD sample were still in high school. However, it should be noted that three of the nine ADHD participants were grade retained in 1st grade. No control participants reported

a history of grade retention. Additionally, four of the nine ADHD participants received special education services during middle school or high school. One of the four individuals was classified as twice exceptional, as he qualified for special education services in reading and was also enrolled in the gifted program. In contrast, none of the control participants reported a history of requiring special education services, and four of the twelve reported enrollment in gifted academic programming. Of the nine participants diagnosed with ADHD, only two were taking stimulant medication. Medication use for these participants was discontinued 16 hours prior to the neuropsychological testing and the MRI scan. One participant was prescribed Welbutrin. Of the remaining six participants in the ADHD group, five had completed previous trials of stimulant medications, with medication discontinuation occurring between 6 months and five years prior to the second data collection time point.

For the third follow-up data collection point, all participants who participated in the study between 2005 and 2008 were contacted by letter and a follow-up phone call. Of the 21 participants who completed neuropsychological and neuroimaging components of the study, 10 agreed to participate in the study, while only 8 returned completed packets of questionnaires.

Procedures

Collection of the reported neuroimaging and neuropsychological test data occurred between 2005 and 2008. All participants from the preliminary study were contacted by letter and follow-up phone call. Prior to arrival for the study, medicated participants in the ADHD cohort were asked to obtain verbal consent from their physician to stop stimulant medication use for at least 16 hours prior to completing study

procedures. Families who agreed to participate in the study presented to the Center for Neuropsychological Services to complete the neuropsychological test battery. For participants under 18, parents reviewed and signed the consent form. Adolescents were also provided with information about the study and asked to provide verbal assent for study participation. Parents were asked to complete behavioral ratings for their child. For participants 18 and older, written consent was obtained from the subject. Behavioral ratings are not available for these participants. Once written informed consent and assent was obtained, a neuropsychological technician, supervised by a licensed psychologist and pediatric neuropsychologist, administered an abbreviated battery of neuropsychological tests to the adolescent and young adult subjects.

After the neuropsychological assessment was completed, participants completed an MRI scan at the Mind Research Network. Parents and participants were given an opportunity to familiarize themselves with the MRI room, instrumentation, and procedure. An extensive metal screening form was completed for each participant, either by themselves (for subjects 18 and older) or by their parent. This form was reviewed by MRI staff before participants were allowed to enter the MRI environment. MRI scans were obtained using a 1.5 Tesla clinical Siemens scanner. Imaging sequences included T1-weighted volume axial series (Fast=SPGR, TE = 6.9ms, TR = 17.7 ms, flip angle = 25, 256 x 192 matrix, 3-mm contiguous slices). Using images acquired during the structural scan, a supraventricular SI slice was positioned for each subject. The slab, located above the lateral ventricles, was large enough to extend from the frontal to the occipital lobes, and the width encompassed both right and left parietal lobes (15mm slice, TE=30ms, Tr=1500ms, 24*24 phase encoding matrix, 20cm FOV). Gray and white

matter tissue was included in this region. Figure 1 shows the spectroscopic region of interest in the sagittal plane (A) and axial plane (C). An example of an acquired spectrum from a single voxel is also provided (D). A point-resolved spectroscopy sequence (PRESS) was run with and without water pre-saturation. The MRI scan took approximately 40 minutes to complete. A radiologist reviewed all scans, and no clinically significant findings were reported for either adolescents diagnosed with ADHD or controls. Following completion of the MRI, participants received $50.00 for completing both components of the study.

Functional Outcome Data Collection

For the third phase of data collection, participants from the second study were contacted by letter and follow-up phone call. Verbal consent to participate was obtained over the phone. Following informed consent, participants were offered the option of completing several follow-up questionnaires via a paper format sent in the mail or via a secure website. The questionnaires took approximately 30 minutes to complete and covered current demographics (SES, level of education completed), current symptoms of ADHD and diagnostic categorization, level of current functional impairment, medication history, and ratings of quality of life. Once all study measures were completed, a check for $25 was sent by mail.

Measures

Neuropsychological Measures

Wechsler Intelligence Scale for Children - Third Edition (WISC III: Wechsler, 1991)

The WISC III is a standard measure used to assess of intelligence in children ages 6 to 16. The test consists of various subtests which measure aspects of verbal

comprehension, perceptual reasoning, working memory, and processing speed. For the current study, participants 16 and younger were administered the Vocabulary, Block Design, and Digit Span subtests. Full Scale IQ will be estimated using the scaled scores from the Vocabulary and Block Design subtests. This measure has been found to be a reliable and valid measure of current intellectual functioning (Wechsler, 1991).

Wechsler Adult Intelligence Scale – Third Edition (WAIS III: Wechsler, 1997)

The WAIS III is a measure of adult intelligence normed on individuals 17 and older. The test consists of thirteen subtests which measure aspects of verbal intelligence, performance-based intelligence, working memory, and processing speed. For the current study, participants 17 and older were administered the Vocabulary, Block Design, and Digit Span subtests. Full Scale IQ will be estimated using the scaled scores from the Vocabulary and Block Design subtests. This measure has been found to be a valid and reliable measure of intellectual functioning, and is comparable to the WISC-III, making possible the comparison of subjects of different ages (Wechsler, 1997).

Woodcock-Johnson Achievement Tests-Revised (WJ-R: Woodcock & Johnson, 1989).

The WJ-R is a standard assessment of academic achievement for adolescents and young adults. Subtests from the WJ-R, including Letter/Word Identification, Calculation, and Dictation, were administered to determine current level of academic achievement in reading, mathematics, and written language. Standard scores for the selected subtests will be calculated for each subtest. This measure has been shown to be valid and reliable, and has published normative data (Woodcock & Johnson, 1989).

Stroop Color-Word Test (Golden et al., 2002)

The Stroop Color-Word Test measures selective attention and cognitive flexibility (Strauss, Sherman, & Spreen, 2006). The test consists of three parts. First, subjects are provided with a card with color names printed in black ink and asked to read the words as fast as they can. The next card contains blocks of color, and the subject is asked to name the colors as quickly as they can. The final page includes words from the first page randomly printed in un-matching colors from the second page (ex., the word "red" might be printed in green ink). The subject is asked to name the color of the ink. Time and errors are calculated. Versions of this test are frequently included to measure interference, an aspect of attention that may require more executive control.

Conners' Continuous Performance Test (CPT-3.0 version: Conners, 1994).

The Conners' CPT is a test of sustained attention and inhibition. Participants are seated before a PC computer. A string of letters flash one at a time in the middle of the screen, and participants are instructed to press the space bar as quickly as possible for all letters except for the letter X. Participants were provided a brief practice during which the test administrator provided feedback on performance. The CPT lasts approximately 15 minutes. Throughout the course of the test, the speed with which the letters are presented varies from one to four seconds. Percentile scores and t-scores are obtained for 12 variables. Four variables of interest were selected for the current study, including number of omission errors (i.e., the number of nontarget items that the subject failed to respond to), commission errors (i.e., the number of target items that the subject erroneously responded to), Hit RT SE (a measure of consistency of response times as measured by the standard error for responses to targets), and Variability (a measure of response consistency over time calculated by standard deviation of the standard error values for

each of the six time blocks) (Conners, 1994). This measure was originally normed on a large nonclinical sample, and a clinical sample which included a large number of individuals with ADHD and other neurological disorders (Conners, 1994). The measure has shown adequate reliability and validity (Conners, 1994) and is frequently employed in studies of attention deficits related to a diagnosis of ADHD (i.e., Colla et al., 2008).

Behavioral Measures

Conners' Parent Rating Scale (CPRS; Conners, 1990) & Conners' Parent Rating Scales-Revised: Long Form (CPRS-R:L, Conners, 1997).

The CRS is a 48-item rating scale which allows parents to rate their child's behavior on Conduct Disorder, Learning Problems, Psychosomatic, Impulsive-Hyperactive, and Anxiety scales. A Hyperactivity Index is also provided. Ratings are made on a four-point Likert scale (not at all, just a little, pretty much, very much). The original version of the CRS was administered during the initial data collection point for this longitudinal study. In 1997, the measure was revised and lengthened to include 80 items. The updated factor structure includes seven subscales (oppositional, cognitive problems/inattention, hyperactivity, anxious-shy, perfectionism, social problems, and psychosomatic), and three DSM-IV symptom subscales (DSM Inattentive, DSM Hyperactive-Impulsive, and DSM Total). The measure is appropriate for parents of children ages 3 to 17 years. The revised measure has shown adequate reliability and validity in the assessment of symptoms of ADHD (Conners et al., 1998).

Child Symptom Inventory - 4: Parent Checklist (CSI; Gadow & Sprafkin, 1994).

The CSI is a 97 item scale which allows for screening of ADHD and other emotional and behavioral disorders. Parents rate their child's behavior using a four

category scale (never, sometimes, often, very often). For the purposes of the present study, this measure provides a symptom count of inattentive and hyperactive/impulsive symptoms.

Functional Outcome Measures

The Adult ADHD Quality of Life Questionnaire (AAQOL; Brod, Perwien, Adler & Spencer 2005; Brod, Johnston, Able & Swindle, 2006)

The AAQOL is a 29-item self report measure which examines four QOL domains frequently impacted by a diagnosis of ADHD, including life productivity, psychological health, life outlook, and relationships (Gjervan & Nordahl, 2010). Items are rated on a five-point Likert scale, ranging from “not at all/never” to “extremely/very often.” All negatively worded items are reverse scored, so that a higher score indicates better ratings of QOL. The measure has been found to be a reliable and valid measure of the impact of ADHD in adulthood (Brod et al., 2006). Additionally, the measure has previously been used to discriminate between control participants and adults diagnosed with ADHD (Able et al., 2007). This measure is appropriate for use in individuals aged 18 and older.

Conners Adult ADHD Rating Scale Self-Report Short Version (CAARS-S:S; Conners, 1999)

The CAARS short version is a 26-item measure which allows for self-report of behaviors associated with ADHD (Conners, 1999). The measure includes a 12-item ADHD Index which yields a t-score value. T-scores greater than 65 on this index indicate clinically significant problems. This index scale has been used to reliably and validly distinguish adults with ADHD from nonclinical adults (Kooij et al., 2008). Items are rated on a 4-point Likert scale, with choices ranging from “0=not at all/never” to “3=very

much/very frequently." The scale assesses both frequency and severity of symptoms. This measure is indicated for use in individuals 18 years of age and older.

Imaging Analysis Procedures

Spectroscopic imaging data was analyzed using LCModel (Provencher, 1993). Using tissue water as a concentration reference, the LCModel software provides information about metabolite concentrations for each voxel within the supraventricular slice. In order to avoid lipid artifacts, the outer voxels from all four sides of the slice were eliminated from data analysis. Given differences in brain sizes and the quality of the LCModel data, individual subjects usable region of interest ranged from 64 voxels (8 rows by 8 columns) to 120 voxels (12 rows by 10 columns). Figure 2 provides an illustration of the LCModel spectral analysis of a single voxel in the region of interest. Spectroscopic values for Glx (combined glutamate and glutamine), NAA (combined N-acetyl-aspartate and N-acetyl-aspartylglutamate), Cho (combined glycerophosphorylcholine and phosphorylcholine), and Cr (combined creatine and phosphocreatine) were calculated for each voxel included in the SI slab. Although Myo (myoinositol) is reported in some studies of individuals diagnosed with ADHD, Myo was not reliably detectable at the 1.5T field strength and chosen ^{1}H-MRS acquisition parameters.

The LCModel software also reports the Cramer-Rao lower bound, a measure of standard deviation, for each metabolite in each voxel (Provencher, 2010). Following the common practice, voxels with a SD less than 20% were considered acceptably reliable, and included in subsequent analyses (Provencher, 2010), while voxels with a 20% or higher SD were excluded. The Cramer-Rao lower bound accounts for noise level and

resolution of the data, eliminating the need for use of other quality control measures such as FWHM (full width at half-maximum, a rough estimate of linewidth of the spectrum) or S/N (the ration of the maximum in the spectrum subtracting the baseline) (Provencher, 2010). Given individual differences in sizes of the overall slab as well as individual differences in Cramer-Rao lower bounds for each neurometabolite, information iregarding the mean number of voxels included in each analysis are provided to give the reader a better sense of the quality of the data.

In order to quantify the voxel tissue type, tissue segmentation was performed on the T1 weighted images acquired for each subject using SPM8 software (Ashburner et al., 2012). Given the range of ages in the current study, an adult template was selected for analysis purposes. The T1 weighted images were reoriented to match the template prior to segmentation. Gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) maps were registered to the SI region of interest, and the maps were smoothed to the resolution of the ^{1}H-MRS data (Gasparovic et al., 2009). According to previously specified procedures (Gasparovic et al., 2006), pixel values of the smoothed maps were summed and normalized over the volume of the voxels, fractional estimates of GM, WM, and CSF were calculated for each voxel. Given that CSF contributes no measurable neurometabolite concentrations, fractional tissue estimates were corrected for partial volume effects of CSF. Using the normalized GM fraction in each voxel ($f_{GM\_Vol}/(f_{GM\_Vol} + f_{WM\_Vol})$), a linear regression of each metabolite concentration was conducted for each subject. Values from each linear regression were input into a regression formula (y=mx +B), and extrapolation of the regression line to 1 (GM) or 0 (WM) was calculated, providing an estimate of the metabolite concentrations in GM and WM tissue (y). This

method has been demonstrated to provide superior results in comparison to the threshold voxel classification, which only classifies voxels consisting of greater than 66.67% of GM or WM (Yeo et al., 2010).

