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Functional Significance of Corpus Callosum Anatomy

in Chronically Treated and Treatment Naïve ADHD

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Functional Significance of Corpus Callosum Anatomy in Chronically Treated and Treatment Naïve ADHD

by

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Neuroimaging has revealed differences between control and ADHD groups in corpus callsoum (CC) size, although the reported findings have been somewhat variable. Since ADHD is commonly treated with stimulants, concerns have been raised about the long-term neurological consequences of chronic stimulant treatment, yet this has not been controlled for in previous studies. Furthermore, since all previous studies have utilized the mid-sagittal area of the CC as the unit of measurement, additional objectives of this investigation were to determine 1) whether CC volume could be reliably measured and 2) whether using mid-sagittal CC area provides a valid estimation of CC volume. Anatomical MRI's were obtained from children aged 9-15 in three diagnostic groups 1) chronically-treated ADHD (n=12), 2) stimulant-naïve ADHD (n=13), and 3) a

control group (n=15) to determine whether differences in CC size existed. These children also completed a battery of neuropsychological tests to determine whether the functions of sustained attention, speed of information processing, planning, and inhibitory control were related to CC size. Parental ratings of hyperactive and impulsive behavior were also collected. The three groups did not differ in overall CC volume. Differences between the groups in the area of the splenium were approaching significance, with the treatment-naïve group exhibiting the smallest splenium area. Therefore, the results of this investigation do not indicate maladaptive structural changes in the CC associated with chronic (at least one year) stimulant use. It was also found that volume of the CC can be reliably obtained when strict definitional criteria are applied. However, mid-sagittal area is highly related to CC volume and therefore is likely an accurate estimate, an important finding given the significant time required to obtain volumetric measures. Finally, smaller splenium size was found to be related to higher levels of hyperactivity and restlessness; however, no associations between measures of CC size and neuropsychological measures were found.

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Chapter 1: Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is one of the most prevalent (American Psychiatric Association (APA), 2000), as well as one of the most extensively studied (Wolraich, 1999), childhood disorders. Although generally considered to be biologically based, numerous theories regarding the underlying neurological dysfunction in this disorder have been posited (e.g., Barkley, 1997; Schachar, Tannock, & Logan, 1993; for a review of earlier hypotheses, see Zametkin & Rapoport, 1986). New imaging methods provide scientists with increased research capabilities with which to analyze the brain and test theories regarding the neurological substrates of mental disorders, including ADHD. The most important imaging methods for pediatric research have been magnetic resonance imaging (MRI) and functional MRI (fMRI), both of which offer the distinct advantage of utilizing the magnetic principles inherent in bodily tissue and therefore avoiding the radiation exposure present in earlier imaging methods (Savoy, 2001).

One frequent anatomical finding in individuals with ADHD has been abnormalities in the corpus callosum (Giedd et al., 1994; Hill et al., 2003; Hynd, Semrud-Clikeman, Lorys, Novery, & Eliopulous, 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). The corpus callosum (CC) is functionally significant in that it serves as the largest interhemispheric fiber tract in the brain. This structure's involvement in the information transfer and coordination process between the hemispheres has been well-established (for a review, see Gazzaniga, 2000). However, it has recently been suggested

that the CC also plays a key role in some higher order functions, and that, in particular, interhemispheric interaction contributes to attentional processing ability (Banich, 1998). Data have also indicated that the CC may be implicated in specific executive functions, such as sustained attention (Fischer, Ryan, & Dobyns, 1992; Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989; Rueckert, Sorensen, & Levy, 1994; Rueckert, Baboorian, Stavropoulous, & Yasukate, 1999; Rueckert & Levy, 1996), speed of information processing (Hoff, Neal, Kushner, & DeLisis, 1994; Janenck & Steinmetz, 1994; Verger et al., 2001), and problem solving or abstract reasoning (Brown & Paul, 2000). Those familiar with the ADHD literature will recognize these processes as frequently observed areas of difficulty for children with ADHD (e.g. Pennington & Ozonoff, 1996).

It has been articulated that CC abnormalities in subjects with ADHD fail to become meaningful until linked to behavior and symptoms common to the disorder (Hill et al., 2003; Hynd et al., 1991). However, only in one published case has performance on neuropsychological or behavioral measures been related to CC size in an ADHD sample (Giedd et al., 1994). Giedd and collegues found an association between smaller anterior regions of the CC and higher ratings of impulsivity and hyperactivity. However, a battery of computerized attentional measures showed no significant correlations with CC size. The authors suggested that in addition to the low statistical power of their study, the focus on purely attentional tasks may have resulted in the lack of findings when considering that the emerging dominant neuropsychological conceptualization of ADHD to be a deficit of inhibitory control (Barkley, Grodzinksy, & DuPaul, 1992). Therefore, it was of

interest to examine the relationship between corpus callosum size and measures of a variety of neuropsychological processes, including both inhibitory control and attention, as well as functions such as speeded information processing and problem solving, in individuals with attention deficits as well as healthy control subjects.

In addition to contributing to the scant literature available on the relationship between corpus callosum abnormalities and cognitive symptoms noted in ADHD, the current investigation is one of the first to utilize volume as the unit of measurement of the CC. Previous studies have relied on the calculation of the area of a single midsagittal slice from MRI images. Although recent studies have frequently used volumetric data in examining various brain structure differences in pathological groups (e.g. Castellanos et al., 1994, 1996; Hill et al., 2003; Filipek et al., 1997; Semrud-Clikeman et al., 2000), to date, there has been no volumetric data analysis of the corpus callosum in imaging studies of ADHD. Therefore, this investigation sought to determine if volumetric measurement of the corpus callosum in ADHD subjects revealed similar abnormalities as reported by previous studies of CC area. Furthermore, it was important to determine if the additional effort required to obtain volumetric measurement offers any additional predictive power over simple area measurements as to the performance on neuropsychological measures across both impaired and healthy groups.

Since ADHD is commonly treated with the use of stimulant medication, concerns have been raised as to the long-term neurological consequences of chronic stimulant treatment, or "methylphenidate-induced plasticity" (Hyman, 2003). As highlighted by Pliszka and colleagues (under review), the majority of previous neuroimaging studies

have not controlled for long-term stimulant treatment, either because stimulant naïve and chronically treated subjects were included in a single group (Rubia et al., 1999) or only chronically treated subjects were studied (Durston et al., 2003; Pliszka, Liotti, Woldorff, 2000; Vaidya et al., 1998). Therefore, researchers have not been able to definitely state whether the neuroimaging differences noted between subjects with ADHD and healthy controls are representative of pre-existing differences or result from chronic stimulant administration (Pliszka et al., under review). Initial reports by Pliszka and colleagues regarding the effects of long-term stimulant treatment suggest that both treatment naïve and chronically treated ADHD subjects show reduced activation in the dorsolateral prefrontal cortex and anterior cingulate when required to perform a task of inhibitory control. However, the chronically treated subjects in their sample showed a trend toward greater activation in these regions when compared to the treatment naïve group, even when withdrawn from medication, suggesting a potential "normalization" of brain function. However, it remains to be determined whether or not long-term stimulant treatment affects the brain structurally. The current investigation included both a stimulant naïve and a chronically treated ADHD group in order to determine if corpus callosum size in ADHD subjects is related to long-term stimulant usage.

In the following chapter, literature relevant to the topic will be reviewed, beginning with a description of the clinical features of ADHD. Considering the neurological focus of this study, support for a biological basis of ADHD will be presented. The functional significance and developmental trajectory of the corpus callosum will also be discussed, especially as related to research implicating CC

abnormalities in individuals with ADHD. Finally, the literature regarding the relationship between CC size and neuropsychological function will be examined, both in terms of CC findings in individuals with disorders other than ADHD that present with dysexecutive symptoms and investigations linking cognitive functions to CC size and shape in healthy subjects.

Chapter 2: Literature Review

Attention Deficit/Hyperactivity Disorder: Clinical Features

ADHD: Scope and Impact

According to the Diagnostic and Statistical Manual-IV (American Psychiatric Association (APA), 1994), the prevalence of Attention Deficit Hyperactivity Disorder (ADHD) is estimated to be between 3 and 7% of the school-aged population, making it one of the most common childhood disorders. In a statement of practice parameters, the American Academy of Child and Adolescent Psychiatry (AACAP) estimated that as many as 10% of boys and 5% of girls in the elementary age range may be diagnosable for ADHD (1997). More notable than the sheer number of individuals affected by ADHD, however, is the pervasive and persistent nature of the difficulties associated with the disorder. Children with ADHD appear to remain impaired into adolescence on measures of attention, academic achievement, and inhibition (e.g., Fischer, Barkley, Edelbrock, & Smallish, 1990) and exhibit elevated rates of antisocial activity and drug use beyond childhood (Mannuzza et al., 1991). This disorder often results in significant social impairment (Barkley, 2000; Gentschel & McLaughlin, 2000), for which even giftedness does not provide a buffer (Moon, 2001).

Diagnostic criteria and concerns

Before coming to its current label of ADHD, this disorder was known by several other, often more stigmatizing, terms such as minimal brain dysfunction/damage (MBD),

hyperkinetic reaction, and hyperkinesis (AACAP, 1997). Furthermore, the Diagnostic and Statistical Manual (DSM) has changed positions on the existence of ADHD subtypes from a multidimensional description of the disorder in the DSM-III (ADD with hyperactivity (ADD/H) and ADD without hyperactivity (ADD/WO)) to the one-dimensional diagnosis of ADHD in the DSM-III-R (Morgan, Hynd, Riccio, & Hall, 1996). The DSM-IV re-introduced ADHD subtyping, offering criteria for the predominantly hyperactive, predominantly inattentive, and combined types. Both clinical evidence and factor analytical studies appear to support the current DSM-IV subtypes (Morgan et al., 1996), although some research questions the validity of the hyperactive-impulsive subtype, as it is difficult to distinguish between this subtype and the combined subtype at older ages (Paterine, Loney, & Roberts, 1996). Children diagnosed with the different ADHD subtypes were found to have divergent patterns of impairment in social, academic, and behavioral functioning (Gaub & Carlson, 1997; Morgan et al., 1996). While impaired compared to controls in all domains, those children diagnosed with the predominantly inattentive subtype exhibit more internalizing problems but generally more appropriate social behavior than children diagnosed as having the hyperactive/impulsive or combined types. Although peers generally do not reject these predominantly inattentive children, they tend to be neglected and withdrawn (APA, 2000). The hyperactive/impulsive group appears to be at a lesser risk for comorbid internalizing disorders but has been rated as demonstrating more aggressive behavior and social difficulties (APA, 2000). Finally, students with ADHD-combined type consistently demonstrate significant difficulties in all domains (e.g., Gaub & Carlson, 1997; Graetz,

Sawyer, Hazell, Arney, & Baghurst, 2001). The current investigation was interested in children with the combined type.

Comorbidity with other forms of childhood psychopathology

As is the case with many forms of childhood psychopathology, comorbidity is the rule, rather than the exception. As one of the most common childhood disorders, it follows that ADHD would tout an impressive list of comorbid conditions. Of all disorders coexisting with ADHD, learning disabilities are perhaps the most readily identified, given the difficulties students with LD and ADHD often exhibit in school. Reported estimates of the co-occurrence of LD and ADHD fall within the broad range of 10-92% (Semrud-Clikeman et al., 1992), although more conservative estimates place this rate at approximately 20% (Hinshaw & Zalecki, 2001; Semrud-Clikeman et al., 1992).

Oppositional Defiant Disorder and Conduct Disorder co-occur in approximately half of children diagnosed with ADHD (e.g., Biederman et al., 1991), most commonly in the hyperactive/impulsive and combined subtypes (APA, 2000; Hynd, Lorys et al., 1991). Regarding this pattern of comorbidity, Hinshaw (1987) reported a broad range of overlap between ADHD and disruptive behaviors, from 30-90%. Reviews of the literature on the comorbidity of ADHD and other disruptive behavioral disorders have highlighted the debate as to whether or not ADHD and CD are actually manifestations of a single disorder (Biederman et al., 1991; Campbell, 2000). In their review, Biederman and colleagues (1991) conclude that the majority of the literature suggests ADHD and CD are indeed distinct entities.

Furthermore, ADHD is often associated with mood and anxiety disorders (APA 2000; Butler, Arrendondo, & McCloskey, 1995). Beiderman et al. (1991) estimated the rate of co-occurrence of mood disorders (major depression, dysthymia, and bipolar disorder) and ADHD to range from 15 to 75% of ADHD cases. A controversial issue in child psychopathology is the diagnosis of early-onset bipolar disorder, where ADHD plays a prominent role as both a rule out (Geller et al., 1998) and a potential comorbid condition (e.g. Faraone, Biederman, & Wozniak, et al., 1997; Faraone, Biederman, Mennin, Woziak, & Spencer, 1997). Up to one-third of children with ADHD also present with an anxiety disorder (Hinshaw & Zalecki, 2001). Additionally, ADHD is commonly present in neurobehavioral disorders, such as Tourette's Syndrome (TS) and Obsessive-Compulsive Disorder (OCD) (Peterson, Pine, Cohen, & Brook, 2001). These high rates of comorbidity suggest that the attentional/inhibitory system is one of the most fragile functions of the brain, explaining why the ability to attend and inhibit is commonly compromised in acquired disorders such as traumatic brain injury, fetal alcohol syndrome, metabolic disorders, and in utero exposure to toxins, such as drugs and alcohol (Teeter & Semrud-Clikeman, 1997).

Biological Basis of ADHD

Biological theories regarding the etiology of ADHD have been present since early in the study of children presenting with hyperactive and impulsive symptoms. In order to explain the variety of difficulties children with ADHD experience, Barkley (2000) conceptualizes this cluster of symptoms as a deficit in inhibitory control or a "developmental disorder of self-control," suggesting inattention to actually result from

the lack of inhibitory control. Noting that children with ADHD tend to exhibit difficulties in a variety of global and specific executive functions, many theorists have proposed that disinhibition may serve as a foundational component for higher order executive dysfunction (e.g., Barkley, 1997a; Gorenstein & Newman, 1980; Schachar, Tannock, & Logan, 1993). Empirical studies of neuropsychological tests (e.g., Barkley, Grodzinsky, & DuPaul, 1992; Chulene, Ferguson, Koon, & Dickey, 1986; Pennington & Ozonoff, 1996) appear to converge on such a hypothesis, although not without dissenters (e.g., Loge, Staton, & Beatty, 1990). Therefore, the umbrella term "executive functions" will be discussed, followed by a review of the neuroimaging literature relevant to ADHD.

Because of apparent difficulties in performing tasks considered to be "executive" in nature, such as planning, organization, attention, and inhibition, the neural anatomy and function of individuals with ADHD has long been of interest to the field of cognitive neuroscience. Executive functions have been historically attributed to the prefrontal cortex, and the higher order nature of such activities is captured in Luria's statement, "…the tertiary portions of the frontal lobes are in fact a superstructure above all other parts of the cerebral cortex; so that they perform a far more universal function of general regulation of behavior than that performed by the …tertiary areas of the second functional unit." (1973, p. 89). Evidence from lesion studies and the widespread use of functional neuroimaging within the last several years has provided verification for Luria's proposition of frontal lobe involvement. Although the frontal lobes have received the bulk of attention in the executive function literature (Dempster, 1992), a more accurate description of the brain areas activated during such tasks is a "distributed

cortical-basoganglionic neural network" (Pliszka, 2001, p. 42), also called the frontal-striatal network.

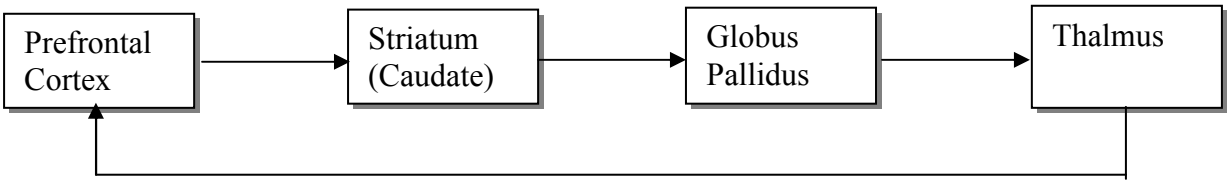

Figure 1. Inhibitory control represented by a fronto-striatial-thalamic circuit.

Considering the emphasis placed on the frontal-striatal pathways and inhibitory control processes, it is fitting that the bulk of functional neuroimaging research has focused on these topics. For example, several investigators have provided evidence for the frontal-striatal pathway as a mediator of inhibitory control. A frequently reported finding has been a dissociation between the neural regions activated during execution (go) processes and inhibitory (stop) processes. Healthy adults have been found to display increased activation in the right frontal regions during stop tasks (Garavan, Ross, & Stein, 1999; Rubia et al., 1999) but activate the motor circuit (contralateral primary motor strip, supplementary motor areas, striatal, and cerebellar areas) during go task responses (Garavan et al., 1999). Furthermore, subjects displaying a faster reaction time to the primary (go) task demonstrated larger frontal activation during the inhibitory trials, reflective of the greater inhibitory effort required (Garavan et al., 1999). Additionally, a growing body of literature suggests that the "braking" mechanism of the brain is lateralized to the right hemisphere (e.g., Casey, Castellanos et al., 1997; Castellanos et al., 1996; Pliskza et al., 2001; Rubia et al., 1999; Semrud-Clikeman et al., 2000),

congruent with theoretical accounts of a right-hemispheric dominant attentional/inhibitory system (Heilman, Voeller, & Nadeau, 1991).

Since individuals with ADHD are thought to have deficient inhibitory control, research attention turned to an examination of the regions implicated above in subjects with ADHD. Earlier studies revealed that children with ADHD and adults with a history of the disorder demonstrate general reductions in cerebral blood flow and glucose metabolism in the frontal and striatal areas (Lou, Henriksen, & Bruhn, 1984; Lou, Henriksen, Bruhn, Borner, & Nielson, 1989; Zametkin et al., 1990), although Vaidya and collegues (1998) found greater frontal activity in ADHD subjects during a go/no-go task. However, the subjects in the latter study displayed reduced activation in the caudate and putamen when compared to controls. Methylphenidate increased the level of striatal activation in the ADHD group only and actually caused a decrease of activation in the controls (Vaidya, 1998). The authors suggested methylphenidate uniquely affected the dopamine-rich striatal areas in the ADHD subjects. A recent study of children aged 6 to 10 revealed that in a go/no-go paradigm, healthy controls activated frontal-striatal and anterior regions during inhibitory trials to a greater extent than the ADHD subjects (Durston et al., 2003). The authors also noted individuals with ADHD exhibited a more diffuse region of interaction, including additional frontal and posterior regions, potentially reflective of a less mature, less efficient inhibitory system. Furthermore, children who suffered head injuries were shown to be more likely to develop a secondary attentional disorder if damage was incurred in either the basal ganglia or thalamus, lending further support for the frontal-striatal network (Gerring et al., 2000).

Anatomical MRI studies have paralleled these findings by reporting morphological differences in the brains of subjects with ADHD and those without. Reductions in the size of the frontal lobes have been frequently reported (Castellanos et al., 1996; Filipek et al., 1997; Overmeyer et al., 2001; Semrud-Clikeman et al., 2000). As would be predicted by frontal-striatal models, abnormalities in basal ganglia structures have also been a common finding (e.g., Aylward et al., 1996), with caudate size and asymmetry most frequently found to distinguish ADHD children from normal controls (Castellanos et al., 1994, 1996; Filipek et al., 1997; Hynd et al., 1993; Overmeyer et al., 2001). Studies correlating performance on neuropsychological measures of attention and inhibitory control with neuroanatomical volumes have provided intriguing support for the relationship of the cortical-striatal network to inhibition and attention. A cross-sectional developmental study of normal children revealed that performance on an attentional task was correlated with the area of the right anterior cingulate, a structure in the frontal region of the brain (Casey, Trainor, & Giedd, 1997). Furthermore, performance on response inhibition tasks was related to the volume of the prefrontal cortex and caudate (Casey, Castellanos et al., 1997; Semrud-Clikeman et al., 2000) and globus pallidus (Casey, Castellanos, et al., 1997) in ADHD and control children.

Although the body of literature discussed above provides compelling evidence for a biological basis of ADHD, the frontal and striatal regions have not been the only areas to be implicated in ADHD. As will be discussed below, the anatomy of the corpus callosum has been frequently found to differ in subjects with ADHD when compared to healthy controls (Giedd et al., 1994; Hill et al., 2003; Hynd, Semrud-Clikeman, et al. 1991; Lyoo et

al., 1996; Semrud-Clikeman et al., 1994), although there have been some inconsistencies in reports of the specific areas of abnormality within this relatively large structure. Because of the key role the CC plays in interhemispheric communication, it has been argued that the callosum should be investigated as a potential player in the attentional network (Banich, 1998). Prior to outlining the research suggestive of CC involvement in ADHD, the functional significance of the CC will be discussed, with particular reference to the cognitive functions supported by this structure. Since it has been argued that ADHD represents a difference in neurological development (Barkley, 1997a), information about what has been discovered about the typical developmental trajectory of the CC will also be presented. Finally, the CC has been thought to vary based on demographic factors (e.g. Witelson, 1985, 1989), in particular, gender (e.g. Allen, Richey, Chai, & Gorski. 1991; Clarke, Kraftisk, Van Der Loos, & Innocenti, 1988; DeLacoste-Utamsing & Halloway, 1982); therefore this research will be discussed as well.

Functional Significance of the Corpus Callosum

The corpus callosum (see figure below) serves as the largest interhemispheric fiber tract in the brain and contains approximately 190 million axons connecting homologous areas of the hemispheres (Tomasch, 1954). In general, these fibers are thought to maintain topographic consistency in which the anterior portion of the CC connects the frontal hemispheres, the middle area connects the middle cortical areas, including the motor, somatosensory, and auditory cortices, and the posterior section links the most caudal regions of the brain, which include fibers from the temporal, parietal, and occipital lobes (Giedd et al., 1999; Thompson, Narr, Blanton, & Toga, 2003). However, it

is important to note that heterotopic connections also do exist (Di Virgilio & Clarke, 1997). When considering the function of the CC, one must recognize that humankind is unique in that, compared to other animals, humans exhibit a large degree of lateralized cerebral specialization (Gazzaniga, 2000). Decades of research on disconnection syndromes have revealed several domains in which function has been specialized to one hemisphere or another, such as the left hemisphere for language and speech and the right hemisphere for attention and some visual-spatial tasks (Gazzaniga, 2000). With the largest number of interhemispheric connections in the brain, the corpus callosum facilitates this lateralization of functional specialization by allowing one hemisphere to, in effect, carry out a specific task for the entire brain, or as Gazzaniga stated "the callosum allowed a no-cost extension; cortical capacity could expand by reducing redundancy and extending its space for new cortical zones" (p. 1294).

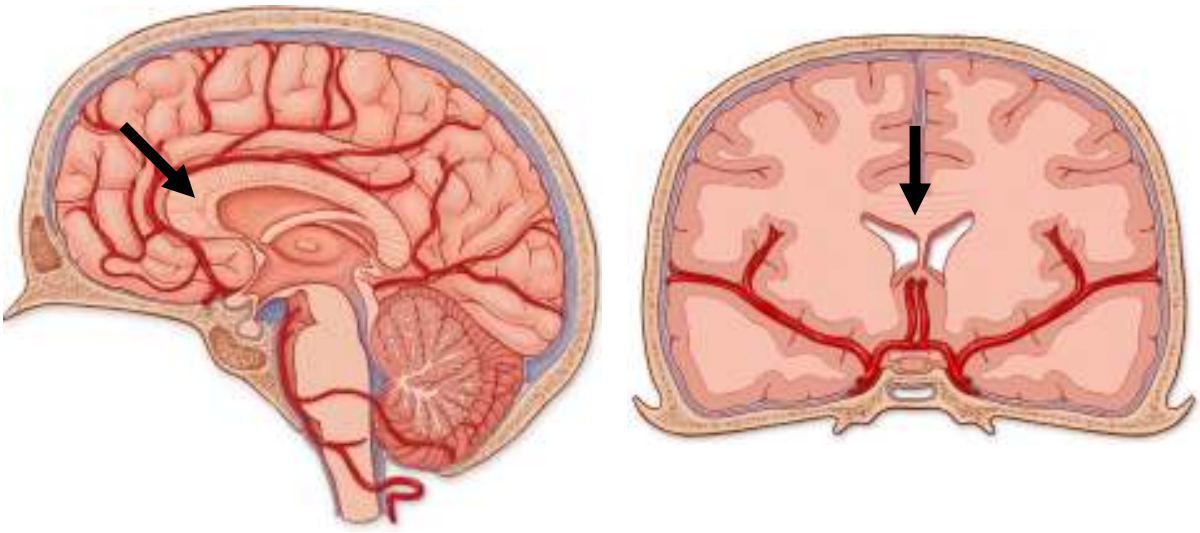

Figure 2. The corpus callosum as seen mid-sagittally (left) and coronally (right). *Source:* Medical Imagery. Copyright 2005. Reprinted with permission of Medical Imagery.

Because the CC offers no clear anatomical landmarks by which to create subdivisions (Peterson, Feineigle, Staib, & Gore, 2001; Thompson et al., 2003), several different parcellation methods have been employed. The most commonly used method in the study of ADHD have been those based on the Witelson (1989) partition, which divides the callosum into seven subdivisions, or the O'Kusky (1988) method, with five subdivisions (see figure below). The method utilized in the current study is based on the latter and represents a radial partition, with five subdivisions delineated on the basis of equal angular rays from the center of mass (O'Kusky et al., 1988).