In order to examine morphological differences between the two groups, the segmented T1 weighted images were loaded into the Voxel Based Morphometry (VBM) tool bar for SPM8 software (Ashburner et al., 2012). The segmented images were smoothed by convolving with an isotropic Gaussian kernel (Ashburner & Friston, 2000), a process where the content of each voxel is replaced by the weighted average of voxels in close proximity, blurring the segmented image (Whitewell, 2009). Additionally, this step results in an image that is more normally distributed, increasing the validity of parametric tests, and helps to compensate for the inexact spatial normalization that occurs during segmentation (Ashburner & Friston, 2000). Using the VBM toolbox, regression analyses were run to determine whether morphological differences correlated with variables of interest (i.e., group classification, neurometabolite concentration, and neuropsychological test performance).

Statistical Analysis Plan

All statistical analyses were conducted using SPSS software. For comparisons of participant performance on neuropsychological measures and for determination of differences in functional impairment, independent samples t-tests were run. Cohen's d was calculated to determine the effect size for significant analyses. For the initial analysis of spectroscopy data, independent samples t-tests were run with the total neurometabolite concentrations. Between-subjects two-way ANCOVAs were conducted with group and sex as the independent variables and GM and WM neurometabolite concentration ratios

as the dependent variables, controlling for the effect of age. When appropriate, follow-up t-tests were run. In order to determine the relationship between metabolite concentrations and test performance on measures of attention, Spearman correlations were calculated.

RESULTS

Prior to initiating analyses relevant for the proposed aims, the ADHD group and the control group were characterized based on parent report of symptoms of inattention and hyperactivity. Results are summarized in Table 2. When the currently reported neuroimaging and neuropsychological test data were collected at the second longitudinal time point, only a subset of participants between the ages of 15 and 17 required the presence of parents for consent purposes. Additionally, normative data for the CPRS-R:L is not available for individuals 18 years or older. Thus, only a subset of parents completed forms rating their child's behavior (6 ADHD participants, 4 control participants). Given the small sample size included in these analyses, all three subscales failed to meet the assumption of equality of variance based on Levene's Test. Adjusted t-values are reported, with equality of variance not assumed. On the CPRS-R:L, ADHD participants had significantly higher scores than controls on the DSM- Inattentive ($t = 3.675$, $p = 0.012$; $d = 2.14$), DSM- Hyperactive ($t = -6.284$, $p = 0.001$; 3.89), and DSM-Total ADHD ($t = 4.679$, $p = 0.005$; $d = 2.71$) subscales.

Given the small sample of behavioral reports available at the second data collection time point, scores on the CPRS and CSI from the initial data collection are reported to provide a more complete description of all participants. These preliminary ratings were collected when the study participants were between ages 7 and 12 years. On the original CPRS, ADHD participants obtained significantly higher scores on the

Impulsive-Hyperactive (t = 2.848, p = 0.011; d = 1.88) and Learning (t = 4.021, p = 0.001; 1.79) subscales. The two groups were not significantly different on the Conduct or Anxious subscales. The primary goal in employing the CSI data from the initial data collection point was to provide a symptom count for ADHD subtype classification within the ADHD sample. However, because several parents of ADHD participants completed the questionnaire rating their child's behavior while the child was on medication, subtype classification could not be completed using this method. Overall, parents of ADHD participants reported significantly more symptoms of inattention, hyperactivity, and impulsivity on the CSI measure than parents of control participants.

Aim 1

Means and standard deviations for all neuropsychological test performance data are provided in Table 1. Independent samples t-tests were conducted to compare performance between the ADHD group and controls on all measures. Given the large number of analyses run for this aim, adjusted p-values were used in determining significance of results for each scale (p = 0.013 for the WAIS-III/WISC-III; p = 0.017 for WJ-R; p = 0.013 for CPT; p = 0.017 for Stroop). Effect sizes are also reported. On subtests from the WAIS-III and WISC-III, mean scores on the Vocabulary and Digit Span subtests were not significantly different between groups. Performance was significantly different on the Block Design subtest (t = 3.479, p = 0.003; d = 1.55), with control participants scoring higher than ADHD participants. An estimated full scale IQ was calculated for each participant based on scaled scores from the Vocabulary and Block Design subtests. This two-subtest estimation has shown high reliability and correlates well with FSIQ (Strauss, Sherman & Spreen, 2006). Control participants' FSIQ

scores were significantly higher than ADHD participants (t = 2.815, p = 0.011; d = 1.24). On the WJ-R: Tests of Achievement, control participants scored significantly higher on the Letter-Word Identification (t = 4.119, p = 0.001; d = 1.89) and Dictation (t = 3.825, p = 0.001; d = 1.79), while performance approached significance (adjusted p-value of 0.0167) on the Calculation (t = 2.414, p = 0.027; d = 1.13) subtest. No significant differences in performance were found on the four scales of interest from the CPT. Qualitatively, three participants in the ADHD group and two control participants performed in the clinical range on this measure. On the Stroop Color-Word Test, ADHD participants and controls performed similarly on the Word and Color Naming subtests, while the ADHD group performed significantly worse on the Color-Word subtest (t = 3.187, p =0.005; d = 1.41).

Aim 2

Basic descriptive statistics for the total ^{1}H-MRS data are included in Table 4. For each of the four neurometabolites of interest, the mean number of voxels with usable spectra, total neurometabolite concentrations and mean standard deviations are reported. Independent samples t-tests between the ADHD group and the control group revealed no significant differences along these three measures for Cre, Glx, Cho, or NAA.

Using the regression-based estimates of neurometabolite concentrations for GM and WM tissue (Table 5), paired-samples t-tests were run for each neurometabolite (Cr, Glx, Cho, NAA) comparing the mean concentration in GM and WM tissue. These preliminary analyses were conducted to determine whether subsequent analyses should proceed with the tissue types separated or whether total neurometabolite mean concentrations should be used. The analyses were conducted independently for the

ADHD sample and the control group, thus an adjusted significance level was employed to account for the number of analyses ($p < 0.006$). For both groups, paired samples t-tests were significant ($p < 0.0001$) for Cho, Cr, and Glx, indicating differences in neurometabolite concentration across tissue types. Results for NAA approached significance in the control sample ($t = 2.616$, $p = 0.024$) but were non-significant for the ADHD group ($t = 0.533$, $p = 0.608$). For the following analyses included in Aim 2, neurometabolite concentrations in the GM and WM tissue were considered separately for Cho, Cr, and Glx, while analyses with NAA were conducted using total tissue concentration.

Two-way ANCOVAS were conducted to determine the interaction between group and sex, controlling for the continuous variable of age. Some caution is recommended when interpreting the following results, given the lack of equal distribution of sex in the ADHD sample. For GM Cr, the interaction between group and sex was not significant. The group main effect was non-significant, while the main effect of sex approached significance ($F = 3.654$, $p = 0.07$). This relationship is presented graphically in Figure 3. For WM Cr, the group by sex interaction was not significant, and there was no main effect of group or sex, although results followed a similar trend as the GM Cr analyses. The covariate of age did not significantly impact the models for GM or WM Cr. For GM Glx, the group by sex interaction and main effects of group and sex were non-significant. Age, entered into the model as a covariate, approached significance ($F = 4.428$, $p = 0.05$). A Pearson correlation was run between age and concentration of GM Glx to better characterize this relationship. A significant positive correlation was revealed ($r = 0.53$, $p = 0.14$), indicating that the concentration of GM Glx was higher in the older participants.

No significant results were found for the WM Glx ANCOVA, although a trend for a main effect of group is indicated (Figure 4). No significant results were found for the GM Cho ANCOVA, although there was a trend for a main effect of sex (Figure 5). No significant results were found for the WM Cho ANCOVA, although there was a trend for an interaction between group and sex (Figure 6). No significant results were found for the total NAA ANCOVA, although there was a trend for a main effect of sex (Figure 7). Age was not a significant factor in the GM or WM analyses for Cho or NAA.

In order to further characterize the distribution of neurometabolites in the two groups, the SI slab was divided into an anterior and posterior section. Independent samples t-tests were nonsignificant between the ADHD group and controls for Cre, Cho, and NAA across the anterior and posterior regions. The anterior t-test for Glx was non-significant, but the posterior region approached significance ($t = 2.113$, $p = 0.048$; $d = 0.93$), with lower concentrations of Glx in the ADHD group.

In order to examine the issue of within-subject variability in neurometabolite concentrations between the ADHD group and the control subjects, independent sample t-tests were run comparing means of voxel standard deviations for each neurometabolite. T-test values were non-significant for all four neurometabolites.

Aim 3

To explore the relationship between neurometabolite concentration and performance on neuropsychological measures related to attention, scores from the neuropsychological battery were z-transformed to aid in comparison of associations across measures. Three variables of interest were selected. Following procedures outlined in Yeo et al. (2003), a composite z-score from the CPT was created, incorporating three

of the primary measures of inattention (Omissions, Hit Rt SE, and Variability). Digit Span from the WAIS-III/WISC-III was selected as a measure of working memory, and the Color-Word subtest from the Stroop was selected as a measure of response inhibition and cognitive flexibility. Of note, the three measures of interest were not significantly correlated with each other for either the ADHD group or the controls.

Pearson correlations were conducted between these three measures of interest and mean concentrations in the GM and WM tissue across all four neurometabolites by group (Table 6). Given that eight correlations were conducted for each neuropsychological measure of interest, an adjusted p-value of 0.006 was selected. For the ADHD sample, none of the correlations met the stringent significance criteria. Of note, two associations approached significance. The CPT Inattention composite score was negatively correlated with GM Cr ($r = -0.722$, $p = 0.028$) and GM Glx ($r = -0.633$, $p = 0.068$). No significant associations were observed for performance on Digit Span or the Stroop Color-Word subtest. Similarly, for the control sample, none of the associations reached significance. For the CPT, the relationship between WM Glx and the CPT Inattention composite score approached significance ($r = -0.569$, $p = 0.05$). A positive association was observed between performance on the Stroop Color-Word subtest and WM NAA ($r = 0.601$, $p = 0.04$).

Aim 4

A VBM regression analysis was run entering group, sex, and age as the variables of interest. A p-value of 0.001, uncorrected for multiple comparisons, was selected, and regions of difference were required to be greater than 10 voxels in a single cluster to demonstrate a difference in gray matter tissue density. No differences in gray matter

tissue were detected based on the variables of sex and age. For the variable of group, the ADHD group demonstrated no regions of interest with greater gray matter volume than the control group. Twelve regions of interest were identified in which the ADHD participants had significantly lower gray matter volumes than controls. Descriptive information for each of the thirteen regions is provided in Table 7, including the size of each region in voxels (k_E), the t-test value, the uncorrected p-value, the MNI coordinates, and a brief description of the region. The MNI coordinates provided by SPM were converted to Talairach coordinates to determine approximate locations of the regions of interest. Figure 8 shows the regions of interest overlaid on an adult brain template. Gray matter differences were noted in the left frontal lobe (inferior frontal gyrus), left parietal lobe (precuneus and inferior parietal lobule), and left temporal lobe (inferior temporal gyrus). Right hemisphere differences were noted in the parietal lobe (inferior parietal lobule) and temporal lobe (middle temporal gyrus, superior temporal gyrus, and fusiform gyrus), as well as sub-lobar differences in the thalamus. Bilateral differences were noted in the posterior lobe of the cerebellum.

Given previous research concerning correlations with neuropsychological test performance on measures of attention and brain morphology in ADHD samples, a VBM regression analysis was run with the Stroop Color-Word subtest, the only measure of attention that differed between the control and ADHD groups. No associations between Stroop performance and brain morphology were found for the control participants. There were no positive associations between Stroop performance and brain morphology in the ADHD group. Two regions of interest were negatively associated with performance, including the middle frontal gyrus of the right frontal lobe ($k_E = 12$; $T = 9.22$, $p < 0.0001$;

MNI: 36, 20, 30) and the inferior parietal lobule of the left parietal lobe (k_E = 10; T = 7.22, p< 0.0001; MNI: -44, -40, 40). Regions of interest are presented in Figure 9.

Aim 5

Due to inadequate success of recruitment efforts, it was not possible to run analyses comparing the two groups on follow-up outcome measures. Of the nine ADHD participants who had neuroimaging from the second longitudinal time point, three agreed to participate in the follow-up study, but only two returned completed questionnaires. Of the twelve control participants with neuroimaging data from the second longitudinal time point, seven agreed to participate, and six successfully completed the follow-up study. Given the significant imbalance in groups, group comparisons were not possible. Qualitatively, the two ADHD participants who completed the CAARS received ADHD Index t-scores below the clinical cut-off. Although both participants graduated from high school, neither had completed a higher degree. One of the two was enrolled part-time in a community college. Of the six controls who completed the follow-up study, one completed a master's degree, four completed a bachelor's degree, and two were currently enrolled (one full-time, one part-time) in a university setting.