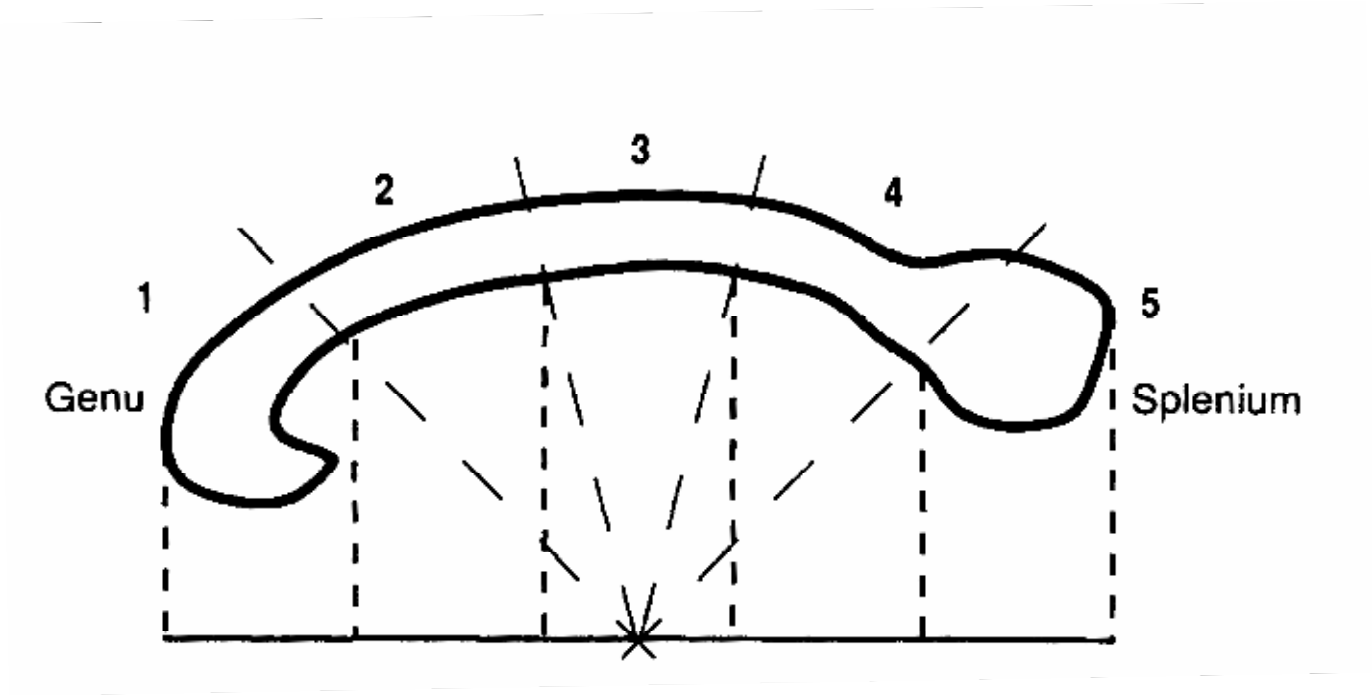

Figure 3. Adapted O'Kusky et al. (1998) five-segment subdivision procedure
Source: "Corpus callosum morphology in attention deficit-hyperactivity disorder" by G.W. Hynd, M. Semrud-Clikeman, A.R. Lorys, E.S. Novey, D. Eliopulos, & H. Lyytinen, 1991, *The Journal of Learning Disabilities*, p. 143. Copyright 1991 by PRO-ED, Inc. Reprinted with permission.

Cognitive Function of the Corpus Callosum

The fibers in the corpus callosum are also generally segregated according to function (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). In the midbody of the CC, the majority of fibers are larger in diameter than in the anteriorly located genu. These thicker fibers represent a higher conduction velocity, necessary for the fast transmission of motor and sensory information. In the genu of the corpus callosum, fibers are thinner. Since the fibers of the genu provide interhemispheric transfer for regions of the prefrontal lobes, the thinner fibers represent a slower conduction potential, reflective of the planning and organizational role of the pre-frontal cortex. Considering the greater complexity of planning and organizational functions, these processes would be expected to occur more slowly than sensory and motor responses. Thinner fibers are present in greater percentage not only in the anterior region of the CC but also in the splenium; however, the posterior pole of the splenium shows a dramatic decrease in the percentage of thin fibers, representing the area of visual processing (Aboitiz et al., 1992).

Much of the early research regarding the functions of the CC focused on patients who had underwent a surgical operation to sever the interhemispheric connections of the CC in intractable epilepsy (for a comprehensive review, see Gazzaniga, 2000). The classical findings of lateralization testing in these patients indicate that sensory information, as well as thoughts and memories, processed in one hemisphere are not available to the other hemisphere (Sperry, 1984). Split-brain research has also been informative regarding the laterality of higher order functions, including language, speech, and problem solving to the left hemisphere and facial recognition, perceptual distinction,

and attention to the right hemisphere (Gazzaniga, 2000). Certainly, without the two hemispheres of the brain communicating information, functioning would be impaired.

Therefore, one might ask to what degree individuals with mild CC abnormalities suffer functional impairment. The literature suggests individuals with callosal agenesis (the CC was incompletely or never formed during neural development) do not show the same extreme deficits in information transfer as those experiencing the surgical removal of this brain structure (Jeeves & Silver, 1988), perhaps due to the hypothesized reorganization and compensation that occurs in acallosal patients (Gazzaniga, 2000). However, studies have shown that mild deficits of interhemispheric transfer are apparent in individuals with callosal agenesis (e.g. Aglioti, Berlucchi, Pallini, Rossi, & Tossinari, 1993; Lassonde, Sauerwein, & Lepore, 1995). Recent research has also suggested that individuals with callosal agenesis, even when displaying normal intelligence, demonstrate difficulties in understanding nonliteral language and affective prosody, a result of compromised interhemispheric processing between the emotional-processing right hemisphere and language-dominant left hemisphere (Paul, Lancker-Sidtis, Schieffer, Dietrich, & Brown, 2003).

Furthermore, it should be noted that split-brain research has indicated recisions in different portions of the CC result in unique deficits, an important concept considering the ADHD literature to be described later which is suggestive of abnormalities in specific CC regions. Studies have indicated that although the posterior half of the CC is responsible for the transfer of visual, tactile, and auditory information, the anterior callosum is involved in the transfer of higher order information (Gazzaniga, 2000). In

particular, a case study which involved a callosal resection in two stages, first the posterior and then the anterior, revealed that when the anterior portion of the callosum remained, objects presented in left hemispace (visual information is crossed in the brain, therefore, the right hemipshere processes stimuli presented in the left visual field) could be named in spite of the absence of sensory information transfer from the right hemisphere to the language-dominant left hemisphere (Sidtis, Vope, Holtzman, Wilson, & Gazzaniga, 1981). In an evaluation of the patient's strategies, it was apparent that the right hemisphere was sending the patient "gnostic clues" (Gazzaniga, 2000) about the nature of the object through the preserved anterior pathways. However, once the callosum was completely severed, the patient denied any stimulus presentation in right hemispace (Sidtis et al., 1981).

If ADHD is thought to be related to neurodevelopmental abnormalities and if the corpus callosum is implicated, it is of interest to determine whether a relationship exits between CC abnormalities and deficits on tasks thought to measure higher order executive functioning, including inhibitory control, speed of information processing, problem solving, and attention. In a later section, the research regarding the corpus callosum in respect to these functions, which are hypothesized to be impaired in subjects with ADHD, will be reviewed. Prior to discussing some of these specific functions, however, it is important to recognize the literature describing the relationship between CC morphology and morphometry and general intelligence.

One early study indicated individuals with mental retardation had smaller CC area (Gray, 1934). Stauss, Wada, and Hunter (1994) found that, in individuals with epilepsy,

the size of the posterior region of the corpus callosum was positively related to intellectual ability. In the face of literature suggesting that individuals with surgical resection and developmental agenesis of the CC can show normal intelligence in the absence of other brain damage (e.g. Paul et al., 2003; Sperry, 1984), Stauss and colleagues propose the higher ability might actually be associated with a greater number of neurons in the posterior association areas thought to be responsible for psychometric IQ (Kolb & Whishaw, 1985) and the resulting interconnections rather than the larger splenial area per se. In another study, when IQ was regressed on CC area, Baumgardner et al. (1996) found no relationship between CC size and IQ. Although higher IQ appeared to be related to reduced thickness of the anterior region of the CC in one study of adults, this was only in the absence of a normal upward arching of the anterior body (region directly posterior to the genu) (Peterson et al., 2001). Therefore, the influence of the CC on intelligence remains controversial. The current study addresses the relationship of CC morphometry to specific neuropsychological measures of processing speed, inhibitory control, sustained attention, and problem-solving. In a later section, evidence for impairment in these tasks in ADHD and possible CC involvement will be discussed.

Development of the Corpus Callosum in Humans

In humans, the corpus callosum continues to increase in size until the middle of the third decade and therefore may be part of the "highest order-latest maturing neural network of the brain" (Pujol, Vendrell, Junque, Marti-Vilalta, & Capdevila, 1993, p. 74). Important to note is the fact that the frontal lobes, also implicated in "higher order" processing are also not thought to be mature until early adulthood (Chungani, Phelps, &

Mazziotta, 1987; Fischer & Rose, 1994). Several studies have reported growth in the CC across development (Allen, Richey, Chai, & Gorske, 1991; Giedd et al., 1999; Pujol et al., 1993; Schaefer, Bodensteiner, Thompson, & Wilson, 1991). A larger CC area is thought to be suggestive of either an increased number of neuron axons or increased myelination of these axons (Baumgardner et al., 1996), although research in nonhuman primates argues for the increased myelination hypothesis (Innocenti, 1986).

Research suggests that growth trend of the CC is nonlinear, especially in the most posterior portion, and that the greatest rates are noted between ages 5 and 12 (Giedd et al., 1999). Rakic and Yakovlev (1968) found that prior to birth, the genu exhibits a faster rate of growth than the body of the CC. After birth, the splenium becomes the faster growing region, consistent with the finding of Giedd and colleagues (1999). Other research indicates a bimodal period of significant growth (Njiokiktijien, de Sonneville, Vaal, 1994), with the callosum approximately doubling in size from birth to two and then again from two to adulthood. Also suggestive of a bimodal growth spurt, Schaefer and colleagues (1991) found significant growth periods in the 6-10 and 11-15 age ranges. Furthermore, myelination of the CC is not thought to be complete until adulthood (Yakovlev & Lecours, 1967).

Giedd and colleagues suggested that their finding of a greater rate of growth in the posterior area of CC could be a result of increased myelination in these connections between the association cortices (1999). According to Lurian theory (1980), the association cortices represent the integration of functioning in the temporal, occipital, and parietal lobes and, as noted earlier, are thought to be involved in intelligence as measured

by standardized tests (Kolb & Whishaw, 1985). Therefore, the more advanced intellectual capabilities observed during the 5-12 age range may accompany an increased facilitation of interhemispheric information transfer in regions responsible, in part, for cognitive processing. It should be noted that within adult samples, there has been some evidence of an age by sex interaction in CC development, with several studies suggesting an age-related decrease in CC size for males but not females (Burke & Yeo, 1994; Byne, Bleier, & Houston, 1988; Witelson, 1989). However, Byne and collegues reported this gender difference only in males over 40 (their sample included subjects as young as 14), and even then labeled their finding as "marginally significant." Furthermore, the youngest individual in Witelson's sample was 25. In sum, although both neural growth and pruning are tools of brain plasticity (Chugani, 1996) and the CC clearly participates in this process (Innocenti, 1981), it is likely that increasing age across the sample of school-aged children in the current investigation would be more likely associated with increased, rather than decreased, CC size. However, although Giedd's large-scale longitudinal study reported an increase in CC area with increasing age, clinical studies with significantly fewer subjects have been contradictory in their reports of correlation between CC area and age, with some finding no relationship (Semrud-Clikeman et al., 1994) and others reporting age-size relationships in some clinical groups but not all (Baumgardner et al., 1996; Kayl et al., 2000). Lack of age-related findings in these latter studies could be due to relatively restricted age ranges included in such samples, in addition to smaller sample sizes. Therefore, it is prudent to control for CC variations resulting from age and brain size when examining morphometry in both clinical and healthy control samples.

Demographic Differences and Variations in Corpus Callosum Morphology

The morphology of the CC has been studied with respect to a variety of human differences, some of them specifically related to processes thought to be compromised in children with ADHD. Furthermore, as will be reviewed in the next section, a small body of literature regarding CC differences in individuals diagnosed with ADHD has emerged. The corpus callosum has been found to vary with traits such as handedness (Witelson, 1985, 1989), although not always (Kertesz, Polk, Howell, & Black, 1987), degree of lateralization in brain representation of language (O'Kusky et al., 1988), and verbal fluency (Hines et al., 1992). During the 1980's the topic of sexual dimorphism of the human corpus callosum received significant research attention. The original study positing such a sex-related difference suggested that women exhibited greater overall splenial width and area when compared to men, which the authors interpreted as reduced lateralization of visual-spatial functions (DeLacoste-Utamsing & Halloway, 1982). Although a few additional studies indicated that females exhibited a greater ratio of splenial to overall (Allen et al., 1991; Holloway & De Lacoste, 1986) or posterior (Clarke et al., 1989) CC area, the majority of later investigations failed to replicate the splenial difference (Bell et al. 1985 (with outliers removed); Byne et al., 1988; Kertesz et al., 1987; Oppenheim et al., 1987; Weber & Weis, 1986, as cited in Weis, Weber, Wenger, & Kimbacher, 1989; Weis, Weber, Wenger, & Kimbacher, 1988; Witelson, 1985, 1989) and have called into question the interpretation that degree of functional lateralization can even be related to callosal size (Kertesz et al., 1987). Furthermore, in the initial study, DeLacoste-Utamsing and Holloway (1982) also reported a greater ratio of overall CC

area to brain weight in females, which has received only marginally more research support (Holloway & DeLacoste, 1986; Kertesz, 1987) with some groups reporting no difference (Demeter et al., 1988; Bell et al., 1985; Witelson, 1989). However, it should be noted that in a number of studies, this ratio was not assessed. In the face of contradictory morphometric results, two independent investigators have reported the female splenium morphology to be more "bulbous" and the male splenium to be more "tubular" (Allen et al., 1991; DeLacoste-Utamsing & Holloway, 1992), although this difference was not observed children aged 2 to 16 (Allen et al., 1991).