DISCUSSION

Neuropsychological Profiles of Individuals with ADHD

Global Neurocognitive Function

Although an abbreviated neuropsychological battery was administered during the second longitudinal data collection point, the selected tests provide information about the global cognitive profile of the study participants. Given the large number of tests conducted to examine this aim, adjusted p-values were used to determine significant

results. All reported significant differences on the neuropsychological measures demonstrated large effects sizes, imparting the reader with confidence that the observed differences are not due to chance. Estimated FSIQ scores for the control participants were significantly higher than the participants diagnosed with ADHD. This finding is in contrast to the initial study completed when the participants were between the ages of 7 and 12 years, which reported no significant group differences in FSIQ (Hill et al., 2003). Findings of lower FSIQ or global intelligence have been reported in some studies (i.e., Batty et al., 2010; Shaw et al., 2006), while others find no differences along this domain (i.e., Hill et al., 2003; Seidman et al., 2006).

This difference in FSIQ should be interpreted with some caution. The mean estimated FSIQ for the ADHD sample was solidly in the average range (Mean = 99.89), while the mean estimated FSIQ for the control group fell in the lower end of the superior range (Mean = 120.17). At least four of the control participants were enrolled in gifted academic programming. The current control group is not representative of cognitive abilities typically reported in the general population. An additional caveat when interpreting the FSIQ results is related to differences in participant age. Study participants took different versions of the IQ measure dependent on age. The WISC-III was administered to participants who were 15 and 16 years of age, while older participants were administered the WAIS-III. Although the two Wechsler measures are highly correlated ($r = 0.88$ for FSIQ), factors such as practice effects, subtest design differences, effects of restricted floor or ceiling, and other psychometric factors could influence performance (Tulsky, Zhu, & Prifitera, 2000). Therefore, it is possible that differences in measures administered could have resulted in an elevated discrepancy between groups.

A further analysis of subtests from the WAIS-III and WISC-III indicated that ADHD participants performed similarly to control participants on measures of expressive vocabulary. The FSIQ differences were largely driven by significant differences in performance on the Block Design subtest, which examines visual-spatial problem solving and construction skills. Deficits in visual processing and visual attention have been reported in studies of ADHD (Boles et al., 2009), and these difficulties could impact performance on the construction task. Block Design also requires some level of planning and organization, skills that are frequently impaired in subjects with ADHD (Barkley, 2006).

Academic Achievement

On measures of academic achievement, the control participants performed significantly higher on tests of single-word reading (WJ-R Letter Word Identification) and complex sentence writing (WJ-R Dictation) in comparison to the ADHD participants. Although differences in performance in the area of calculation only approached significance, a large effect size was calculated, suggesting that the ADHD participants were significantly delayed in academic achievement in mathematics, as well as reading and written language. Findings regarding discrepancies in academic performance are congruent with findings from the initial data collection point of this study (Hill et al., 2003), as well as broader findings in the ADHD literature (Barkley, 2006).

Academic results are of particular clinical relevance. All participants were screened for learning disorders as part of the initial recruitment process. Despite this initial precaution, individuals in the ADHD group are significantly delayed in academic achievement in comparison to the control sample. This speaks to the impact that

symptoms of ADHD can have on academic achievement, which potentially influences measures of functional outcome, including years of completed schooling and SES status in adulthood (Able et al., 2007; Barkley, 2006; Barkley et al., 2006; Biederman et al., 2010).

Working Memory, Sustained Attention, and Cognitive Flexibility

In order to further assess cognitive skills directly impacted by difficulties with attention and hyperactivity, all participants completed measures of working memory, sustained visual attention, brief visual attention, and cognitive flexibility. Deficits in verbal working memory are often considered a core component of an ADHD neuropsychological profile (Barkley, 2006). It was hypothesized that the ADHD participants would demonstrate lower scores on the WISC-III/WAIS-III Digit Span subtest. Contrary to expectations, no significant differences in performance were observed on this measure of auditory working memory.

Hypotheses concerning performance on measures of sustained attention were also disconfirmed. Three variables from the CPT were selected to examine inattention (Omissions, Hit RT SE, and Variability). A fourth variable of interest was selected to examine impulsive responding (Commissions), as current ADHD participants continued to demonstrated significant hyperactivity and impulsiveness based on parent ratings of behavior. These measures were felt to be the best representations of performance on the CPT, as scores on the Hit RT SE and Commission scales have been shown to discriminate between ADHD participants and controls in subjects ages 6 to 17 years, while the Omission scale was the most discriminative factor for subjects 18 years and older (Strauss et al., 2006).

Performance by the ADHD group and controls was similar across all four scales of the CPT. Means for both groups along all four measures fell in the average range, indicating no significant clinical impairment. This is a significant contrast to findings involving the larger sample at the initial data collection point when participants were between the ages of 7 and 12 years old (Hill et al., 2003; Yeo et al., 2003). At the initial data collection point, Hill et al. reported a significant main effect of group, with participants in the ADHD group demonstrating poorer sustained attention. Yeo et al. (2003) reported three variables of interest from the CPT, noting a significant group difference on the indices of Variability and Omissions, with ADHD participants performing significantly worse, but no group difference was observed on the Hit RT SE scale. Overall, the means reported during the first data collection point (collected 7 to 10 years prior) were significantly higher than the current findings, with higher scores indicating greater impairment (for the ADHD group and control group respectively: Variability M = 63.04, SD = 7.98 vs. M = 56.12, SD = 11.95; Omissions M = 87.80, SD = 13.88 vs. M = 76.03, SD = 23.84; Hit RT SE M = 60.0, SD = 10.55 vs. M = 59.67, SD = 14.39). The present findings may be indicative of age-related improvements of self monitoring and maintenance of attentional control during boring tasks, as both the ADHD group and control group means were higher (more impaired) when the participants were younger. These higher order skills which are necessary for performance on tasks of sustained attention are still developing in early adolescence, but are likely to be more advanced by late adolescence and early adulthood.

Qualitatively, on the CPT, three of the nine participants in the ADHD group received a Confidence Index score in the clinical range, indicating that their pattern of

performance more closely matched a clinical sample. Two of the twelve control participants also received clinically significant Confidence Index scores, with one of these controls presenting as a significant outlier on this measure (i.e., receiving the highest Confidence Index Percentile score of the total sample, including the ADHD participants). Given the extreme discrepancy in this subject's scores, CPT analyses were also conducted removing this subject, but no changes in results were observed. A follow-up review of prior test performance indicated that during the initial study, both control participants in question performed in the normal range on this measure. Although their pattern of performance more closely matched the ADHD normative sample, it is unlikely that their clinical performance is indicative of a diagnosis of ADHD. Other factors, including poor effort or symptoms of depression and anxiety, can impact performance on measures of sustained attention. Thus, their performance likely indicates typical variability in measures of sustained attention in non-clinical samples.

A final measure of selective attention and cognitive flexibility (Strauss et al., 2006) was administered. On the two initial subtests of the Stroop, group differences did not reach significance, although the Word Naming subtest approached significance. The Word Naming and Color Naming subtests are thought to be somewhat automatic tasks, although slow processing speed will negatively impact performance (Strauss et al., 2006). Deficits in processing speed have been reported in studies of ADHD (i.e., Depue et al., 2010), so it is possible that the reduction in scores on Word Reading is related to this cognitive domain. However, given the reported academic difficulties in single-word reading skills in the ADHD group, word naming, even for familiar words, may be more cognitively labor intensive. The ADHD sample performed significantly worse than the

control group on the Color-Word task, which requires response inhibition (i.e., inhibiting the automatic response of reading the printed word in order to produce the requested response of saying the color of the ink). Increased interference in Stroop performance has been frequently reported in studies of executive function in ADHD samples (Strauss et al., 2006). However, IQ has also been found to correlate highly with performance on the Stroop Color-Word subtest (Strauss et al., 2006). It is possible that the observed difference on this measure is related to the significant differences between the two groups on estimated FSIQ.

One of the difficulties in the neuropsychological literature on ADHD is the failure for consistent diagnosis based on neurocognitive test performance. Despite Barkley's (2006) assertion that clearly defined categories of deficits are observable in individuals diagnosed with ADHD, the research does not consistently support this assertion. For example, executive function difficulties are theorized to be an underlying cause of the behavioral symptoms of ADHD, but meta-analytic approaches fail to differentiate individuals diagnosed with ADHD from controls based solely on performance on measures of executive function (Willcutt et al., 2005). Although there are many researchers in the field who would like to create an objective diagnostic test battery, the heterogeneity of ADHD cognitive profiles forces the field to continue to rely solely on behavioral ratings from multiple respondents for diagnosis.

For many years, researchers have proposed that our current classification of individuals diagnosed with ADHD may be too simplistic. Some researchers suggest that although the hyperactive and inattentive types of ADHD are housed under a broad diagnostic category, these subtypes may even represent neurobiologically distinct

disorders (Diamond, 2005). More recent research has incorporated a neurospcyhological profiling approach to gain a better understanding of the heterogeneity of ADHD (Fair et al., 2012). Fair et al. examined neuropsychological test performance on 20 different measures of cognitive functions in a large sample of control participants and participants diagnosed with ADHD. Using graph theory, a mathematical approach that involves the study of networks, they were able to empirically derive four unique patterns of neuropsychological test performance in the ADHD sample, with different groups showing impairment in response variability (subgroup 1), working memory, inhibition, and output speed (subgroup 2), accuracy of temporal information processing (subgroup 3), or signal detection suggestive of altered arousal needs (subgroup 4). Of particular interest, control participants also fit into these four performance profiles with less clinically significant impairment observed in the areas of interest. This is important as it speaks to the developmental nature of ADHD, suggesting that the problematic neuropsychological sequelae of the disorder may simply be extreme variations of cognitive profiles that exist in the general population (Fair et al., 2012).

Unfortunately, the abbreviated neuropsychological battery administered and the small sample size included in the present study eliminated the possibility of examining subtypes of neuropsychological performance. However, this could help to explain why significant differences in performance on measures of working memory and sustained attention were not discovered. Potential heterogeneity in both the ADHD group and control group could obscure a larger effect of group enrollment. This will be an important area of study, with particular interest in expanding this type of sub-classification to

longitudinal investigations of neuropsychological performance and report of symptoms of inattention and hyperactivity.

A Preliminary Exploration of Gray and White Matter Neurometabolites

Similar to the single voxel spectroscopy findings reported by Yeo et al. (2003), group differences were not detected in total neurometabolite concentration for Cre, Glx, Cho, or NAA across the spectroscopic region of interest. The total concentration analyses represent an examination of combined concentrations in the gray and white matter brain tissue, so there was interest in performing a more nuanced analysis to determine if separation of neurometabolite concentrations across tissue type could reveal group differences in brain chemistry. Given frequently reported differences in gray matter volume, it was hypothesized that more significant gray matter differences would be detected. However, there was also interest in white matter connections. Attention and executive function are rather distributed cognitive functions which incorporate multiple brain regions through networks of white matter tracts. For this reason, there was interest in comparing neurometabolite concentrations in both brain tissue types. Based on interactions reported by Yeo et al. (2003), there was interest in exploring the impact of sex in the context of group membership. Although the ADHD and control groups did not differ significantly along the variable of age, age was entered into the analyses as a covariate. Brain development and cortical thinning continues into late adolescence (Shaw et al., 2008), so there was interest in exploring the potential influence of age on neurometabolite concentration.

Due to the small sample size, the following results are presented with some caution. Significant findings were not found, but trends in the data are reported. The

small sample size significantly limited the power of the current analyses to detect clinically relevant group differences. Similar to previously reported findings of gray and white matter tissue (Wiedermann et al., 2010), concentration of Cr was significantly higher in gray matter than white matter for both the ADHD participants and controls. For gray matter and white matter Cr, there was a trend for the influence of sex, with females demonstrating lower concentrations of Cr than males. Age and group were not significantly related to Cr. Sex differences in neurometabolite concentrations are not well understood, given that most studies fail to explore sex as a significant factor or lack the power to detect differences in sex or interactions related to sex (Jung et al., 2009). The limited literature base on sex specific neurometabolite profiles makes it difficult to place the finding of lower Cr concentrations in the female subjects.

For the ADHD group and controls, Glx concentration was significantly higher in the gray matter tissue than in the white matter tissue, similar to previous findings (Wiedermann et al., 2010). Group and sex were not significantly related to gray matter Glx concentrations, although there was a positive correlation between gray matter Glx and age. Older participants demonstrated higher concentrations of gray matter Glx. Age and sex were not related to white matter Glx, but a trend for group was discovered, with the ADHD participants demonstrating lower mean concentrations of white matter Glx. This is in contrast to most reported single voxel studies which report elevated Glx in ADHD participants (Carrey et al., 2007; Ferreira et al., 2009; Moore et al., 2006). One study identified that subjects diagnosed with combined-type ADHD demonstrated higher Glx/Cr in the right ventromedial prefrontal cortex (Ferreira et al., 2009). This elevation was not observed in participants diagnosed with inattentive-type ADHD. Although the

current sample could not be accurately coded by sub-type, it is expected that at their present ages (between 15 years and 23 years of age), more inattentive symptoms were present than hyperactive symptoms. This reduction in Glx could potentially be an artifact of comparisons with studies of younger, more hyperactive subjects. Additionally, it is possible that an elevation of Glx in a particular region of interest could be masked by averaging neurometabolite concentrations across the SI slab.