If there were no real difference in overall CC area, it would be likely that women would generally have a greater CC area to total brain size ratio since women generally have brains 10% smaller than men (Durston et al., 2001). In fact, this is the conclusion Jancke and Steinmetz (2003) came to in their review. They found that increases in overall brain size are accompanied by proportionally smaller increases in overall CC size. Therefore, by definition, larger brains are more "lateralized" than smaller brains (Jancke & Steinmetz, 2003), assuming CC size is a valid measure of lateralization. This finding of relatively less interhemispheric connectivity in larger brains has been replicated in a study comparing the ratio of CC to brain size in several species of primates, including humans (Rilling & Insel, 1999). However, the formula Jancke and Steinmetz arrived at to describe the nonlinear relationship between CC area and brain size accounted for only 30% of the variance. As has been noted by a variety of investigators, a significant amount of individual variability in CC size is present in both adult (Byne et al., 1988; Clark et al., 1989) and child (Giedd, 1999; Njiokiktjien, de Sonneville, & Vaal, 1994) brains. Jancke

and Steinmetz (2003) therefore suggest that many other factors may be related to size differences.

In the 1980's, the quest for relating anatomical CC differences to individual variation in normal populations ended somewhat unfruitfully, as captured in Byne and collegue's (1988) statement, "Existing knowledge of the functions of the corpus callosum does not permit correlations between variations in callosal size and shape and variations in cognitive functions" (p. 222). However, the future of the next decade was foreshadowed in the words of another group of investigators "The existing scientific trend of trying to relate nonpathological behavioral differences to differences in gross anatomy appears to be premature and of debatable value" (Weis et al., 1988, p. 414). Therefore, attention now turns to the series of studies examining callosal differences in pathological populations, in particular, ADHD.

Corpus Callosum Anomalies in Individuals with ADHD

Several studies have investigated differences in CC size in individuals presenting with ADHD. However, all of these studies have used CC area as measured in the mid-sagittal plane. Although recent studies have frequently used volumetric data in examining potential brain structure differences in pathological groups (e.g. Castellanos et al., 1994, 1996; Hill et al., 2003; Filipek et al., 1997; Semrud-Clikeman et al., 2000), to date, no research team has employed volumetric data analysis of the corpus callosum in imaging studies of an ADHD sample. One of the aims of this investigation is to determine whether the traditional area measurements are as effective as volumetric measurements in predicting performance on neuropsychological measures. Since the CC is easily viewed

and measured in the midsaggital plane, it is important to determine whether the area of the CC midsaggitally accurately portrays CC size. Researchers (e.g. Rilling & Insel, 1999) argue the midsaggital plane represents an accurate estimate of overall CC size, citing literature showing that callosal fiber diameter remains consistent across the callosum (Ringo, Doty, Demeter, & Simard, 1994) and fiber density is consistent across variations in size of CC area (Aboitiz et al., 1992). However, this remains to be empirically tested in a direct comparison of overall CC volume and midsaggital area, in both healthy and pathological groups.

The first report of differences in the CC area in ADHD came from Hynd and colleagues (1991). They found that a group of 7 subjects with ADHD, all treated with stimulant medication and judged to be responders, when compared with 10 healthy controls, were shown to have overall smaller CC areas and regional differences in the genu, splenium, and area directly anterior to the splenium (isthmus). Several years later, two independent groups with larger sample sizes (15 per group and 18 per group) published findings confirming differences in ADHD subjects, although with slightly different results. One group reported smaller posterior CC regions, especially in the splenium, with no difference in anterior regions, including the genu, callosal length or total area, in subjects with a history of medication use (Semrud-Clikeman et al., 1994). Giedd and colleagues (1994) also found no difference in total CC area but did report smaller areas in anterior regions of the rostrum and rostral body, which was consistent with the earlier finding of a reduced genu in ADHD subjects (Hynd et al., 1991). Both of

these latter groups utilized Witelson's (1989) 7-subdivision method of parcellation whereas Hynd (1991) used the 5-subdivion method (O'Kusky et al., 1988).

However, when Giedd's research team attempted to replicate their initial findings with a large sample size (57 ADHD; 55 controls), they failed to find differences between the two groups in total CC area or any of the subregions (Castellanos et al., 1996). That same year, though, another large scale study was published reporting differences between subjects with ADHD and healthy controls (Lyoo et al., 1996). Again, using the 7-subdivion method, it was observed that the splenium was significantly smaller in children with ADHD, whether the diagnosis was given based on chart review or through a structured interview. Only in subjects diagnosed through the structured interview was the isthmus (area immediately anterior to the splenium) also significantly smaller in subjects with ADHD.

A recent study including a relatively large and well-defined ADHD sample (23 subjects with no comorbid learning or behavioral disorder with the exception of Oppositional Defiant Disorder) found subjects with ADHD to have a smaller overall CC area and a smaller splenium with a trend toward a smaller genu (Hill et al., 2003). Post hoc analysis comparing only male subjects revealed that ADHD males exhibited a smaller genu than non-ADHD males (Hill et al., 2003). Additionally, subjects having comorbid ADHD and Tourette's Syndrome were found to have a smaller rostral body area when compared to either normal controls or subjects with only Tourette's Syndrome (Baumgardner et al., 1996). However, when 15 males diagnosed with ADHD were compared to 15 non-affected siblings of children with ADHD, no differences were found

between groups for any of the CC regions, controlling for age, global brain size, and handedness (Overmeyer et al., 2000). These authors concluded that "morphological differences in brain structures such as the corpus callosum do not necessarily lead to the phenotypic expression of the disorder," (p. 11). However, it should be noted that the study did not include a control group of healthy subjects without siblings with ADHD.

Certainly, it is a relatively common finding that individuals are capable of possessing behavioral and neurological trait markers for a variety of disorders without manifesting the disorder, often termed as "incomplete penetrance" in reference to genetic disorders (Zalla et al., 2004). For example, healthy siblings of schizophrenic patients were reported to show similar MRI abnormalities as their affected siblings (e.g. Gogtay et al., 2003). Healthy first-degree relatives of individuals diagnosed with bipolar disorder and schizophrenia have been observed to exhibit an increased susceptibility to interference as measured on neuropsychological tests when compared to a healthy, unrelated control group (Zalla et al., 2004).

As discussed earlier, comorbidity is a frequent phenomenon in children diagnosed with ADHD. Therefore, it is important to consider the effects common co-occurring disorders, specifically Reading Disorder and Oppositional Defiant Disorder (ODD), may have played in influencing the findings reported in the studies described above. The literature regarding CC abnormalities in Reading Disorder has been inconsistent, with some researchers reporting no differences between children with reading disorders and controls in overall or regional CC area (Larsen, Hoien, & Odegaard, 1992; Njiokiktjien et al., 1994; von Plessen et al., 2002) and others reporting larger splenial (Duara et al.,

1991; Rumsey et al., 1996) and isthmus (Robichon & Habib, 1988) areas. Smaller anterior areas of the CC in reading disordered subjects have also been reported (Hynd et al., 1995), although the reading disordered subjects in this sample had a high rate of comorbid ADHD. Other investigators have observed differences in shape (Robichon & Habib, 1988; von Plessen et al., 2002); and spatial position (Robichon, Bouchard, Demonet, & Habib, 2000) in reading disordered individuals.

Subjects with a family history of dyslexia exhibited a large CC compared to those subjects without the family history; the authors interpreted the larger CC to be representative of a reduction of normal asymmetry (Njiokiktjien et al., 1994), paralleling the finding of adult reading disordered subjects having reversed brain asymmetry in the region of the angular gyrus and a larger splenium than normal readers (Duara et al., 1991). However, reading disordered subjects who had suffered an adverse perinatal incident were more likely to have smaller CCs (Njiokiktjien et al., 1994).

Fittingly, comorbidity has been addressed in many of the ADHD studies described above. In Lyoo's (1996) investigation, the ADHD sample displayed high comorbidity with reading disorder. When only non-reading disordered subjects were compared, the differences in the callosal regions of the ADHD and nonADHD subjects were not significant. Furthermore, in the Castellanos et al. (1996) study, which reported a finding of no significant differences between ADHD and controls, 9 of the 57 ADHD subjects were diagnosed with a comorbid learning disability, leaving one to question whether the findings reported in ADHD studies have more to do with the comorbid learning disorders than the attention disorder. However, it should be noted one of the

earlier reports of ADHD-linked CC abnormalities included a sample without comorbid reading disorder (Semrud-Clikeman et al., 1994), although learning disability comorbidity was not addressed in Hynd's work (1991). Furthermore, the sample included in the Hill et al. (2003) study was completely free of comorbid reading disorders.

In sum, research suggests pure ADHD and reading disorders may display a somewhat different morphological manifestation of the CC, with a larger posterior CC area potentially implicated in reading disorders due to the location of the language areas of the brain and possible absence of the normal lateralization of language. Therefore, the current investigation employs a sample carefully screened to ensure the absence of comorbid learning disorders. The comorbidity of ADHD and ODD has received less attention in the existing literature regarding CC differences in ADHD. Only one study statistically examined this question and found that although no difference existed between ADHD and ADHD + ODD subjects in terms of total CC or genu area, a difference was present for splenium area, with the ADHD + ODD subjects having a larger splenium than subjects with ADHD alone (Hill et al., 2003).

Corpus Callosum in ADHD as Related to Behavioral Manifestations

From the earliest investigations of differential CC morphometry in ADHD, it has been recognized that such differences do not become meaningful until linked to behavior commonly noted in children with ADHD (Hynd et al., 1991), an idea echoed in even the most recent studies (Hill et al., 2003). Although relationships between anatomy and performance on cognitive or behavioral tasks tend to be relatively crude (Casey, Trainor, & Giedd, 1997), the examination of such relationships in both control and disordered

subject groups provides important information. As pointed out by Hill and colleagues (2003), the same brain region may not contribute to tasks in the same way across comparison groups. The current study represents an extensive investigation of a variety of neuropsychological tasks thought to be impaired in ADHD as related to CC size in children with ADHD and healthy control children. With one notable exception (Giedd et al., 1994), studies of CC morphometry in ADHD have failed to examine the relationship between this brain structure and behavioral measures. In the relative absence of such literature, two other lines of research can be helpful in elucidating potential areas of relationship between CC structure and function in ADHD subjects. The first of these are investigations of CC morphology in subjects manifesting disorders other than ADHD but yet present with similar symptom profiles of impaired attention and inhibitory control. If some neuropsychological or behavioral aspects of ADHD are indeed related to the CC, it would be likely that individuals with different disorders but overlapping symptoms may show some of the same abnormalities. The second line of research focuses upon studies relating structure to function, especially those executive functions thought to be impaired in ADHD, in various samples.

Corpus Callosum Abnormalities in Other Disorders

Head Injury

Head injury serves as an interesting comparison for ADHD since attentional difficulties are frequently noted after head injury (Teeter & Semrud-Clikeman, 1997). Furthermore, the CC has been found to be particularly vulnerable in cases of head injury (Adams et al., 1989), and several imaging studies have documented CC atrophy in brain

injury patients (e.g. Anderson & Bigler, 1994; Benavidez et al., 1999). For example, a study comparing two types of brain damage revealed that those patients with severe diffuse injury of the white matter-rich brainstem and corpus callosum showed greater impairment in speed of information processing compared to individuals suffering severe focal injuries (Wilson, Hadley, Wiedmann, & Teasdale, 1995).Verger and colleagues attribute reduced CC area after head injury to both shear injury and neuronal loss in the hemispheres (2001). In a population of moderately to severely head-injured children evaluated at least six years post-TBI, it was found that, after controlling for the effects of age, CC area was highly correlated with processing speed, as measured by Trail Making Test A and B (Reitan & Wolfson, 1985), visual reaction time, and visuospatial functioning, as measured by Performance Intelligence Quotient from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) and the Judgment of Line Orientation (JLO; Benton, Varney, & Hamsher, 1987) (Verger et al., 2001) after controlling for the effects of age.

Multiple Sclerosis

Multiple sclerosis (MS) is a disease involving white matter degeneration, including the corpus callosum. MS generally affects adults, although 2.7 to 5% of cases are children under the age of 15 (Gadoth, 2003). Because of the frequent involvement of the CC (Brown, 2003; Dietemann et al., 1988; Simon et al., 1986), studies which include comparisons of MRI findings and neuropsychological measures in samples of MS patients can provide insight into the function of the CC and are therefore pertinent to the current investigation. Patients with MS and confirmed CC atrophy have been shown to

demonstrate impairment in the interhemispheric transfer of auditory, sensory/motor, and visual information compared to MS patients without atrophy and normal controls (Pelletier et al., 1993; Rao, Bernardin, et al., 1989). Furthermore, CC atrophy was found to predict poorer performance on tasks of speeded information processing, abstract reasoning or problem solving, and sustained attention (Rao, Leo, Haughton, St. Aubin-Faubert, & Bernardin, 1989). It has also been reported that CC size is related to auditory and visual attention, word fluency, verbal learning over repeated trials, and visuo-spatial tasks in MS subjects (Rao, Leo et al., 1989; Ryan, Clark, Klonoff, Li, & Paty, 1996; Swirsky-Sacchetti et al., 1992).

Prenatal Exposure to Alcohol

Children who have experienced prenatal exposure to alcohol often present with inattentive and hyperactive symptoms (Nanson & Hiscock, 1990); thus serving as an interesting comparison for children with ADHD. In subjects with prenatal alcohol exposure, the corpus callosum has been found to be selectively vulnerable (for a review, see Mattson, Schoenfeld, & Riley, 2001). Smaller areas have been reported in overall CC area and in four out of five regions, including the most anterior area as well as the splenium and posterior midbody (Riley et al., 1995). Furthermore, although the effect for overall CC size disappeared when controlling for brain size, the differences in the most anterior and posterior regions of the CC remained, suggesting that these areas are proportionally smaller in children with prenatal exposure to alcohol (Riley et al., 1995). In addition to smaller CC areas, especially in the isthmus and splenium, other investigators have also reported displacement of the CC positionally within the brain

(Sowell et al., 2001). As indicated earlier, the most anterior and posterior regions of the CC are the areas most frequently implicated in ADHD. Furthermore, one investigation reported correlations between poor performance on an interhemispheric transfer task and reduced CC area in a sample which included normal controls and children exposed prenatally to alcohol (Roebuck, Mattson, & Riley, 2002).

Genetic Disorders

Finally, the corpus callosum has been implicated in several genetic and developmental disorders, and such disorders are often comorbid with either the ADHD diagnosis or marked attentional difficulties. Unfortunately, the reports of CC involvement in some of these disorders has been inconsistent. Is important to note that the basis for inattentive symptoms in these other developmental disorders could be etiologically distinct from uncomplicated ADHD.

Neurofibromatosis. Attentional difficulties have been found to occur in individuals with Neurofibromatosis (NF) at a higher prevalence rate than the general population (North et al., 1995). However, one imaging study unexpectedly found that subjects with NF had a larger CC area compared to healthy controls. Moreover, a trend toward a larger CC area for those NF subjects with comorbid ADHD was present compared to NF-only subjects (Kayl, Moore, Slopis, Jackson, & Leeds, 2000). Despite the overall larger areas in both the NF and NF + ADHD groups, severity of attentional disturbance as measured by teacher report was associated with smaller total callosal areas (Kayl et al., 2000).

Williams Syndrome. Because of the suspected white matter deficits in Williams Syndrome (WS) (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001), CC morphology and morphometry has also been examined in children presenting with this disorder. The neuropsychological profile of children with WS includes deficits in visual-spatial processing and psychomotor ability with preservation of linguistic abilities and facial processing (Braden & Obrzut, 2002). Furthermore, research indicates that children with WS are four times as likely to be diagnosed with ADHD than children in the general population (Finegan, Sitarensios, Smith, & Meschino, 1994).

Imaging studies have found reduced overall posterior areas of the CC in subjects with WS, in particular the isthmus and splenium (Schmitt et al., 2001; Tomaiuolo et al., 2002), although not consistently (Wang, Doherty, Hesselink, & Bellugi, 1992). However, it is important to note that although subjects with ADHD have been reported to have reduced posterior CC areas, this same finding in the WS subjects could be due to either attentional deficits or difficulties with visual processing as the posterior region of the CC connects the parietal-occipital regions of the brain. Furthermore, the anterior subregions of the CC appear to be relatively preserved in subjects with WS (Schmitt et al., 2001), which is inconsistent with some of the findings in the ADHD literature (Baumgardner et al., 1996; Giedd et al, 1994; Hynd et al., 1991).

Summary

As knowledge regarding the relationship of the corpus callosum to ADHD symptomology is accumulated, it will be important to further specify the uniqueness of CC abnormalities to either ADHD or the deficits of attention and executive functioning

observed in individuals with ADHD. Although the literature regarding the role of the CC in developmental and genetic disorders presents a complicated picture in terms of the overlap with ADHD, the research linking CC involvement to head injury, multiple sclerosis, and fetal alcohol involvement and the specific cognitive impairments secondary to these conditions suggests the relationship between cognitive functions and the CC may be a fruitful avenue of investigation. The discussion now turns to the available literature regarding executive processes commonly reported to be deficient in the ADHD population and the potential involvement of the CC in these difficulties.

Executive Functioning Deficits in ADHD and Potential CC Involvement

One of the major reasons for studying the corpus callosum in subjects with ADHD is articulated by Yazgan and Kinsbourne (2003), "Among the functions that have been proposed for the CC is mediation of interaction between the extensive territories of the hemispheres that is links homotopically" (p. 423). In particular, the anterior regions of the genu and rostrum and the posterior splenium are of interest because of their higher percentage of the thin fibers thought to be implicated in the facilitation of the cognitive process (Aboitiz et al., 1992), as well as the involvement of the frontal (e.g. Garavan et al., 1999; Lou et al., 1984, Lou et al., 1989; Rubia et al., 1999; Zametkin, 1990) and posterior (Posner & Petersen, 1990) regions in attentional and inhibitory control functions outlined in the earlier description of the biological bais of ADHD. The current study represents an investigation of the relationship between corpus callosum anatomy and the specific executive functions of processing speed, inhibition, sustained attention, and problem solving in children with and without ADHD.

Processing Speed

While often considered in the realm of executive functions, processing speed, or perceptual speed, has also been implicated as an underlying explanation of more general intellectual functioning (Eysenck, 1982; Jensen, 1982; Neubauer, Riemann, Mayer, & Angleitner, 1995; Vernon, 1987). Other theorists have suggested processing speed, with labels such as "Broad Cognitive Speediness" (Carroll, 1997, p.125) or "Cognitive Processing Speed" (McGrew, 1997, p. 155), functions as a component of psychometric intelligence. Mental speed has also been conceptualized differently from the information-processing and psychometric approaches, with the former interested in speed in all processes and the latter narrowing its conceptualization to perceptual and motor processes (Vigneau, Blanchet, Loranger, & Pepin, 2002). Ultimately, beyond simple reaction time tests, most tasks designed to tap mental speed involve elements of both the information processing and perceptual-motor aspects of speed. Furthermore, some research has indicated that the relationship between speed and psychometric IQ increases as the complexity of the speeded task increases (Vigneau et al., 2002).

Processing or perceptual speed has also been an area of interest in the ADHD literature. Barkley (1997a) has suggested that mild IQ reductions in comparison to normal subjects is a possible result of ADHD. This finding is particularly interesting when considering individuals with ADHD tend to reveal difficulties on measures of executive functioning, including perceptual speed, while performing comparably to their nonaffected peers on verbal and spatial measures often used in intelligence testing (Barkley, 1997a; Pennington & Ozonoff, 1996). Thus, it may be the contribution of the

processing speed measures in some traditional IQ tests (such as Coding or Symbol Search on the Wechsler Intelligence Scale for Children—Third Edition (WISC-III); Wechsler, 1991), that contribute to the finding of mild IQ deficits in ADHD subjects.

Some researchers have moved toward greater specificity and argued ADHD subtypes present with different neuropsychological profiles. It has been suggested that subjects with hyperactive/impulsive symptoms show impairments in behavioral inhibition and subjects with predominantly inattentive symptoms reveal deficits in processing speed and vigilance (Barkley, 1997b; Barkley et al., 1990). As mentioned earlier, it is often difficult to distinguish between the hyperactive/impulsive and the combined subtypes of ADHD (Paterine et al., 1996); therefore, especially in older child and adolescent samples, most participants are likely to be classified as presenting with either combined type or predominantly inattentive.

Although it has been proposed that a deficit in processing speed may distinguish between combined and inattentive types, recent research suggests both subtypes exhibit slower processing speed. For example, one study reported that although male (but not female) subjects with ADHD (Combined Type) exhibited the expected deficit in inhibitory control in comparison to those with the inattentive subtype, both groups revealed impaired speed compared to controls (Nigg, Blaskey, Huang-Pollack, & Rappley, 2002). Another recent study has also indicated both the combined and inattentive types display deficits on processing speed tasks, with the inattentive type perhaps having greater impairment (Chhabildas, Pennington, & Willcutt, 2001). And

when considered as a unitary group, subjects with ADHD underperform on measures of processing speed (Barkley, 1997b; Pennington & Ozonoff, 1996).

Recognizing the potential importance of processing speed in the neuropsychological description of ADHD, it is of interest to determine whether deficits in this function are related to the previously noted differences in CC anatomy in subjects with ADHD. Only a few studies to date have directly reported a relationship between larger CC sizes and faster information processing. Jaenck and Steinmetz (1994) demonstrated that all subareas of the CC, with the exception of the isthmus, were related to mean reaction time in dichotic listening tasks in normal adults. Another group reported a positive relationship between CC size and performance on processing speed, as measured by tasks such as the Trail Making Test (Reitan & Wolfson, 1985), Symbol Digit Modalities Test (Smith, 1982), and a cancellation test, in healthy controls but not in subjects diagnosed with schizophrenia (Hoff, Neal, Kushner, & DeLisis, 1994). In a sample of head injured children and adolescents (at least six years post-injury), Verger et al. (2001) reported a strong correlation between CC area and measures of processing speed, including visual reaction time and the Trail Making Test (Reitan & Wolfson, 1985). Furthermore, processing speed is a significant area of impairment in other disorders with proposed abnormalities of the CC, such as multiple sclerosis (e.g. Mendez, 1995; Rao, Leo et al., 1989).

Inhibitory Control

As reviewed earlier, inhibitory control has been suggested to be significantly impaired in individuals with ADHD (Barkley, 1997ab; Nigg, 2001; Pennington &

Ozonoff, 1996). In many ways, inhibitory control is thought to be a building block of executive functioning. Although the processes underlying executive functions are described differently in the literature, inhibition is generally considered to be important in most models (e.g., Bunge, Ochsner, Desmond, Glover & Gabrieli, 2001; Roberts & Pennington, 1996) as it serves to facilitate higher order executive functions and self-regulation. For example, unless one is able to inhibit attention to irrelevant stimuli, it is difficult to mobilize the cognitive resources necessary to engage in working memory. Without sufficient working memory, it would be challenging to hold a goal in mind while evaluating alternatives, thus making the higher order functions of planning or organization challenging. Executive inhibitory control can be further subdivided into motor inhibition and interference control (Nigg, 2001), both of which will be examined in the current study in relation to the size of the CC.

The role of the corpus callosum in the inhibitory control process as measured by laboratory tasks has not received a significant amount of attention. Using a modified Stroop task which allowed for an examination of inter-hemispheric communication through unilateral and bilateral presentations of the stimuli, it was found that both schizophrenics and healthy controls displayed a negative association between CC size and inter-hemispheric interference, such that those individuals with smaller callosum measurements showed greater interference difficulties (Woodruff et al., 1997). Furthermore, another study comparing controls and schizophrenics found that for the controls, larger CC size was related to better performance on a battery of tests tapping inhibition and interference control, including the Wisconsin Card Sorting Test (Heaton,

1981), Booklet Categories Test (DeFilippis & McCampbell, 1998) and Stroop Color Word Test (Golden, 1978), in controls but not in patients (Hoff et al., 1994).

As discussed in the section on the biological basis of ADHD, the majority of literature surrounding the inhibitory function implicates a "distributed cortical-basoganglionic neural network" (Pliszka, 2001, p. 42). Therefore, a finding of no relationship between this function and the CC would serve as additional evidence for the localization of the inhibitory function to frontal and striatal processes. However, a recent study by Pliszka's group found that the dorsal anterior cingulate cortex revealed significant activation in concert with the dorsolateral prefrontal cortex during the inhibitory trials of the Stop Signal Task (Logan, Cowan, & Davis, 1984; Logan, Schachar, & Tannock, 1997) and these activations were significantly smaller in ADHD subjects (Pliszka et al., under review). Considering the close proximity of the anterior cingulate to the corpus callosum and the evidence cited above regarding the possible participation of the CC in inhibitory or interference control activity, the relationship between structure and function in this case remains an empirical question to be tested by the current study.