Concentration of white matter Cho was significantly greater than concentration of gray matter Cho for controls and ADHD participants, similar to previous findings in a typical adult sample (Wiedermann et al., 2001). A trend of sex was identified for gray matter Cho, with female participants demonstrating lower mean concentrations. For white matter Cho, a trend for a group by sex interaction was identified. Male and female ADHD participants demonstrated lower mean concentrations of white matter Cho. Most studies reporting difference in Cho concentrations in ADHD samples indicate that there are elevations when compared to controls (Ferreira et al., 2009; Colla et al., 2008). However, it should be noted that the regions of interest in these single voxel studies were largely gray matter tissue. Additionally, reduced Cho/NAA ratios have been reported in adults with dyslexia, localizing to the left temporal lobe and right cerebellum (Rae et al, 1998). Although the current sample would not meet full criteria for a diagnosis of a specific reading disorder, the ADHD group demonstrated significant delay in academic achievement in reading. It is possible that the reductions in Cho could be indicative of developmental learning problems, rather than symptoms of ADHD. For the control participants, female participants demonstrated higher levels of white matter Cho than the males.

One potential caveat regarding the current neurometabolite findings involves the history of medication use in the current sample. Qualitatively, only two of the nine participants (22%) in the ADHD group continued to take stimulant medications at the second longitudinal time point. At the time of the first longitudinal data collection when the children were between the ages of 7 and 12 years, 74% were prescribed stimulant medication (Yeo et al., 2003). Although the present sample represents only a subset of the original study, this suggests that there was a significant reduction in reliance on stimulant medication for the control of ADHD symptoms by late adolescence and early young adulthood in the present sample. 89% of the participants included in the current study had completed trials of stimulant medication in the past.

Recent single voxel spectroscopy studies have indicated that stimulant medications may alter neurometabolite concentrations. For example, Carrey et al. (2007) demonstrated a reduction in Cr concentration in the left striatum of ADHD participants following an eight-week course of methylphenidate. Following treatment, the ADHD participants Cr levels appeared to match that of controls, although elevations in Glx remained significant. Unfortunately, additional follow-up data is not supplied to indicate whether the reported Cr reduction maintained over time or if Cr levels returned to baseline elevation after medication use discontinued. In order to better understand the impact of stimulant medication on neurometabolite concentrations, additional longitudinal studies are necessary. Although this hypothesis could not be tested in the current study due to small sample size, some group differences may have been obscured due to prior or current use of medications for symptom remediation.

Significant differences in neurometabolite concentrations across the gray and white matter tissue were not observed for NAA, therefore, total NAA concentration was used to explore group differences. In a study of typical differences in gray and white matter concentrations through a multi-slice technique, regional differences in NAA concentration were found, indicating lower NAA in the frontal gray matter when compared to frontal white matter and parietal gray matter (Wiedermann et al., 2010). Given the regionally specific findings suggested for NAA concentrations, the current slab technique may obscure differences in white matter and gray matter levels of NAA. Although there was not a significant effect of group, there was a trend for a main effect of sex, with female participants in both groups demonstrating higher mean concentrations of NAA. Previous research implicated a group by sex interaction for NAA, with females diagnosed with ADHD demonstrating a substantial reduction in NAA concentration (Yeo et al., 2003). Given the imbalance in sex distribution in the ADHD group, an interaction effect could be obscured. Similar to the Yeo et al. (2003) study, female participants demonstrated higher NAA concentrations. This increase in NAA was proposed to be a typical variant of development that occurs in early childhood. The present findings indicate that higher concentrations of NAA in controls are consistent over time. Additional research on sex differences in neurometabolite concentrations in typically developing samples is necessary to better characterize and explain this difference.

Due to the significant discrepancy in estimated FSIQ between the ADHD group and the controls, there was interest in determining whether spectroscopic imaging findings might be related to differences in intelligence rather than group classification. Jung et al. (2009) explored correlations between intelligence and neurometabolite

concentration in a healthy sample of adults using a similar ^{1}H-MRS protocol. Their findings, consistent with other reports in the literature, indicated that NAA was most strongly related to intelligence. Specifically, they found that lower NAA in the right anterior gray matter was predictive of better performance on measures of verbal intelligence, while visual-spatial/performance-based intelligence was associated with increased NAA in right posterior gray matter (Jung et al., 2009). If intelligence was the most important factor influencing the current spectroscopy results, it would be anticipated that significant differences in gray matter NAA concentrations might be detected. The lack of significant NAA findings suggests that trends towards group differences can more confidently attributed to differences in group membership (i.e., ADHD vs. control) or sex.

Neurometabolite Concentrations in Anterior and Posterior Brain Regions

Right frontal abnormalities in single voxel studies of ADHD are commonly reported (i.e., MacMaster et al., 2003; Yang et al., 2010). There was interest in conducting a preliminary analysis with the current sample to determine whether the ADHD group differed from controls in neurometabolite concentrations in the anterior portion of the brain. Due to the small sample size, there was not power to run a more nuanced segmentation of the SI slab by region. Additionally, the anterior-posterior analyses were run with total neurometabolite concentrations rather than tissue-specific regression estimates. It was felt that insufficient voxels were available to run the necessary regression analyses to distinguish differences in gray and white matter concentrations in these two halves of the SI slab.

Contrary to the study hypothesis which anticipated abnormalities in anterior neurometabolite concentrations, the ADHD group appeared remarkably similar to the control group in for all four neurometabolite concentrations in the anterior region. Given that single voxel studies examine neurometabolites in a smaller, more region specific voxel of interest typically placed in the right frontal region, the anterior slab may have been too widely distributed for regional differences in neurometabolite concentrations to be detected. Significant differences in posterior concentrations were not observed between groups for Cre, Cho, or NAA. Posterior Glx concentrations approached significance, with the ADHD sample demonstrating lower total Glx concentration in the posterior region of the SI slab. Although the anterior/posterior analyses could not differentiate between gray and white matter tissue, analyses across the entire SI slab indicated a trend for reduced white matter Glx. It is of interest that no differences were noted in anterior Glx. The elevations in Glx that have been previously reported in the literature focus on frontal regions, including the frontal-striatal circuit (MacMaster et al., 2003) and the bilateral frontal lobes (Courvoisie et al., 2004), as well as the cerebellum (Perlov et al., 2010). It appears that the reductions in Glx in the current study seem to localize to the posterior portion of the brain.

Variability and Quality of ^{1}H-MRS Findings

Based on previous findings (i.e., Yeo et al., 2003), it was anticipated that the ADHD sample would demonstrate poorer quality spectroscopic results, indicated by greater variability in neurometabolite concentrations and reductions in the number of voxels available for analysis. This hypothesis was not supported. The control sample and the ADHD sample had remarkably similar standard deviations in concentration across all

four neurometabolites of interest, and no significant differences in usable spectra by voxel were identified. The lack of difference in data quality between groups in the present study suggests that the late adolescent/early adult ADHD participants were able to manage the MRI environment with less hyperactivity than during the initial imaging data collection when they were significantly younger.

Neurometabolites and Neuropsychological Test Performance

In order to characterize the relationship between neurometabolite concentrations and neuropsychological measures related to attention, three neuropsychological measures were selected, a composite score related to sustained attention from the CPT, working memory from the WAIS-III/WISC-III, and a measure of response inhibition and cognitive flexibility from the Stroop. These three variables have been proposed as core components of executive function relevant in individuals diagnosed with ADHD (Barkley, 2006). Although significant group differences were not found for the current sample on the measures of sustained attention and working memory, there was interest in seeing if within group variability might be related to neurometabolite concentration. The three neurocognitive measures were not significantly correlated, suggesting that three separate constructs of attention and executive function were measured. Given the large number of tests run for this aim and stringent correction criteria, no significant findings were discovered. However, several trends for control participants and ADHD participants are discussed below.

It was anticipated that no significant correlations between neurometabolite concentrations and neuropsychological performance would be found for the control subjects. Previous studies have failed to find associations between typically developing

children and adolescents and measures of attention (Yeo et al., 2003). However, two trends were identified in the current sample. Control performance on the composite measure of sustained attention from the CPT was negatively related with white matter Glx concentration. This is of some interest, given that two control participants performed qualitatively in a similar fashion to the normative ADHD sample on the CPT. Previous research has indicated elevations in Glx in ADHD samples. This correlation between increasing Glx concentrations and poor performance on a sustained attention task may provide further evidence that Glx is involved in attentional control.

Performance on the Stroop Color-Word subtest was positively correlated with white matter NAA concentration. Although NAA is commonly discussed in the literature as an indicator of neuronal dysfunction (Maudsley, 2002) and elevations are noted in populations such as TBI or multiple sclerosis where neuronal recovery is taking place, recent research implicates increased NAA in healthy samples may be positively correlated with intelligence (Jung et al., 2009). Specifically, NAA concentrations in the right posterior region of the brain have been found to positively correlate with performance-based IQ. PIQ on the Wechsler subscales involves visual problem solving and flexible thinking. Given that the Stroop Color-Word subtest also requires higher order executive skills, the trend for a positive relationship with NAA makes sense in this context.

For the ADHD sample, two different trends were identified. Performance on the sustained attention composite from the CPT was negatively correlated with gray matter Cr and gray matter Glx concentrations. As concentration of Cr and Glx in the gray matter increased, performance was worse on the sustained attention task. Yeo et al. (2003) found

that CPT performance was negatively related to right frontal concentrations of Cr and NAA. An additional study also cited an inverse relationship between Cr concentration and performance on measures of attention (Courvoisie et al., 2004). In control populations, increased neurometabolite concentrations typically predict improved performance. The significance of the current findings is unclear, although our study provides further support for the negative relationship between gray matter Cr and sustained attention in individuals diagnosed with ADHD. Yeo et al. (2003) suggested that a proxy variable, such as volume of the right dorsolateral prefrontal cortex, may explain this relationship. Because the current findings involve a larger section of brain tissue, it may speak to a network of brain regions rather than a specific neuroanatomical site. No significant associations were observed for performance on the working memory or response inhibition measures.

Morphological Differences in Gray Matter Volume

Contrary to expectations, reductions in right frontal gray matter volume were not observed between the ADHD sample and controls. This is particularly surprising given previous findings from the initial study, which indicated significantly smaller average superior prefrontal volumes in the ADHD group (Hill et al., 2003). Left superior prefrontal regions were not significantly different in the initial study (Hill et al., 2003; Yeo et al., 2003), but in the present study, the left inferior frontal gyrus was identified as a region of reduced gray matter volume in the ADHD sample. The right inferior frontal gyrus has been commonly cited as a region of reduced gray matter volume in ADHD samples (Batty et al., 2010; Depue et al., 2010), with correlates of this reduction associated with poor performance on measures of processing speed, response inhibition,

and response variability (Depue et al., 2010). It is possible that the grain of analysis chosen in the current VBM analysis obscured subtle, more diffuse differences in right frontal region.

The left inferior frontal gyrus, commonly referred to as Broca's area, is commonly associated with language production and fluency, phonology, and comprehension (Fieze, 1997). There is also limited evidence for left inferior frontal cortex involvement in inhibitory mechanisms related to working memory (Aron, Robbins, & Poldrack, 2004). Current results from the chosen neuropsychological battery cannot be used to corroborate this morphological finding. Performance on the only measure of expressive language administered did not differ between the two groups, and a measure of verbal fluency or comprehension was not administered. It would be of interest to do further research exploring the role of the left inferior frontal gyrus in working memory, as this could be a relevant link to language-based deficits observed in some individuals diagnosed with ADHD. Some caution is recommended regarding this morphological finding, as this region is not commonly reported in VBM studies of ADHD.

Right hemisphere reductions in gray matter were noted in inferior parietal lobule. fMRI studies have indicated that the inferior parietal lobule is activated during tasks of mental arithmetic and mathematical calculation (Arsalidou & Taylor, 2011). This is of interest given the trend of poorer performance by the ADHD group on a measure of mathematical achievement. Additionally, a study of adults diagnosed with ADHD found significant cortical thinning in the inferior parietal lobule, which they hypothesized plays

a role in the cortical networks modulating attention and executive function (Makris et al., 2007).

Bilateral reductions in the temporal lobe were found in the ADHD group, including reduced volume in the left inferior temporal gyrus and the right middle temporal gyrus, superior temporal gyrus, and fusiform gyrus. Temporal lobe gray matter reductions have been reported in previous studies (Castellanos et al., 20002), with the most significant reductions in the right superior temporal and medial temporal gyri (Kobel et al., 2010). Additionally, reductions in gray matter temporal volume have been associated with impaired inhibitory control in individuals diagnosed with ADHD (McAlonan et al., 2009). The temporal lobe has been hypothesized to play multiple roles in the attention network. In addition to a specific role in response inhibition, some research supports its involvement in increasing focus and selective attention when an individual is the presence of distracting stimuli (Mirsky & Duncan, 2001). The temporal lobe is integral to processes of attention and executive function. It is not surprising that this region showed significant gray matter reduction in the ADHD sample.

A right-sided reduction in the thalamus was implicated in the current VBM analysis. The thalamus is a sub-cortical gray matter structure that acts as a relay station for motor and sensory signals traveling to the cortex. Volumetric differences in the thalamus are not frequently reported in studies of ADHD, although one study demonstrated reduced pulvinar volumes, the most posterior region of the thalamus (Ivanov et al., 2010). Perhaps the most interesting finding from their study of the thalamus indicated that individuals diagnosed with ADHD and treated with stimulant medications demonstrated enlargement in the pulvinar region when compared to

unmedicated ADHD participants. Unfortunately, the current methods of analysis do not allow for regional specification of the gray matter reduction within the thalamus. Qualitatively, only two of the ADHD participants were taking stimulant medication at the time of data collection (22%). Although other studies of ADHD have failed to find differences in thalamic volumes, they typically report a much higher percentage of medication responders. Thus, the present sample may demonstrate some differences in brain morphology related to current medication status.