Sustained Attention

Inattentiveness, of course, is one of the hallmark symptoms of ADHD. However, the theoretical and biological underpinnings of ADHD are numerous, as noted earlier, and more recent models tend to describe attention as being represented by "multiple, interactive functional systems," consisting of both cortical and subcortical structures and ascending and descending pathways between the two (Riccio, Reynold, Lowe, & Moore,

2002). One commonly studied aspect of attention in ADHD subjects has been sustained attention, or vigilance. Sustained attention has been defined as the ability to maintain focus over time (Mirsky, Anthony, Duncan, Ahearn, & Kellam 1991). Posner and Petersen (1990) suggested a norepinephrine-innerverated vigilance network consisting of the locus ceruleus, pulvinar, superior colliculus, and posterior parietal regions of the brain. One of the most commonly used clinical tools in ADHD assessment to measure sustained attention or vigilance has been the Continuous Performance Task (CPT; Rosvold, Mirsky, Sarason, Bransome, & Beck, 1956) (DuPaul, Anastopoulos, Shelton, Guevremont, & Metevia, 1992; Riccio et al., 2002). The task requires subjects to watch a computer screen over a relatively long period and make a response when a pre-identified stimuli appears, thus requiring sustained attention. However, the research appears to indicate that although the CPT is sensitive to attentional disturbance, it is not specific to any etiology or disorder (for a comprehensive review, see Riccio et al., 2002). Regardless, these results suggest that sustained attention or vigilance is certainly impaired in ADHD children both in terms of laboratory tasks and behavioral manifestations.

The corpus callosum is important as it is thought to be responsible for the allocation of attention and arousal between the two hemispheres (Guiard, 1980; Kinsbourne, 1974). As suggested by Kinsbourne (1974), "The corpus callosum minimizes disparities in the distribution of mental capacity ('attention') between the two hemispheres so that both can be rapidly involved in any activity" (p. 253). Rueckert, Sorensen, and Levy (1994) summarized findings from studies of split-brain patients (e.g. Ellenberg & Sperry, 1979; Diamond, 1979) which suggest that after commissurotomy,

patients had greater difficulty with sustained attention. Rueckert and colleagues concluded the "corpus callosum is specifically involved in sustaining attention on passive tasks involving little external input and a minimum of active responding on the part of the subjects" (p. 159).

Rueckert and various colleagues have reported on a series of studies that utilized performance on a visual tachistoscopic task as a measure of interhemispheric communication and compared it to performance on a task of sustained attention. The tachistoscope is a device that allows information to be presented to one or both of the visual fields and therefore can assess ipsilateral or bilateral processing, the latter requiring transfer of information across the corpus callosum. The task of sustained attention was a CPT with a short interstimulus interval (ISI) and a long ISI. The authors described these two ISI lengths as the difference between externally and internally maintained attention, in that the longer ISI required greater vigilance (internal maintenance of attention) on the part of the subject. In an initial study with children, it was found that subjects with greater interhemispheric facilitation exhibited faster reaction times on the vigilance trials of the CPT (Rueckert et al., 1994).

The work was replicated, although this time the anterior callosum efficiency was assessed by a task requiring subjects to perform independent, yet simultaneous movements with the left and right hands (draw a line with one hand and a circle with other) (Rueckert et al., 1996). Those subjects experiencing greater interference, or less callosal efficiency, showed more difficulty on the long ISI (sustained attention) task compared to the short ISI task, whereas the more efficient subjects did not show the same

difficulties (Rueckert & Levy, 1996). Finally, these authors replicated these results in adult subjects, using a slightly modified bimanual task to assess anterior CC efficiency and the visual tachistoscopic task to measure posterior CC efficiency (Rueckert, Baboorian, Stavropoulous, & Yasukate, 1999). Although it has been acknowledged that the relationship between proposed callosal efficiency and sustained attention may be indirect as no task has been unquestionably found to measure callosal efficiency (Rueckert & Levy, 1996), the correlation between CC size and attentional performance in patients with MS (Rao. Leo et al., 1989) provides further evidence that the CC is involved in this function.

Problem Solving

Planning and problem solving are higher order tasks which require the integration of several more foundational executive functions. Problem solving difficulties as measured by executive functioning tasks in children with ADHD have been well documented (e.g. Aman, Roberts, & Pennington, 1998; Houghton et al., 1999; Weyandt & Willis, 1994), especially in children with the combined type (Klorman et al., 1999; Nigg et al., 2002; Pennington & Ozonoff, 1996). Although some subjects having experienced either the surgical cutting or developmental agenesis of the CC are capable of obtaining normal IQ scores, deficits in cognitive functions such as concept formation and abstract reasoning have been noted (Brown, 2003). To date, there has not been a significant amount of research regarding the relationship between the corpus callosum and higher order executive functions, such as problem solving and planning. Much of the

limited research available is from work with patients with MS or individuals with callosal agenesis.

Despite the current shortage of data supporting the relationship between the corpus callosum and problem solving or abstract reasoning in normal subjects, the link was hypothesized by Bogen and Bogen (1969). These authors posited that problem solving requires the interaction of both hemispheres, which each processing different types of information. As Brown and Paul (2000) stated of subjects with agenesis of the corpus callosum (ACC):

> The consequences of this reduction in interconnectivity are typically not apparent in tasks demanding rote and overlearned cognitive skills; thus, measured IQ may be normal. However, more complex forms of reasoning, concept formation, and problem solving are maximally demanding of access to multiple processing systems, and particularly of bihemispheric processing interactions. Thus, deficits will be found in more complex and novel cognitive interactions (p. 136).

Case studies of patients with ACC have been suggestive of poor concept formation and abstract reasoning (Brown & Paul, 2000), although not with complete consistency. For example, in Fischer and colleagues' (1992) report of two patients with callosal agenesis and normal intelligence, one exhibited mild deficits in problem solving while the other showed no such deficits. Difficulties in the understanding of nonliteral language and affective prosody has been observed in these subjects (Paul et al., 2003) as well general mild social disturbance (O'Brien, 1994). Deficits in problem solving, or

fluid reasoning, and social information processing have documented to co-occur (Jones & Day, 1996; Schnoebelen, Guy, Semrud-Clikeman, 2002).

Although evidence suggests the corpus callosum is potentially implicated in many of the neuropsychological deficits noted in children diagnosed with ADHD, this question has received relatively little research attention. Giedd and colleagues (1994) reported a smaller rostral body of the CC to be associated with higher ratings of impulsivity and hyperactivity on the Conners' rating forms (Conners, 1994). However, these authors conducted a "non-hypothesis-driven" (p. 667) analysis in which they related several computerized attentional measures (CPT, visual search, divided attention, go/no-go, visual discrimination, delayed match to sample) to all of the CC subregions and found no significant correlations. They suggested this finding was perhaps due to the theoretical idea that symptoms of ADHD are caused by a deficit in response inhibition rather than inattention and therefore the selected tasks were inappropriate. Furthermore, because of the high number of statistical tests performed on the tasks making up the computerized battery, the authors acknowledged the low power of their study.

Therefore, the current investigation sought to once again test the relationship between corpus callosum size and neuropsychological function, this time selecting tasks representing a variety of executive functions. Furthermore, hypotheses about relationships with specific areas of the corpus callosum were set *a priori* to minimize the number of statistical tests run and maximize power. Finally, this will be the first time volume is used as the measure of overall corpus callosum size in a comparison of clinical and nonclinical groups.

Stimulant Naïve versus Chronic Treatment: Structural Ramifications

The widespread use of stimulant medication to treat children with ADHD continues to be an area of controversy (Volkow & Insel, 2003). Despite the documented safety and efficacy of these medications when used as prescribed (for a review, see Spencer et al., 1996), concerns have been raised regarding the long-term use of stimulants in children (National Institutes of Health, 1998). Hyman (2003) articulated one of these worries as "a general concern that the use of psychotropic drugs in children will lead to drug-induced plasticity, introducing irreversible, malign changes in the circuits of developing brains" (p. 1310). Certainly, the age in which children are generally diagnosed with ADHD and commence stimulant treatment coincides with the ongoing development and myelination of many brain structures (Kolb & Fantie, 1989), including the corpus callosum (Giedd et al., 1999; Njiokiktijien et al., 1994; Schaefer et al., 1991; Yakovlev & Lecours, 1967). Furthermore, drug-induced changes in brain size have been observed; for example, the case of striatal enlargement following chronic administration of antipsychotic medication in both animals (Andersson, Hamer, Lawler, Mailman, & Lieberman, 2002) and humans (Chakos et al., 1994; Doraiswamy, Tupler, & Krishman, 1995; Keshavan et al., 1994). Therefore, it becomes important to investigate the effects of long-term stimulant treatment on neuroanatomy, which was one of aims of the current investigation.

A related question is whether the differences in CC morphometry noted in children with ADHD are simply an "artifact" of chronic stimulant treatment (Pliszka et al., under review). Initial evidence from a functional imaging study suggests that neural

activation abnormalities in response to a task of inhibitory control are similar in both treatment naïve and chronically treated subjects. Important to note, however, is the fact that chronically treated children with ADHD showed a nonsignificant trend toward normalized activation when compared to the treatment naïve group (Pliszka et al., under review).

Research with animal models has been supportive of the potential for adaptive neural changes following drug treatment (Miguel-Hidalgo & Rajkowska, 2002). However, much of the literature has focused on the possible maladaptive neural changes resulting from chronic stimulant treatment. Hyman (2003) states that there exists a "specific concern about long-term effects of the stimulant drug class, which also includes cocaine, because stimulants can produce sensitization of certain behaviors in animal models and addiction in humans" (p. 1310). Several studies have indicated exposure to stimulants cause change in dopamine cells and abuse potential in rats (e.g., Bolanos, Barrot, Berton, Wallace-Black & Nestler, 2003; Brandon, Marinelli, & White, 2003), although clinical studies suggest stimulant treatment reduces the chances of substance abuse in ADHD samples (for a recent meta-analysis, see Wilens, Faraone, Biederman, & Gunawardene, 2003). However, there are many questions about the generalizability from animal to human models in terms of developmental trajectory, dosage levels, method of administration, and drug metabolism in different species (Volkow & Insel, 2003). Furthermore, as highlighted by Bolanos and collegues, animal models sample "normal," nonpathological subjects and whether or not the findings are consistent for children with

ADHD is unknown (2003). Therefore, research regarding the long-term effects of stimulant medication is overdue.

Conclusion

It has been articulated that corpus callosum abnormalities in subjects with ADHD fail to become meaningful until linked to behavioral and cognitive symptoms common to the disorder (Hill et al., 2003; Hynd et al., 1991); however, such studies are lacking. The current study examines the relationship between corpus callosum size as measured by MRI and measures of a variety of neuropsychological processes in individuals with attention deficits as well as healthy control subjects. Since ADHD is commonly treated with the use of stimulant medication, concerns have been raised as to the long-term neurological consequences of chronic stimulant treatment, yet the majority of previous neuroimaging studies have not controlled for such long-term treatment. Therefore, researchers have not yet been able to definitely state whether the neuroimaging differences noted between subjects with ADHD and healthy controls are representative of pre-existing differences or result from chronic stimulant administration. The current investigation included both a stimulant naïve and a chronically treated ADHD group, in addition to a healthy control group, in order to determine if corpus callosum size in ADHD subjects is related to long-term stimulant usage. Finally, corpus callosum size has historically been defined as the area of the CC as viewed in the mid-sagittal slice. It remains to be determined whether the size estimate obtained from this single slice is representative of the entire volume of the CC. Therefore, the current study was the first to

employ volume as the unit of CC measure in a sample of ADHD and healthy control children.

Chapter 3: Statement of the Problem

ADHD represents a significant mental health issue considering both the high prevalence rate and the functional impairment often accompanying the disorder. Since ADHD is biologically based, research is continually focused on specifying the underlying neuropathology. As discussed in the previous chapter, a variety of neuroanatomical and neurofunctional abnormalities have been noted in children and adults suffering from deficits of attention. Although recent efforts have focused on a frontal-striatal pathway, many authors agree the neural network responsible for inhibitory control and attention is likely distributed across numerous brain regions. The corpus callosum is the largest interhemispheric fiber track in the brain and its participation in information transfer between the two hemispheres has been well documented (e.g. Gazzaniga, 2000). However, some research has indicated that through this facilitation of interhemispheric communication, the callosum also plays a role in other specific executive functions (e.g. Banich, 1998; Rao, Leo, et al., 1989; Ruekert et al., 1994; Verger et al., 2001; Brown & Paul, 2000). Furthermore, several regions of the corpus callosum have been observed to be smaller in individuals with ADHD compared to controls, and in the one study investigating the relationship between structure and function, this anatomical difference was linked to higher ratings of ADHD symptomology (Giedd et al., 1994).

Although CC abnormalities have been frequently reported, there has been debate as to which specific regions of the callosum are implicated, with the most frequently observed differences in ADHD samples occurring in either the most anterior or posterior

regions. Much of the previously conducted research on the CC in ADHD suffers from poor specification of clinical groups, with many subjects presenting with comorbid disorders, especially learning disabilities. Therefore, the current study employed a carefully selected sample of subjects in an attempt to shed further light on the localization of CC differences in ADHD. Utilizing CC volume as opposed to area as the unit of measure offers the possibility of greater measurement specificity. If volume and area were not found to be highly correlated in the current study, the degree to which volume offers enhanced predictive power over area measurement as to neuropsychological performance was to be tested. Once anatomical abnormalities are outlined, it is important to begin connecting these differences to function. This study aimed to further define the functional significance of the corpus callosum by relating CC size to specific executive functions impacted in individuals with ADHD using data from both healthy control and clinical subjects.

Finally, the widespread use of long-term stimulant medication in children has raised some concerns about its potential impact on the developing brain. Since medication history has generally not been considered in neuroimaging studies of ADHD samples, it has been argued that the differences noted between ADHD and healthy control subjects may be a result of the chronic stimulant exposure (Pliszka et al., under review). Therefore, the current investigation compared two ADHD groups, one chronically treated with stimulants and one treatment naïve, to determine if medication status affects the anatomy of the corpus callosum.

Hypotheses

Hypothesis 1: Subjects with ADHD (both chronically treated and treatment naïve) will show differential overall CC volume and area and differential subregion areas when compared to healthy controls.

a) Both ADHD groups will have smaller overall CC volume and area than healthy controls. There will be no difference between the two ADHD groups.

b) Both ADHD groups will have smaller areas in the genu (most anterior) and splenium (most posterior) regions of the CC when compared to healthy controls. There will be no difference between the two ADHD groups.

Rationale: Differences in overall (Hill et al., 2003; Hynd et al., 1991), genu (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991, in males, Hill et al., 2003), and splenium (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994) corpus callosum area have been reported. The current study seeks to replicate these findings with volumetric measures and to determine whether these abnormalities are exhibited in both stimulant naïve and chronically treated ADHD groups. The genu of the CC provides interhemispheric connections for areas in the frontal lobes. A body of neuroimaging research implicates the frontal lobes in ADHD, both in terms of reduction in size (Castellanos et al., 1996; Filipek et al., 1997; Overmeyer et al., 2001; Semrud-Clikeman et al., 2000) and activation (Lou et al., 1984; Lou et al., 1989; Zametkin et al., 1990). Therefore, the reduced anterior CC area noted in previous studies may be related to frontal lobe abnormalities.

Previously observed posterior CC abnormalities in individuals with ADHD may co-occur with deviations of the brain's posterior attentional system (Posner & Peterson, 1990). Faced with the lack of conclusive data to the contrary, the null hypothesis regarding anatomical differences between the chronically treated and treatment naïve groups was proposed. Furthermore, in a recent fMRI study comparing these two ADHD groups, it was found that both ADHD groups exhibited differential activation compared to healthy controls, although those chronically treated with medication trended toward greater similarity to the healthy controls (Pliszka et al., under review).

Hypothesis 2: Level of behavioral symptomotology of ADHD will be related to CC size.

a) Parent reports of hyperactive and inattentive behavior will be inversely related to overall volume and genu and splenium area when data is collapsed across all groups, such that greater symptomatology is related to smaller size.

Rationale: To date, only one study has examined this question. Giedd and colleagues (1994) reported an association between smaller anterior areas of the CC and higher ratings of impulsivity and hyperactivity, as would be expected based on the evidence suggesting frontal involvement in inhibitory control. Considering that smaller posterior CC area is actually a more consistent finding in the ADHD literature and that the posterior CC has been implicated in tasks of sustained attention (e.g. Rueckert et al., 1999), the failure to notice a relationship between ADHD symptoms and posterior regions is curious. Therefore, the current study tested this hypothesis.

Hypothesis 3: Neuropsychological measures will be related to CC size in both ADHD and control subjects.

a) Planning ability will be related to the overall CC volume, as well as the area of the genu, such that larger size is associated with higher scores on a planning measure.
b) Speed of information processing will be related to larger volumes of the overall CC, such that greater volume is associated with faster performance on a measure of speed of information processing.
c) Sustained attention will be related to the area of the genu and splenium of the CC, such that greater area is associated with higher scores on a measure of sustained attention.
d) Inhibitory control will not be related to the overall CC volume nor the area of any subregion of the CC across groups.

Rationale: Data from both non-ADHD clinical groups exhibiting attentional difficulties, as well as normal control groups, have provided some indication that the neuropsychological functions listed above may be related to CC size. Furthermore, since the CC connects regions in a generally homologous manner, knowledge of the general brain regions mediating these functions allows for hypotheses regarding the corresponding CC area.

Individuals with agenesis of the CC have been shown to have difficulty with abstract reasoning (Brown & Paul, 2000; Paul et al., 2003). Being able to reason abstractly in order to engage in goal-oriented behavior and solve problems likely requires

frontal lobe contributions as well as the integration of information from the posterior association cortices. Therefore, it is likely that the entire CC would be involved in such a task. Furthermore, the genu connects the anterior regions of the brain which are hypothesized to be specifically related to problem solving and novel reasoning (Cabeza & Nyberg, 2000).

Speeded information processing, as measured by the pencil-and-paper task utilized in the current study, was hypothesized to be related to the overall volume of the corpus callosum since it requires both the cognitive decision-making process and the motor response. Furthermore, in their test of this relationship in healthy subjects, Jaenck & Steinmetz (1994) noted the area of all subregions of the CC, with the exception of the isthmus, to be related to reaction time. Other studies have not specified regional differences (Hoff et al., 1994; Verger et al., 2001).

Sustained attention was hypothesized to be related to both the genu and the splenium of the structure, based on previously described abnormalities observed in ADHD subjects as well as the work suggesting these are the regions possessing a higher density of thinner fibers (Aboitiz et al., 1992). Although there has been some evidence relating tasks of inhibitory and interference control to CC size in normal subjects (Hoff et al., 1994; Woodruff et al., 1997), the same relationship has not been studied in samples inclusive of ADHD subjects. Furthermore, current theory suggests the inhibitory network may be localized to the right frontal region (Pliszka, 2001). If this were indeed the case, the CC would not be related to inhibitory control. In the absence of conclusive data, the

hypothesis regarding the relationship of the callosum to inhibitory control was stated in the null.

Hypothesis 4: Using volume as the measure of the corpus callosum will provide no additional data beyond the measure of the mid-sagittal area of the callosum.

Rationale: Since this is the first study focusing on an ADHD sample to examine volume of the corpus callosum, this exploratory hypothesis has also been proposed as the null hypothesis. There is some literature suggesting callosal fiber diameter remains consistent across the structure (Ringo et al., 1994). However, since all ADHD studies to date have relied on mid-sagittal area (front to back) to provide an estimate of CC size, it is unknown whether ADHD and control subjects have equal coronal (ear to ear) lengths of the callosum. Furthermore, the process of selecting the mid-sagittal slice introduces some error and therefore may not be as accurate measure of CC size as is volume.

Chapter 4: Methods

Project Approval

The proposed study complies with the ethical issues and standards of research delineated by the American Psychological Association (2002) and the Procedures Governing Research with Human Subjects of the University of Texas Health Sciences Center in San Antonio. The Departmental Review Committee in the Department of Educational Psychology and the Institutional Review Board of The University of Texas at Austin approved this study.

Participants

Participants were right-handed children and adolescents aged 9 to 16. Twenty-eight males and twelve females participated in the study. There were the three following study groups: controls (n=15, males=11, females=4), participants who meet criteria for ADHD-C (Combined Type) with a history of chronic stimulant treatment (n=12, males=10, females=2), and participants meeting criteria for ADHD-C who had no history of stimulant treatment (n=13, males=7, females=6).

Procedures

Diagnostic Instruments

Diagnosis and group assignment was determined by the administration of the following structured interviews and rating scales. In order to exclude participants with learning disabilities, intellectual and achievement testing was performed. The inclusionary and exclusionary criteria are outlined below.

Symptomology

The *Diagnostic Interview Schedule for Children Version-IV-Parent Version* (DISC-IV-P; National Institute of Mental Health, 1997) is a revision of a structured diagnostic interview designed to meet the classification system of the *Diagnostic and Statistical Manual-IV (*DSM-IV) and was utilized to establish diagnosis and determine group membership. It presents criteria for over 30 psychiatric disorders encountered in child and adolescent populations (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000). The parent version is for caregivers of children aged 6 to 17 and is available in a computer-assisted format, the C-DISC-4.0 (owned and distributed by the Division of Child and Adolescent Psychiatry at Columbia University) (Shaffer et al., 2000). After a general demographic section, the parent answers questions regarding the presence and course of symptomology in six areas: anxiety, mood, disruptive, substance use, schizophrenia, and miscellaneous disorders (Shaffer et al., 2000). DSM-IV diagnostic criteria is closely followed in determining whether or not a child presents with symptoms of a psychological disorder. The most recent validity reports come from the DISC-2.3 (Schwab-Stone et al., 1996). Agreement between the parent DISC endorsements and clinician ratings were generally moderate to good (Shaffer et al., 2000).

The *Conners' Rating Scales-Revised* (Conners, 1997) includes 10-item rating scales completed by both parents and teachers. These scales are well-aligned to DSM-IV criteria for ADHD (Knoff, 2001) and enjoy widespread use within the research community (Hess, 2001; Knoff, 2001). For each item, the respondent rates the behaviors

as present “Not at all,” “Just a little,” “Pretty much,” or “Very much.” Three subscales are calculated on both parent and teacher versions: Restless/Impulsive, Emotional Lability, and Global. For chronically treated subjects, parents were asked to rate the child during a period when the child was not on medication (such as a weekend or holiday) in the past 6 months. Because of the ethical issues surrounding removing children from successful stimulant treatment, teachers were asked to rate the children on stimulant medication, which, in this sample, has served to provide a confirmation of successful stimulant treatment (Pliszka et al., in press). Reliability and validity estimates reported in the manual appear acceptable (Knoff, 2001) although additional peer-reviewed published psychometric research would be beneficial (Hess, 2001).

Intelligence

The *Differential Ability Scales* (DAS; Elliot, 1990), a revision and extension of the British Ability Scales (Elliot, Murray, & Pearson, 1977), is an individually administered battery of core and diagnostic tests of general cognitive ability, appropriate for children from ages 2 years, 6 months to 17 years, 11 months. Consistent with the developmental progression toward greater specification of abilities, the DAS employees a differential hierarchal structure for early preschool, late preschool, and school-aged children. The core cognitive subtests assess the child’s ability to understand and use language and reason both nonverbally and spatially. The general conceptual ability (GCA) score is considered to be a measure of psychometric *g,* and the diagnostic subtests evaluate the child’s short- and long-term memory as well as his or her speed of information processing. Average standard scores for the general cognitive index are

between 85 and 115 with average T-scores for the individual subtests ranging from 40 to 60. The technical manual reports internal consistency estimates of .70-.92 for the subtests, .86-.92 for cluster scores, and .90-.95 for the GCA score. Convergent validity is demonstrated by high correlations of the GCA with other intelligence measure composites. For preschool students, the correlations range from .68 with the Kaufman Assessment Battery for Children (K-ABC; Kaufman & Kaufman, 1983) to .89 with the Wechsler Preschool and Primary Scale of Intelligence (WPPSI; Wechsler, 1967). Correlations for school-aged children range from .84 for 8 to 10-year-old children on the Wechsler Intelligence Scale for Children-III (WISC-III; Wechsler, 1991) and .91 for 14-15 year-olds on the WISC-III. The DAS is considered to be a psychometrically sound instrument for the measurement of intellectual ability (Aylward, 1992; Reinehr, 1992).

Achievement

The *Wechsler Individual Achievement Test, Second Edition* (WIAT-II; Psychological Corporation, 2002) is a measure of general academic functioning in the areas of reading, writing, and arithmetic. On the reading subtests, the child is asked to read single words and pseudowords in addition to reading passages and answering questions about content. On the arithmetic subtests the child is asked to solve word problems as well as general calculation problems. The written expression tasks require the student to spell words and write sentences and either a brief paragraph or essay in response to a prompt. Average standard scores are between 85 and 115. The technical manual reports internal consistency estimates of .80 to .98 on the subtests with an overall total composite reliability of .98. Test-retest reliability ranges from .85 to .98 with the

mean number of days between assessments being 10. Although many of the WIAT subtests are scored dichotomously, several exercises require more subjective scoring. However, these tests, the reading comprehension and written expression sections, demonstrate acceptable reliability. Interscorer agreement on the reading comprehension subtest is .94, with the average interscorer agreement on the written expression subtest standing at .85. The WIAT (first edition; Psychological Corporation, 1992) is considered to have acceptable psychometric properties and to be appropriately normed and standardized (Ackerman, 1998; Ferrara 1998). Many of the subtests in the WIAT-II correlate moderately high to high (.78 to .88 on those subtests that have not received major format modifications) with the initial edition.

Criteria for Group Assignment

Controls •Does not meet criteria for any diagnoses on C-DISC-IV-P. •General cognitive ability (GCA) score of at least 85. No discrepancy between the DAS GCA standard score and the WIAT-II Reading or Mathematics score of greater than 1.5 standard deviations. •Within 1 SD of the mean for age and sex on both parent and teacher ratings of the restless/impulsive subscale of the Conners' Rating Scale. •No history of psychopharmacological treatment.
ADHD (combined type), Chronically Treated •Diagnosed with ADHD-combined type as measured on the C-DISC-IV-P. May meet criteria for Oppositional Defiant Disorder, but not for Conduct Disorder or any anxiety, tic, or affective disorder. •General cognitive ability (GCA) score of at least 85. No discrepancy between the DAS GCA standard score and the WIAT-II Reading or Mathematics score of greater than 1.5 standard deviations. •Documentation of at least one year of successful stimulant treatment. •As rated by a parent when off stimulant medication, a rating on the restless/impulsive scale of the Conners' Rating Scale at least 1.5 standard deviations above the mean.