Consistent with Hill et al. (2003) and other studies of ADHD brain morphology, reductions in cerebellum volume were identified. Cerebellar volume reductions are one of the most commonly reported abnormalities in samples of ADHD participants (i.e., Castellanos et al., 2002; Monteaux et al., 2008). Specifically, in the current sample, bilateral reductions in the posterior lobe of the cerebellum were identified. Through visual examination of the regions of interest and comparison of MNI coordinates with studies of cerebellar anatomy, the bilateral gray matter cerebellar reductions are consistent with the Crus I region of the posterior lobe. Although early research on the function of the cerebellum focused on motor sequencing and coordination, recent studies suggest that the cerebellum plays an important role in higher order functioning. Specifically, the Crus I region of the posterior lobe has been implicated in language, verbal working memory, spatial processing, and executive function (Stoodley & Schmahmann, 2009).

Reductions in Gray Matter Volume Associated with Neuropsychological Performance

Given that only one neuropsychological measure of inattention and executive function discriminated between the ADHD and control groups, there was interest in

exploring whether morphological brain differences correlated with performance on the Stroop Color-Word subtest. Functional neuroimaging and studies of electrophysiological activation during the Stroop task frequently implicate the right frontal region (i.e., Brown et al., 1999; Mead et al., 2002), although inferior temporal and parietal cortices are also activated in healthy adults (Peterson et al., 2002). Similar to prior studies of correlations between neuropsychological performance and VBM gray matter volumes (i.e., Yeo et al., 2003), no significant positive or negative correlations were found between the control group's performance on the Stroop and brain morphology. For the ADHD group, two regions were negatively associated with performance on the Stroop, including the right middle frontal gyrus and the left inferior parietal lobule.

Interestingly, recent work examining the attention control network implicates the left intraparietal sulcus, which separates the left inferior parietal lobule from the superior parietal lobule (Anderson, Ferguson, Lopez-Larson, & Todd, 2010). The attention control network is proposed as a series of brain regions that show reliable, reproducible connectivity during tasks of effortful attentional control (Anderson et al., 2010). Reductions in the gray matter of the left inferior parietal lobule could result in dysfunction to the attention control network, providing further support for the correlation between Stroop performance and this region.

Due to the lack of significant findings regarding group differences in neurometabolite concentrations, additional analyses correlating brain morphology with neurometabolite concentrations were not conducted for the present study. If larger studies can confirm the trends reported in neurometabolite concentrations in the present study, it

will be interesting to explore correlates of gray matter reduction by diagnostic category (ADHD or typically development) and sex.

Lack of Response on Measures of Functional Outcome

The initial goal of the current study was to begin an exploration of the relationship between measures of functional outcome and brain chemistry. Given the reports that many children and adolescents "outgrow" their diagnosis of ADHD, it was hoped that examining patterns of neurometabolite concentrations might provide some initial insight into differences in developmental trajectories in this disorder. Unfortunately, the logistics of conducting the third longitudinal data collection limited the ability of the study to compare outcome measures with the neuroimaging variables.

Despite extensive efforts at recruitment and accommodating modes of data collection (i.e., not requiring an in person visit and providing participants with the option of completing questionnaires by mail or online), few of the 21 participants completed the required study protocol. Additionally, a strong bias was present in the completed sample, in that 6 of the control participants consented and completed questionnaires, but only 2 of the ADHD group followed through with study participation. There was also a significant gender bias, with females being twice as likely to respond and follow through with study procedures.

The third phase of data collection was proposed several years after the participants completed the second longitudinal study. Study participants were unaware that they might be contacted in the future. Additionally, the majority of participants were living with their parents at the time of the first and second phases of data collection. Now that all participants are young adults, it is possible that they may not have received study

recruitment materials. From the initial batch of mailed letters detailing the study information, five letters were returned due to insufficient or incorrect address. Additional searches were completed to ensure an updated and correct address for parents of the study participants, and none of the second batch of letters was returned. It is felt that most participants' parents received information regarding the study by mail. Unfortunately, given the shift in technology to reliance on cellular phones, many of the telephone numbers on file were incorrect and current phone directories did not include updated numbers for most participants. The lack of consistent telephone contact with participants negatively impacted recruitment.

In future studies, it will be of key importance to plan a number of longitudinal follow-up points prior to subject recruitment. If consent for all time points is obtained initially, subjects will have a better understanding of their commitment and more invested in follow-up participation. Additionally, this type of system would encourage frequent contact with participants between data collection points, to ensure that contact information remains current.

Due to the poor overall response rate, particularly in the ADHD group, empirical comparison along measures of functional outcome is not possible. Qualitatively, two characteristics are noted, as they fit with findings commonly reported in the literature. First, the two participants diagnosed with ADHD completed a self-report measure of symptoms of inattention and hyperactivity. Although it would be ideal to have an objective observer, both individuals reported few symptoms, and their overall score on the ADHD index fell in the non-clinical range. This is consistent with findings that a large number of individuals diagnosed with ADHD outgrow symptoms of inattention and

hyperactivity when they reach late adolescence and young adulthood (Spencer et al., 2007). In addition to findings regarding symptom amelioration, there was interest in a preliminary investigation regarding level of academic achievement. For the two individuals diagnosed with ADHD, both graduated from high school, but neither received a higher degree. One participant is currently enrolled part-time at a local community college. The six control participants were much more likely to have completed a higher degree, with one subject obtaining a master's degree and four completing bachelor degrees. The two remaining control participants were enrolled at a local university. Although this qualitative analysis is preliminary in nature, it suggests that the current sample of participants demonstrate a trend commonly reported in the literature on ADHD outcomes. Individuals with ADHD are less likely to seek higher education opportunities, resulting in lower salaries (i.e., Able et al., 2007; Barkley, 2006) and more problematic performance and success in the work environment (Biederman, 2009). These preliminary characteristics emphasize the importance of continued research on functional outcomes. Despite self-report of symptom reduction and impairment, the residual impact of ADHD can have far reaching effects.

CONCLUSION

The body of literature on ADHD is vast, and interest in the neurobiological correlates, neuropsychological profiles, and functional outcomes related to the diagnosis have instigated a resurgence of studies in recent years. Unfortunately, there is a paucity of longitudinal studies that follow the development of children and adolescents into young adulthood. Given reports of lower prevalence rates in adult samples but persistent impairment in quality of life and achievement, this transition from adolescence to

adulthood is of particular clinical significance. The present study hoped to provide additional information about this transition, by correlating functional outcome measures in young adulthood with imaging findings from late adolescence. Unfortunately, given the lack of available outcome data, this aim was not completed. This speaks to an important area of future research. It is imperative that researchers in the ADHD field attempt to complete longitudinal studies of ADHD, following participants from early development into adulthood, rather than simply comparing across groups. This type of within subject design could shed light on the changes that occur and the factors that differentiate individuals who "outgrow" their diagnosis of ADHD from those who have persistent difficulties related to inattention in adulthood.

Many of the current study findings concerning brain morphology and neuropsychological test performance were anticipated based on previous research. In the present sample, neuropsychological test results indicated that individuals diagnosed with ADHD demonstrated lower estimated global intelligence, poorer visual-spatial construction and problem solving, lower academic achievement in reading, written language, and mathematics, as well as difficulties with response inhibition and cognitive flexibility. Contrary to expectations, sustained attention and working memory were not impaired. Morphological analyses indicated that the ADHD subjects had reduced gray matter in commonly reported areas, including sections of the parietal lobe, temporal lobe, the thalamus, and the cerebellum. Contrary to expectations, differences in right frontal morphology were not identified. In fact there was a reduction in the left inferior frontal gyrus, a region typically associated with language deficits. Despite the lack of group differences in gray matter volume in the right frontal lobe, poor performance on the

Stroop task was predicted in the ADHD group by decreased gray matter volume in the right middle frontal gyrus and the left inferior parietal lobule, two regions frequently associated with response inhibition and cognitive control.

Spectroscopic imaging findings are preliminary, as only trends could be identified with the small sample size. The results suggest that there are patterns of differences in individuals diagnosed with ADHD, as well as potential sex differences and group by sex interactions that warrant further study. Differential correlations between performance on measures of sustained attention and cognitive flexibility were also identified in the ADHD sample and the control group.

The primary advantage of employing a spectroscopic imaging technique is the ability to quantify spectra over a broad region of brain tissue. However, for the current disorder of interest, regional studies may be more relevant. By localizing single voxels of regions of previously identified interest, previous researchers have been able to draw more substantial conclusions regarding differences between controls and individuals diagnosed with ADHD. With a larger sample, the SI slab could be segmented into different regions which could be an ideal combination of the two techniques. Jung et al. (2009) proposed a method for splitting an SI slab, similar to the one employed in the current study, into 8 separate regions, allowing for an interesting analysis of regional correlates of intelligence and creativity. Future SI studies of ADHD should incorporate this methodology.

Through attempts to place the current findings in available literature, it was discovered that there is a dearth of research on neurometabolite concentrations in typically developing population. The majority of studies examine disease populations,

including multiple sclerosis, TBI, epilepsy, autism, and ADHD. Recently, there has been some interest in exploring neurometabolite concentrations in normal aging populations, as well as correlating ^{1}H-MRS findings with factors such as intelligence (Jung et al., 2009) and creativity (Jung et al., 2009b). Few studies of typically developing populations or diseases have the power to explore the role or impact of sex on brain chemistry. By collapsing results across sex, studies may be obscuring interesting and clinically relevant group differences and interactions. Future studies should attempt to obtain large enough sample sizes to gain a better understanding of sex related differences, particularly in ADHD populations where trends towards group by sex interactions are frequently reported (Yeo et al., 2003).

Given inconsistent findings regarding performance on various measures of executive function and attention, there is growing interest in exploring patterns of neuropsychological performance (Fair et al., 2012). These proposed subtypes could help to explain discrepancies in the neuroimaging literature on ADHD, particularly regarding findings from studies of magnetic resonance spectroscopy. Preliminary ^{1}H-MRS research shows support for differences in neurometabolite concentrations across ADHD subtypes (Ferreira et al., 2009). Additionally, there is evidence that medication may impact brain chemistry, yielding neurometabolite concentrations that appear more closely matched to control samples (Carrey et al., 2007). By employing the categorization system proposed by Fair et al. (2012) with a magnetic resonance protocol, control participants and participants diagnosed with ADHD could be classified based on patterns of cognitive strengths and weaknesses. By differentiating both groups into these subtypes, important information regarding neurometabolite differences related to various components of

attention and executive function could be uncovered. Additionally, this would strengthen the possibility of discovering group differences, as current studies, including the present study, may obscure differences in brain chemistry due to reliance on heterogeneous, simplistic methods of group classification.

With new advances in technology, it is possible to conduct functional spectroscopic imaging studies. Currently, all reported findings in the ADHD literature are reported for resting state single voxel studies. This is the first study to explore resting state spectroscopic imaging across a slab of gray and white matter tissue, although one prior study used resting state spectroscopic imaging to examine neurometabolite concentrations across a slab of cerebellar tissue. It has been proposed that neurometabolite concentrations may be altered during cognitive activation, including visual or auditory stimulation and language activation (Richards, Dager, & Posse, 1998), so future studies exploring neurometabolite abnormalities could be strengthened by employing functional MRS techniques. It would be of great interest to choose measures of sustained attention or response inhibition to explore differences from resting state to cognitive activation in individuals diagnosed with ADHD.

LIMITATIONS

Sample Characteristics

Prior to beginning exploration of the proposed aims, it was important to demonstrate that the participants diagnosed with ADHD could be distinguished from the control group on measures of inattention and hyperactivity/impulsivity. During the second longitudinal time point, which is the primary data collection phase reported in the current study, only ten of the 21 participants were 17 years of age or younger. A limited

number of parents were available to provide an objective rating of behavior. To better characterize the entire sample, behavioral rating data from the initial study is provided. As anticipated, parents of the ADHD participants reported that their children demonstrated significantly more impulsive and hyperactive behaviors on the CPRS than parents of control children. The original version of the CPRS did not provide a subscale that specifically addressed symptoms of inattention. A basic symptom count from the CSI indicated that symptoms of inattention were also more frequently rated for children in the ADHD sample. Parents of the ADHD participants also reported significant learning problems on the CPRS in comparison to parents of the controls. Children who qualified for a diagnosis of a specific learning disorder were excluded from the study sample, so the reported learning difficulties are likely related to symptoms of inattention and hyperactivity resulting in difficulties functioning in the academic environment. This is commensurate with findings in the broader ADHD literature that commonly indicates lower levels of academic achievement in children, adolescents, and young adults with ADHD (i.e., Barkley, 2006; Barkley et al., 2006, Biederman et al., 2010), and it fits with performance on measures of academic achievement administered in the current study. The ADHD group and the control group were rated similarly in the areas of conduct problems and anxiety.

An additional reason for investigating initial parent ratings of symptoms was for the purpose of subtype classification for the participants diagnosed with ADHD. At the time of the initial study, children were classified as either Predominantly Hyperactive-Impulsive or Predominantly Inattentive type according to DSM-IV criteria. By reviewing parent ratings on the CSI, it was hoped that children could be classified into the three

subtypes (Combined Type, Predominantly Hyperactive-Impulsive, or Predominantly Inattentive), as the Combined Type is more commonly diagnosed and more prevalent (APA, 2000). Several parents completed the CSI rating their child's behavior while on stimulant medication, thus the overall symptom count fell below the clinical cut-off. Subtype reclassification could not be completed using this method. Given the small sample size, analyses comparing individuals by subtype diagnosis would not be possible, so the current ADHD sample is considered to be somewhat heterogeneous, displaying a combination of inattentive, hyperactive, and impulsive symptoms based on parent-report during middle childhood.

Analysis of parent behavioral ratings at the second longitudinal data collection point revealed a similar trend in the participants between ages 15 and 17 years (ADHD n = 6, Control n = 4)). The ADHD participants demonstrated significantly more symptoms associated with a DSM-IV diagnosis of ADHD. Although the sample size for the CPRS-R:L analyses was small, large effect sizes were calculated, lending support for the observed differences. Of interest, analyses were significant for inattentive and hyperactive/impulsive symptoms. Although some researchers have proposed that hyperactive symptoms rapidly remit in adolescence (Spencer et al., 2007), hyperactivity and impulsivity continued to be a concern for adolescents in the current study.

The small sample size and lack of consistently available diagnostic information limited the ability to classify and compare individuals with ADHD across distinct subtypes. Given the recent interest in neurocognitive profiling (Fair et al., 2012) and phenotypic characterization of distinct neural networks in ADHD (Whelan et al., 2012), it

will be important for future spectroscopic imaging studies to include large, diverse samples of ADHD participants which will allow for subgroup comparisons.

Additional group characteristics limit the applicability of the current results. There was a significant discrepancy in FSIQ between the control and ADHD participants. Although IQ discrepancies have been previously reported in the ADHD literature, the current group demonstrates an estimated IQ solidly in the average range. The estimated IQ for the control group was more than a standard deviation above the population mean, and one third of the participants were enrolled in gifted educational programming. Although differences reported in brain structure and neurochemistry are discussed in the context of ADHD, it is possible that morphological differences and trends in neurometabolite concentration differences are driven by differences in IQ. Despite this caveat, the VBM results and results concerning performance on neuropsychological measures are commensurate with previously reported findings in the ADHD literature. It is more difficult to gauge the impact of IQ on the spectroscopy results, although reported trends in group differences are not analogous to the spectroscopic imaging correlates associated with intelligence (Jung et al., 2009).

The uneven sex distribution in the ADHD group is an additional limitation. Imbalances in sex ratio are commonly reported in studies of ADHD, due to the higher detection and diagnosis rate in males (APA, 2000; Spencer et al., 2007). However, the present study was particularly interested in examining the interaction between sex and ADHD diagnosis on the selected spectroscopy variables. Due to the small number of female participants diagnosed with ADHD, it is felt that interaction effects were difficult to identify and may be obscured in the current data set as trends toward a main effect of

sex. In future spectroscopic imaging studies of ADHD, it will be imperative to ensure an equal distribution of male and female subjects in the diagnostic group as well as the controls.

Methodological Limitations

The current study is significantly limited in scope by the small sample size. Given the large number of aims and variables of interest, many statistical analyses were run to explore the proposed hypotheses with limited statistical power. Corrected significance levels were selected to partially account for the large number of tests, but it is possible that significant findings and trends in the data were due to chance rather than indications of true group differences. Although this is a significant limitation, it should be noted that single voxel studies of spectroscopy in the ADHD literature commonly have small sample sizes, similar to the present study (i.e., MacMaster et al., 2003).

Limitations related to imaging techniques and analyses are mentioned briefly. First, all neuroimaging data was collected on a 1.5 Tesla MRI scanner. Higher Tesla scanners are now available, which provide greater spectral resolution, potentially allowing for the reliable detection of additional neurometabolites, therefore improving the overall quality of data. Spectroscopic imaging has some inherent limitations. Although it has the advantage of collecting information on neurometabolite concentrations from multiple brain regions simultaneously, the technique is fairly crude. Constraints imposed by the signal-to-noise ratio limit detection of metabolites that are under a certain volume resolution (Gadian, 1995). Additionally, global shimming techniques provide less desirable results in comparison to shimming techniques used with single-voxel spectroscopy, and longer acquisition times are required for spectroscopic

imaging (Gadian, 1995). Related to field strength, spectroscopy data collected at 3T has shown higher reproducibility and test-retest reliability in gray and white matter tissue when compared to previous studies conducted at 1.5T (Gasparovic et al., 2011).

Given the difficulties in differentiating accurate values for individual neurometabolites, the reported values are groupings of spectrally similar neurometabolites rather than singlet resonances (Govindaraju et al., 2000). Although this strengthens the quality of usable spectra, it may mask group differences in more specific neurometabolite concentrations. Another potential limitation related to the spectroscopy analyses involves the use of "absolute" neurometabolite concentrations rather than ratios. Advances in the available spectroscopy imaging analysis programs allow for fairly accurate report of a variety of neurometabolite combinations, including those reported in the current study (i.e., Cr, Glx, Cho, and NAA). Initially, ratios were used to reduce the impact of the CSF fraction included in each individual voxel. Now that tissue voxel concentration can be normalized to reduce the influence of CSF (Gasparovic et al., 2006), ratios are not as necessary. The use of ratios has been criticized for the reliance on two variables in the exploration of group differences. It can become difficult to determine whether the variable of interest or the numerator (ratio) neurometabolite is driving observed differences. Despite these critiques of the ratio method, it is still commonly reported in the ^{1}H-MRS literature. Because the current study reported absolute concentrations, comparison with studies employing a ratio technique becomes more difficult.

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Table 1

Participant Demographic Characteristics by Group

	ADHD Group	Control Group
	n (%)	*n* (%)
Total	9 (43%)	12 (57%)
Male	7 (78%)	6 (50%)
Female	2 (22%)	6 (50%)
	M (*SD*)	*M* (*SD*)
Age	17.55 (2.00)	19.26 (2.38)
Hollingshead SES	49 (12.87)	46.67 (11.92)
Education	11.56 (1.33)	12.92 (1.73)

Table 2

Parent Report of Behavioral Symptoms

	ADHD Group	Control Group	T-Test Results	
	M (*SD*)	*M* (*SD*)	*p*	*Cohen's d*
Conner's Rating Scales (Time 1)	*n*=9	*n*=12		
Conduct	52.25 (14.65)	48.50 (10.17)	0.506	
Learning	69.50 (14.09)	46.92 (11.02)	0.001	1.79
Impulsive-Hyperactive	64.38 (13.87)	44.83 (15.73)	0.011	1.88
Anxious	47.25 (6.21)	47.17 (4.88)	0.974	
Children's Symptom Inventory (T1)	*n*=9	*n*=12		
Inattentive Symptoms	5.13 (3.40)	1 (1.96)	0.003	
Hyperactive Symptoms	5.25 (3.20)	0.50 (1.45)	0.000	
Conner's Parent Rating Scales (T2)	*n*=6	*n*=4		
DSM-Inattentive	66 (13.31)	45.50 (2.52)	0.012	2.14
DSM-Hyperactive/Impulsive	75.50 (11.45)	43.75 (1.50)	0.001	3.89
DSM-Total	70.83 (13.91)	44 (1.63)	0.005	2.71

Note. CRS and CPRS scores are presented as t-score values (Mean = 50, SD = 10). CSI scores are symptom counts (9 possible inattentive symptoms, 9 possible hyperactive/impulsive symptoms).

Table 3.

Summary of Neuropsychological Test Results

	ADHD Group	Control Group	T-Test Results	
	Mean (*SD*)	*Mean* (*SD*)	*p*	*Cohen's d*
WISC-III/WAIS-III				
Vocabulary	9.78 (3.87)	12.08 (3.90)	0.194	0.59
Block Design*	10.22 (3.38)	15.09 (2.88)	0.003	1.55
Digit Span	9.67 (3.94)	11.36 (3.78)	0.340	0.44
Estimated FSIQ*	99.89 (17.03)	120.17 (15.82)	0.011	1.24
WJ-R				
Letter-Word Identification*	87.56 (10.67)	108.40 (11.32)	0.001	1.89
Calculation	87.67 (8.80)	105.60 (20.61)	0.027	1.13
Dictation*	75.78 (8.93)	101.10 (17.86)	0.001	1.79
CPT-II				
Omissions	47.50 (7.71)	46.55 (4.19)	0.720	0.15
Commissions	45.93 (8.19)	51.66 (9.65)	0.168	0.64
Hit RT SE	47.48 (10.88)	46.68 (12.22)	0.878	0.06
Variability	45.46 (7.94)	48.16 (11.56)	0.556	0.27
Stroop Test				
Word	38.78 (7.48)	46.67 (10.53)	0.071	0.86
Color	39.22 (11.14)	44.42 (9.29)	0.258	0.51
Color-Word*	41.22 (8.57)	53.25 (8.55)	0.005	1.41

Note. WISC-III/WAIS-III subtests are reported as scaled scores (Mean = 10, SD = 3). FSIQ and scores on the WJ-R are reported as standard scores (Mean = 100, SD = 15). CPT-II and Stroop scores are presented as t-test values (Mean = 50, SD =10).

Table 4.

Summary of Total Neurometabolite Concentrations by Group

	ADHD Group			Control Group		
	Mean (*SD*)			*Mean* (*SD*)		
	Voxels	Concentration	SD	Voxels	Concentration	SD
Total Cr	104.44 (21.02)	7.39 (0.37)	1.38 (0.47)	101 (18.14)	7.16 (0.47)	1.45 (0.62)
Total Glx	83.33 (15.60)	18.68 (1.52)	3.88 (1.38)	80.58 (13.04)	19.50 (1.01)	4.16 (1.67)
Total Cho	99.44 (19.05)	1.69 (0.21)	0.38 (0.10)	97.67 (17.10)	1.67 (0.19)	0.36 (0.09)
Total NAA	104.44 (21.02)	11.95 (0.69)	1.64 (0.84)	101 (18.14)	11.96 (0.60)	2.03 (1.61)

Table 5

Gray Matter and White Matter Neurometabolite Concentration Estimates

	ADHD Group	Control Group	
	Mean (*SD*)	*Mean* (*SD*)	*Cohen's d*
GM Cr	8.72 (0.67)	8.76 (0.79)	0.05
WM Cr	6.22 (0.88)	6.01 (0.44)	0.30
GM Glx	21.84 (3.70)	23.60 (1.98)	0.59
WM Glx	14.80 (2.46)	15.72 (1.43)	0.46
GM Cho	1.43 (0.41)	1.32 (0.21)	0.34
WM Cho	1.85 (0.29)	1.90 (0.26)	0.18
GM NAA	11.53 (1.79)	11.29 (1.23)	0.16
WM NAA	12.05 (1.29)	12.39 (0.65)	0.33

Table 6

Correlations of Neuropsychological Measures and Neurometabolite Concentrations by Group

	Cr GM	Cr WM	Glx GM	Glx WM	Cho GM	Cho WM	NAA GM	NAA WM
				ADHD Group *r* (*p*)				
Digit Span	0.33 (0.38)	-0.03 (0.94)	0.08 (0.85)	-0.17 (0.66)	0.20 (0.61)	0.43 (0.25)	0.23 (0.55)	0.17 (0.66)
CPT Inattention	**-0.72 (0.03)***	0.35 (0.36)	**-0.63 (0.07)***	0.34 (0.37)	-0.54 (0.14)	0.13 (0.73)	-0.42 (0.27)	0.37 (0.32)
Stroop Color-Word	-0.15 (0.70)	0.11 (0.79)	-0.41 (0.27)	0.24 (0.54)	-0.48 (0.19)	0.19 (0.63)	-0.41 (0.28)	0.43 (0.25)
				Control Group *r* (*p*)				
Digit Span	-0.49 (0.13)	-0.54 (0.09)	-0.07 (0.85)	-0.07 (0.85)	-0.23 (0.51)	-0.44 (0.17)	-0.08 (0.82)	-0.15 (0.66)
CP Inattention	-0.18 (0.58)	-0.41 (0.19)	0.06 (0.86)	**-0.57 (0.05)***	-0.38 (0.23)	-0.38 (0.22)	0.13 (0.69)	0.33 (0.29)
Stroop Color-Word	-0.33 (0.30)	0.18 (0.58)	-0.08 (0.82)	-0.14 (0.66)	-0.16 (0.63)	0.26 (0.41)	-0.02 (0.95)	**0.60 (0.04)***

Note. Z-transformed scores for Digit Span, CPT-II Inattention, and Stroop Color-Word were used in the correlation analyses.
* A revised p-value of 0.006 was required for significance. Given that no results met this criteria, the * is used to indicate values that approached significance.

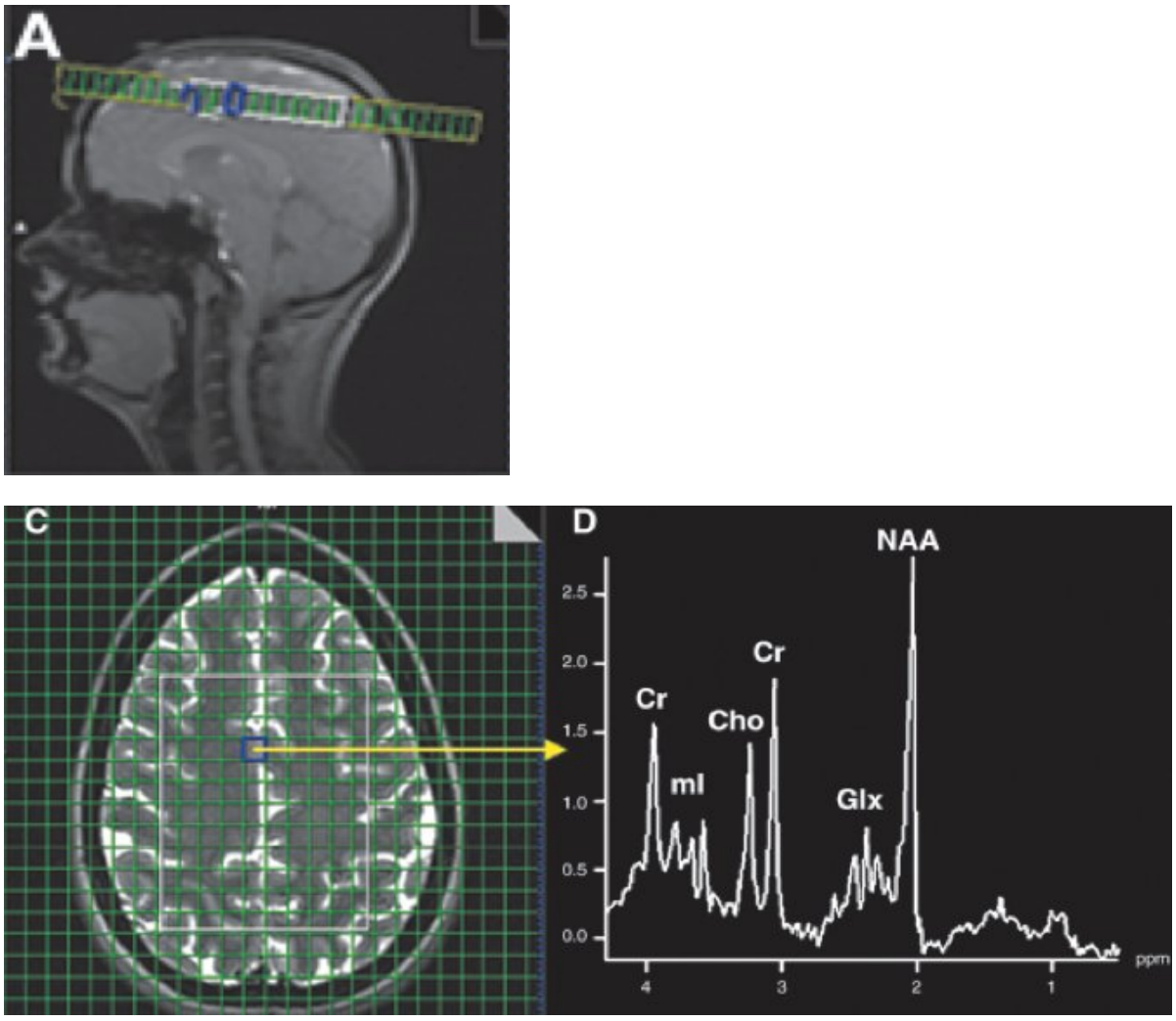
Table 7

Regions of Reduced Gray Matter Volume in the ADHD Participants

Region	k_E	T	p	mni Coordinates	Description of Region
1	34	4.54	<0.0001	(-44, 24, 6)	Left Frontal Lobe; Inferior Frontal Gyrus
2	68	4.52	<0.0001	(38, -68, 38)	Right Parietal Lobe; Inferior Parietal Lobule
3	31	4.47	<0.0001	(-32, -74, 30)	Left Parietal Lobe; Precuneus
4	46	4.38	<0.0001	(-48, -30, -16)	Left Temporal Lobe; Inferior Temporal Gyrus
5	93	4.30	<0.0001	(-12, -84, -28)	Left Cerebellum; Posterior Lobe
6	37	4.28	<0.0001	(52, -48, -4)	Right Temporal Lobe; Middle Temporal Gyrus
7	32	4.13	<0.0001	(16, -86, -26)	Right Cerebellum; Posterior Lobe
8	12	4.09	<0.0001	(-44, -26, 26)	Left Parietal Lobe; Inferior Parietal Lobule
9	24	4.03	<0.0001	(34, 18, -40)	Right Temporal Lobe; Superior Temporal Gyrus
10	13	3.91	0.001	(44, -44, -22)	Right Temporal Lobe; Fusiform Gyrus
11	13	3.83	0.001	(20, -34, 6)	Right Thalamus
12	11	3.78	0.001	(-52, -42, 22)	Left Parietal Lobe; Inferior Parietal Lobule

Figure 1

Spectroscopic Region of Interest and Example Spectrum



Note. Figure illustrates the spectroscopic region of interest in the sagittal (A) and axial (C) planes, as well as showing an example of obtained spectrum from a single voxel in the region of interest.

Figure 2

Example of LCModel Spectrum Analysis of a Single Voxel from the Spectroscopic Region of Interest

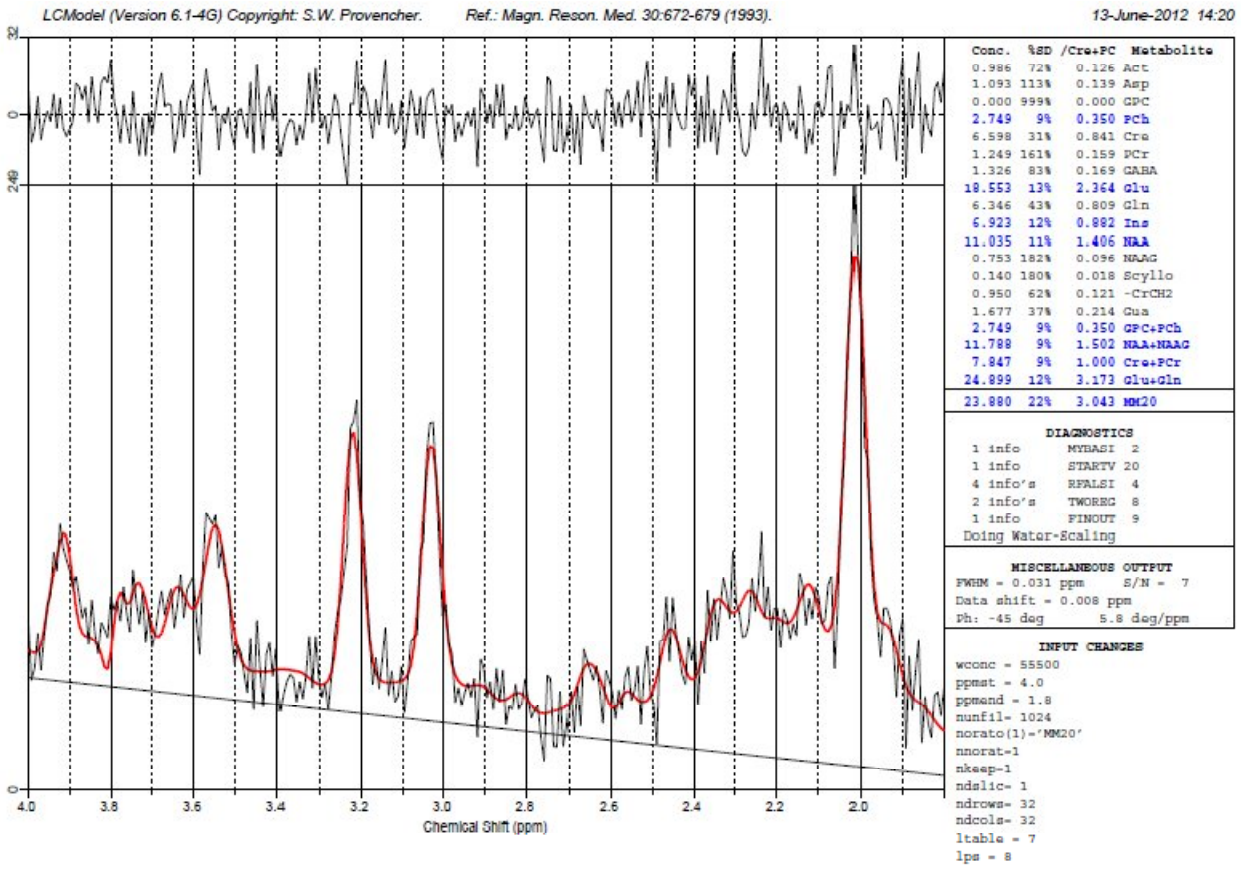


Figure 3

Mean Estimated GM Cr Concentrations

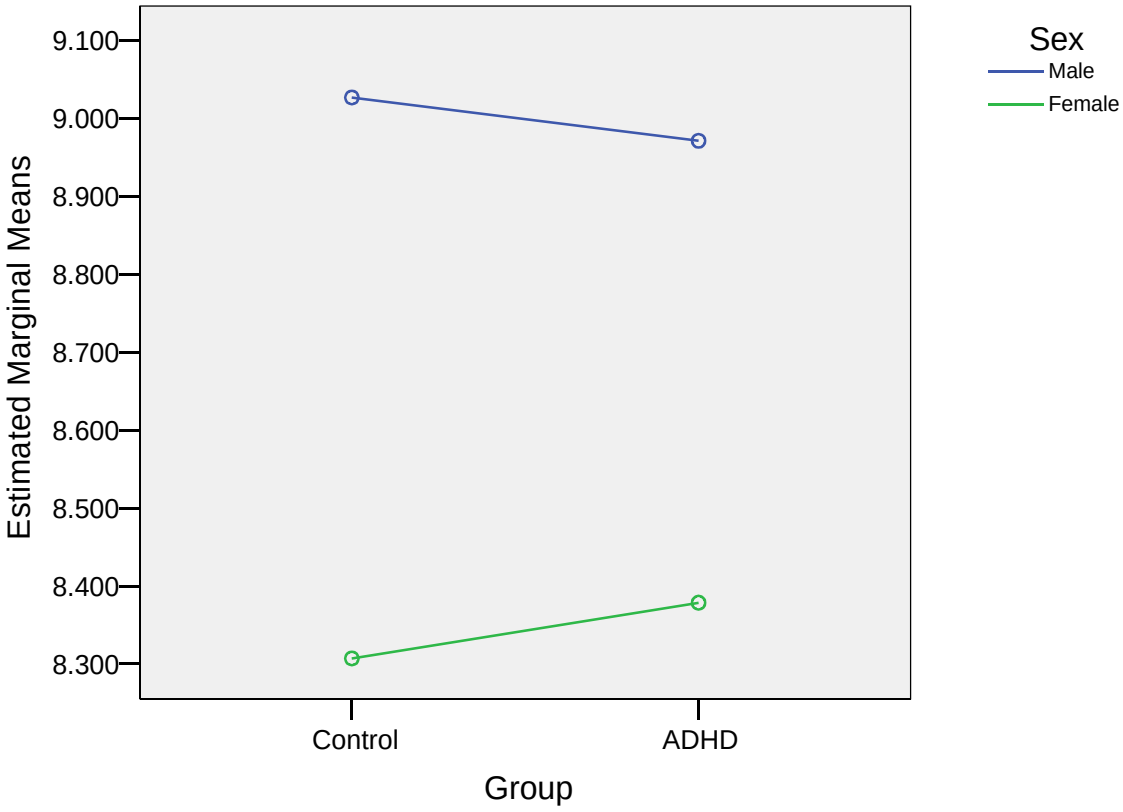


Figure 4

Mean Estimated WM Glx Concentrations

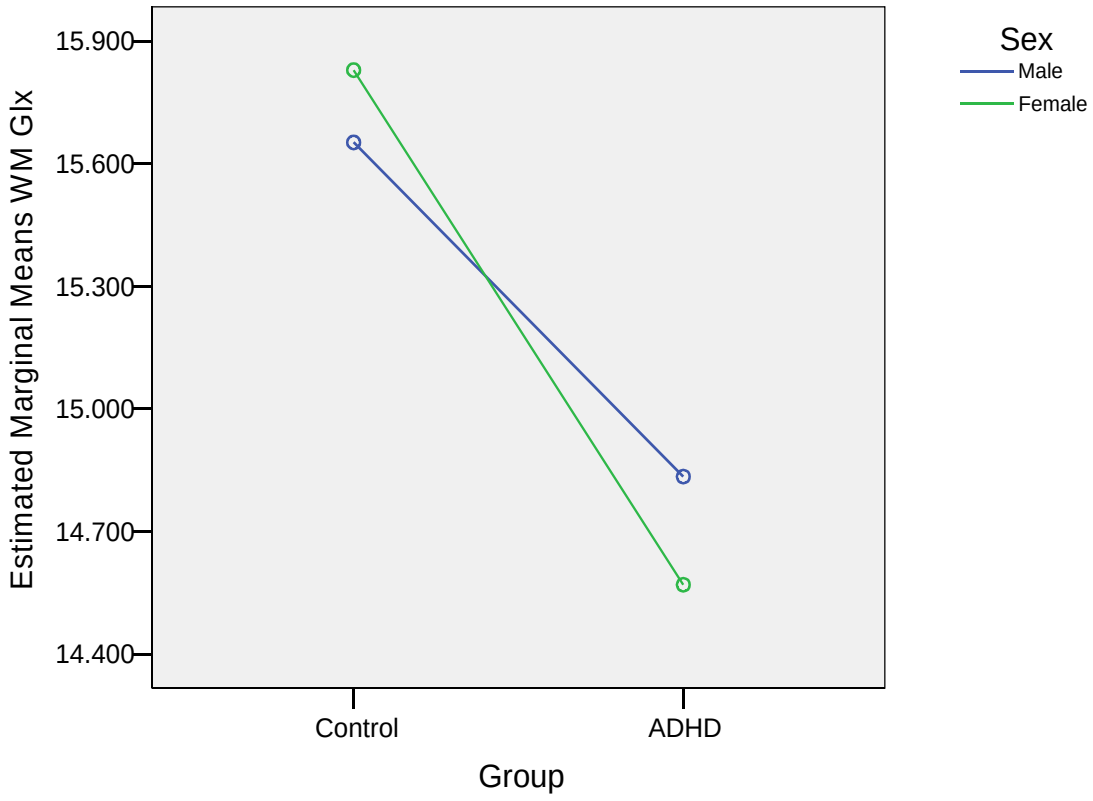


Figure 5

Mean Estimated GM Cho

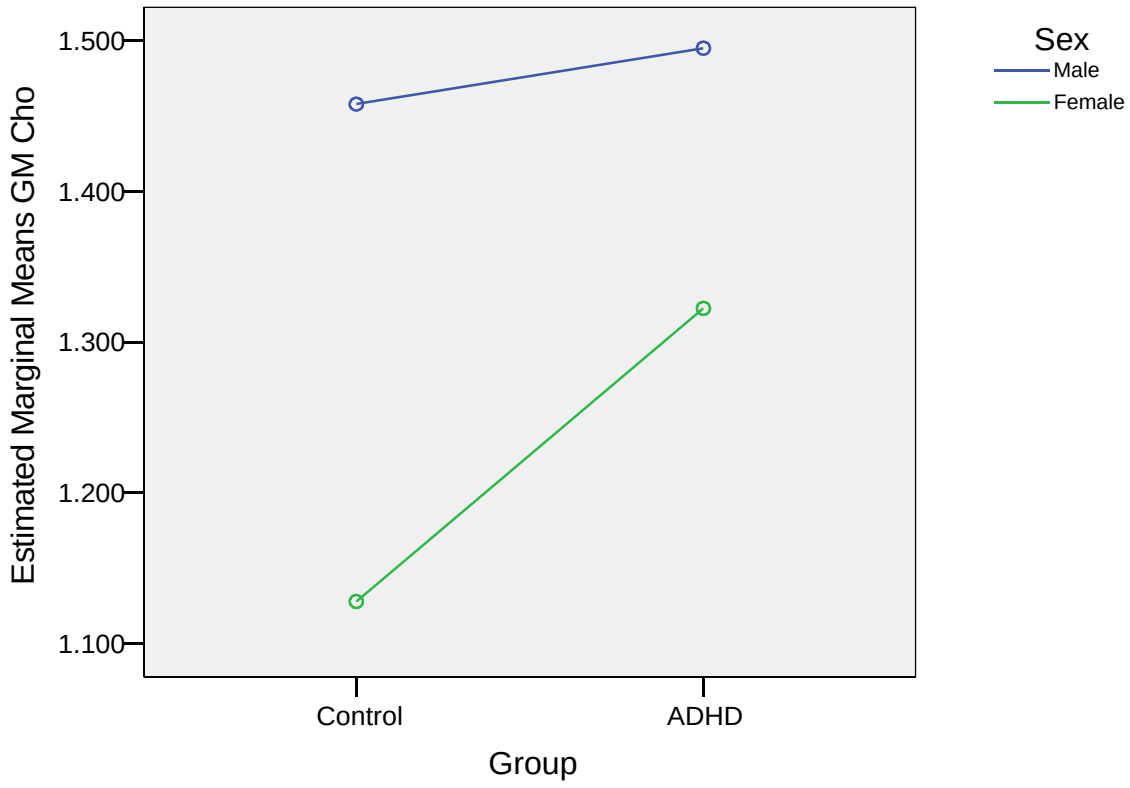


Figure 6

Mean Estimated WM Cho

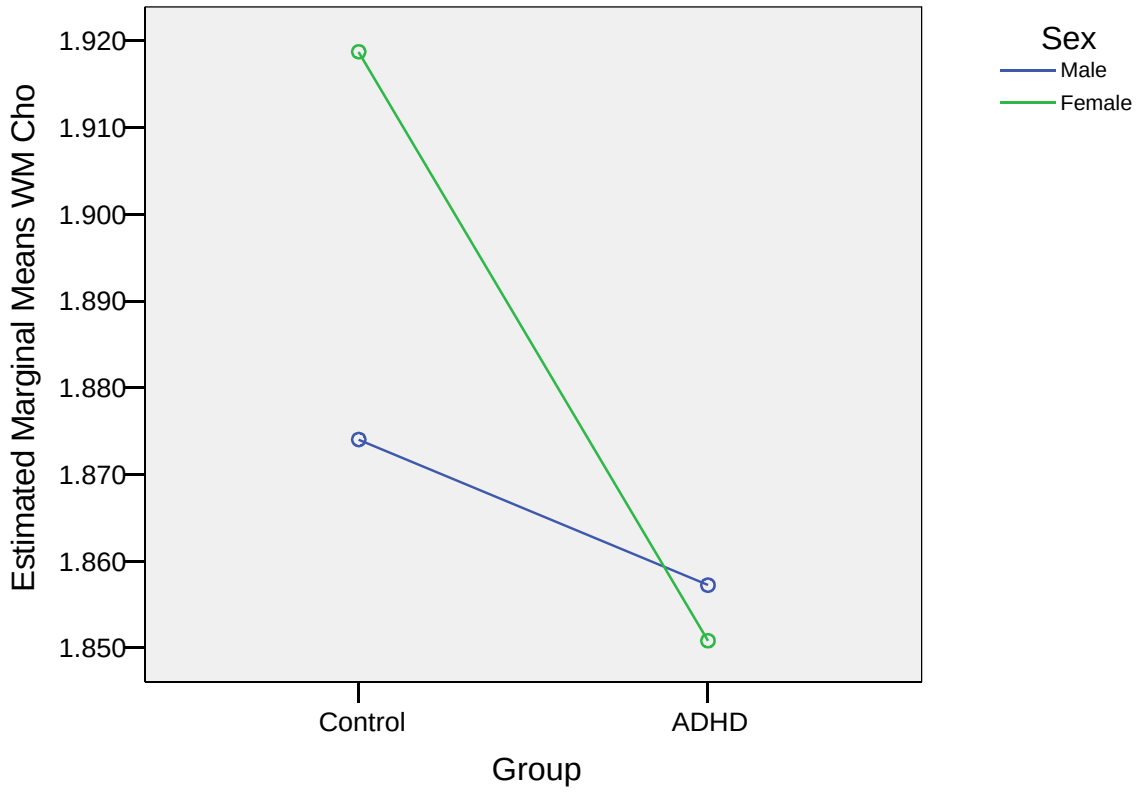


Figure 7

Mean estimated Total NAA

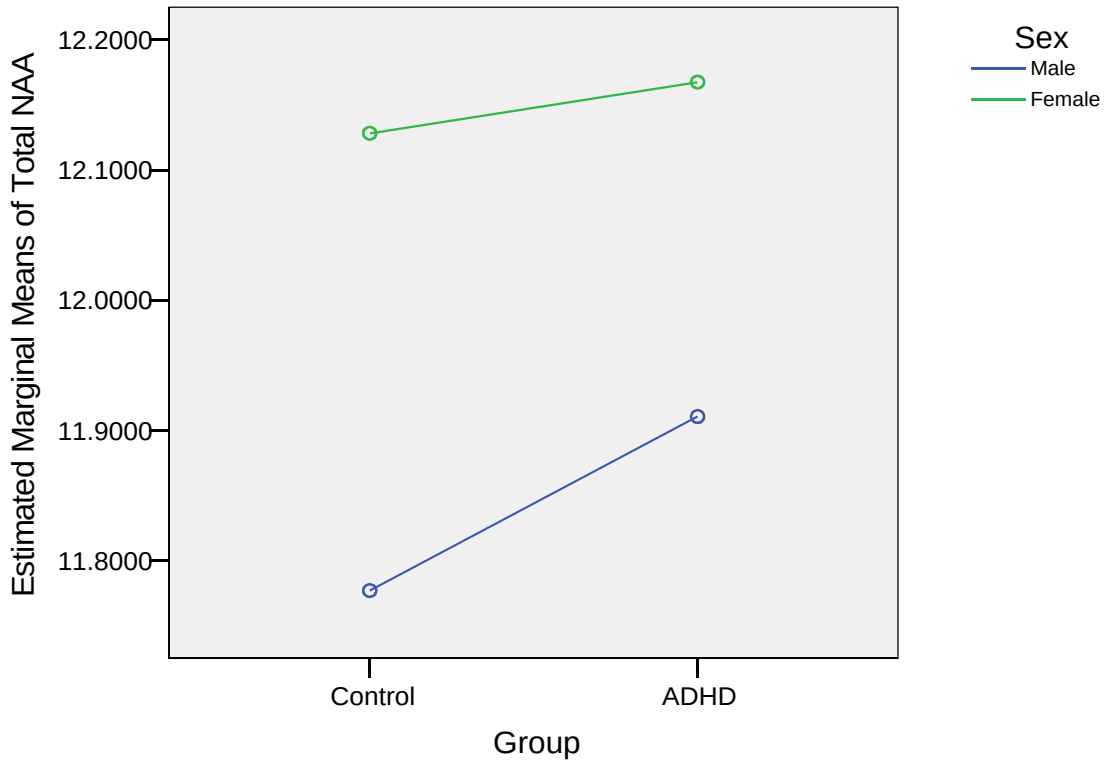


Figure 8

Regions of Reduced Gray Matter Volume in the ADHD Sample

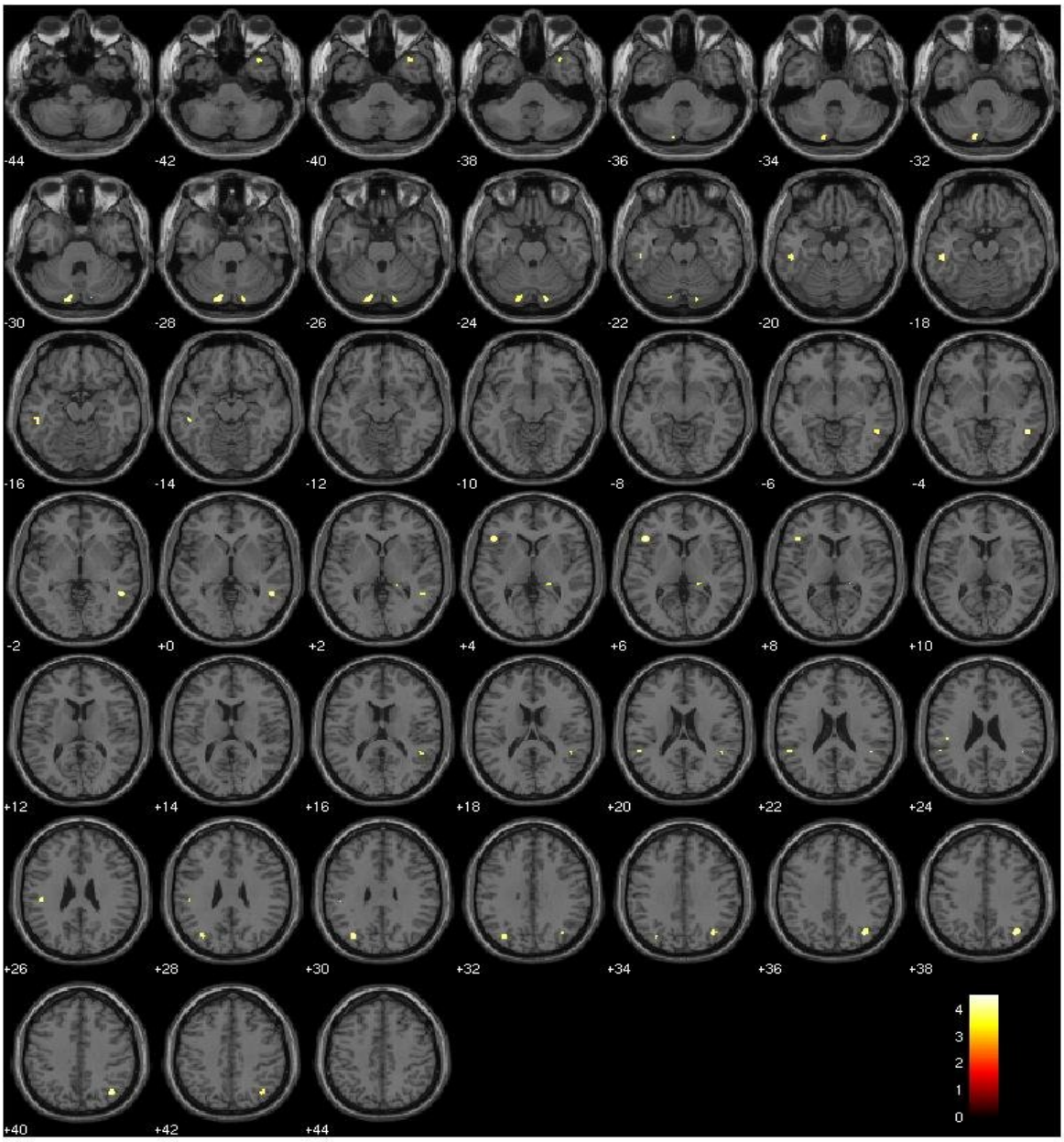


Figure 9

Regions of Reduced Gray Matter Negatively Correlated with Stroop Color-Word Performance in the ADHD Sample