ADHD (combined type), Treatment Naïve

•Diagnosed with ADHD-combined type as measured on the C-DISC-IV-P. May meet criteria for Oppositional Defiant Disorder, but not for Conduct Disorder or any anxiety, tic, or affective disorder.

•General cognitive ability (GCA) score of at least 85. No discrepancy between the DAS GCA standard score and the WIAT-II Reading or Mathematics score of greater than 1.5 standard deviations.

•No history of psychopharmacological treatment.

•As rated by both teachers and parents, a rating on the restless/impulsive scale of the Conners' Rating Scale at least 1.5 standard deviations above the mean.

Neuropsychological Measures

Each of the participants completed the following neuropsychological measures on the same day as the intellectual and achievement testing. The battery was administered in the same order across participants to control for fatigue effects.

Vigilance

Vigilance was assessed by the *d2 Test of Attention* (Brickenkamp & Zillmer, 1998), a measure of sustained visual attention. The participant is presented with 14 rows of *d*'s and *p*'s, each having one to four dashes above or below it. The participant is then instructed to scan the array line by line and cross out any *d* with two dashes and is allowed 20 seconds per line. Several standard scores are available, including total number of items processed, errors of commission and omission, and fluctuation rate. The most commonly utilized score and among the most reliable is the total number of items processed, corrected for the number of errors (Brickenkamp & Zillmer, 1998) and was used in the current study as a measure of sustained attention.

Speed of Information Processing

Speed of performing simple mental operations was assessed by a diagnostic subtest on the DAS (Elliott, 1990), entitled *Speed of Information Processing*. As a diagnostic subtest, this task is not included when calculating the General Conceptual

Ability. Examinees are required to scan rows of numbers and cross out the largest number in each row and are encouraged to work both quickly and accurately. There are three different stimulus booklets, each with a different level of difficulty. The level of difficulty presented to the subject is based on his or her age. The participants are timed and raw scores are converted into standard scores. Hierarchical confirmatory analysis of the DAS suggests that the Speed of Information Processing subtest loads on its own factor and does appear to be measuring processing speed (Keith, 1990). Furthermore, it does not contribute significantly to the higher order general intelligence factor, *g* (Keith, 1990). Both of these findings have been replicated by Dunham, McIntosh, and Gridley with an independent sample (2002).

Problem Solving

The *Tower of London-Drexel* (TOL^{DX}, Culbertson & Zillmer, 1995), modified from the original task by Shallice (1982), is a measure of planning and problem solving ability. The examiner and examinee each have a board with three upright wood pegs of incremental lengths and a red, blue, and green wooden ball. The examiner sets up a design on his or her board, and the examinee is directed to make the same design on his or her board in as few moves as possible without breaking specific rules outlined at the beginning of the task. Several scores can be computed, including a total move score, total correct score, total initiation time, total execution time, and total problem-solving time. Many problem-solving tasks are confounded by processing speed or timed elements; therefore the total move score allows a determination of the efficiency of problem solving without the confound of time. The TOL^{DX} was found to have moderate to high test-retest

reliability (r=.81, Culbertson & Zillmer, 1998b) and demonstrated criterion validity in that ADHD subjects performed significantly worse on the task than normal controls (Culbertson & Zillmer, 1998b), as would be expected given the literature noting poor performance on problem solving measures in ADHD samples (e.g. Aman et al., 1998; Houghton et al., 1999; Weyandt & Willis, 1994). Older versions of the *Tower of London* (Shallice, 1982) have also been shown to discriminate between normal controls and other groups with executive dysfunction (e.g. Hanes, Andrews, Smith, & Pantelis, 1996). Construct validity was described in an exploratory factor analysis which found the TOL^{DX} to load on an "executive planning/inhibition" factor but not on the psychometric intelligence factor (Culbertson & Zillmer, 1998a).

Inhibitory Control

The *Stop Signal Task* (Logan, Cowan, & Davis, 1984; Logan, Schachar, & Tannock, 1997) serves as a more "elegant" version of the go/no-go test by requiring subjects to respond to both primary-task (response-eliciting) stimuli and the stop signal (inhibitory) stimuli. This task serves as a mechanism to measure inhibitory control by creating a "race" paradigm between the go reaction time and the stop signal reaction time (Logan, et al., 1984). The primary task involves the discrimination of an A from a B, which the subject demonstrates by pressing different keys for each letter. On 25% of the trials, the computer provides the stop signal, an S below the presentation of the A or B, which indicates the subject must inhibit the proponent response to the primary task.

Although the go reaction time can be measured, the stop signal reaction time must be calculated indirectly. As explained by Logan and colleagues (1984, 1997), since the go

signal reaction time and the stop-signal delay are known, it is possible to infer the mean stop-signal reaction time (SSRT), an important behavioral variable that distinguishes ADHD children from normal controls. The SSRT is calculated based on the subjects' reaction times, which are normally distributed, and the probability of inhibition at a specific delay period. Assume, for instance, a subject achieves a 60% success rate at inhibiting on the stop signal at a delay of 300 msec and the numbers listed below are a sample of his reaction times to individual go stimuli.

450
475
480
490
500 ◄
500
510
520
525
550

Figure 4. Determining Stop Signal Reaction Time (SSRT).
Source: Adapted from Jennings, van der Molen, Pelham, Debski, & Hoza, 1997.

The reaction times are arranged in increasing order, and the reaction time which is as fast or faster than 60% of the trials is identified. The SSRT is determined by subtracting the delay period from the reaction time (500-300), yielding a stop signal reaction time of 200 msec. SSRT is estimated at each stop signal delay and is averaged across all trials for the subject's overall SSRT.

Another important metric derived from the Stop Signal task is that of the probability of inhibition [P(I)] and the slope of [P(I)] (Pliszka et al., 1997). The probability of inhibition at each level of stop signal delay is calculated, and probability

can then be plotted as a function of time. Both the reliability and validity of the Stop Signal Task have been established (Kindlon, Mezzacappa, & Earls, 1995; Tannock, Schachar, Carr, Chajczyk, & Logan, 1989).

The *Stroop* task (Golden, 1978) is a widely used measure of attention and interference control. In the first condition, the participant reads aloud the names of colors printed in black ink. Next, the participant is presented with a sheet of XXXXX printed in red, green, or blue ink. The interference trial presents the subject with a list of color words printed in an incongruent ink color (e.g., the word *blue* printed in green ink). Since reading is a more automatic process than color naming, examinees respond more slowly on this final task. When compared to the color-naming task without the distraction (XXXXX as opposed to color words), this test provides an index of one's ability to control interference and inhibit the preponent response (Nigg, 2001). In a review of executive function tasks, the Stroop test was stated to be "especially sensitive to ADHD" (Pennington & Ozonoff, 1996) and one of the best discriminators for ADHD (Gorenstein, 1989). Principal components analysis found the Stroop interference time to load on an orthogonal factor labeled, "resistance to distraction" (Das et al., 1992), reflecting the ability to inhibit a preponent response. Furthermore, the response time was found to be more predictive than error rate on the interference task (Barkley et al., 1992; Leung & Connolly, 1996). However, because ADHD children have been found to differ at the baseline condition of the Stoop (Gorenstein et al., 1989), it is important that the interference trial be controlled for both naming speed and reading ability (Nigg, 2001).

Therefore, the interference score for this study will be calculated as outlined by Golden (1978):

Interference score = Actual score on color-word card - Predicted score on color-word card

$$\text{Predicted Score} = \frac{(W \times C) \text{ where } W = \text{read word}}{(W + C) \text{ where } C = \text{name color}}$$

Limited psychometric studies of the task indicate high test-retest reliability (Golden, 1978; Spreen & Strauss, 1998), although evidence of a practice effect does exist. Findings are mixed regarding the relationship between intelligence and Stroop performance, with some studies reporting correlations between IQ and Stroop scores (e.g., Spreen & Strauss, 1998) and others reporting no relationship (MacLeod & Prior, 1996). The Stroop task consistently exhibits relationships with other tests of executive functioning (Spreen & Strauss, 1998). Although a relationship between the Stroop and reading ability exists, the participants in the study will have sufficient reading ability as subjects with a reading disability are excluded. Furthermore, utilizing the interference score will control for differences in reading levels. The Stroop appears to discriminate between brain-injured individuals and controls (Meier, 1992; Spreen & Strauss, 1998), although further research is needed to determine the Stroop's sensitivity to more subtle neural anomalies (Meier, 1992), such as those in ADHD.

MRI Acquisition

All scanning was conducted with a GE/Elscint 2 T Prestige system located in the Research Imaging Center of the University of Texas Health Science Center at San Antonio. A high-resolution EPI axial T1-weighted series was obtained for each subject

(TR (repetition time)=6000 ms, TE (echo time)=54 ms, flip angle=90°, 30 axial slices, field of view=20 x 20 cm). Overall brain volume was calculated in Medx (Sensor Systems), a software program which automatically stripped the skull and eyes from the image. The cerebellum and brainstem were cropped from the image manually. To facilitate multi-subject analysis, the three dimensional images were mid-sagittally aligned to standard stereotactic space (Talairach & Tournoux, 1988) using a 12 linear-parameter model. The mid-sagittal area and total volume analysis of the corpus callosum were conducted using a PC version of Display developed by the Montreal Neurological Institute. The mid-sagittal slice for each subject was utilized in the determination of corpus callosum area (see figure below). In order to verify the accuracy of the obtained areas and volumes, these measures of the corpus callosum were collected a second time on approximately 30% of the scans, and intra-rater reliability was calculated. The definition of the borders of the corpus callosum was as follows:

Coronal Plane: The corpus callosum was defined as the white matter immediately above the lateral ventricles, which served as the ventral border. The dorsal border was defined as the longitudinal cerebral fissure. The width was defined as those MRI slices included when a line is drawn from the gray matter surrounding the fissure to the lateral ventricles at a 45° angle.

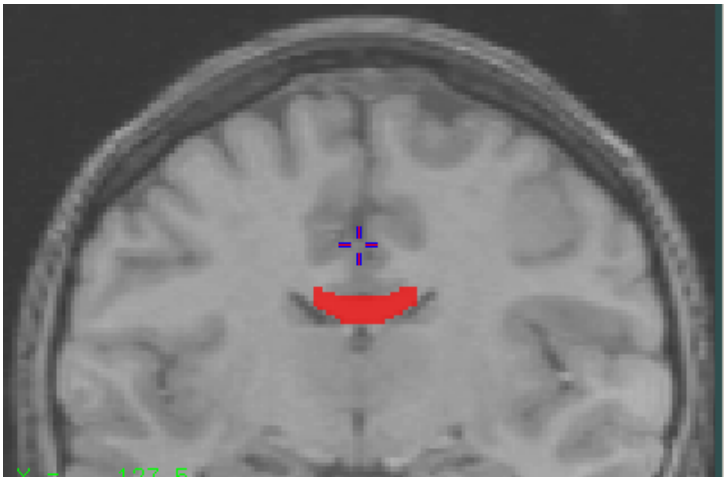

Figure 5. The corpus callosum as viewed in the coronal plane.

Sagittal Plane: As shown below, the corpus callosum is easily visualized in the mid-sagittal plane. It was defined as the higher-density band of fibers directly above the lateral ventricle and thalmus and below the cingulate gyrus in all sagittal planes.

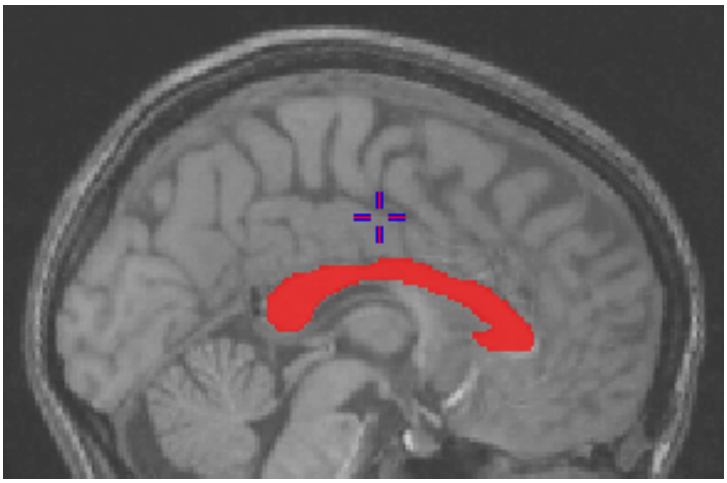

Figure 6. The corpus callosum as viewed in the sagittal plane.

For both volume and area measurements, the subdivisions of the corpus callosum were determined according to the procedure outlined by O'Kusky et al. (1988) and also utilized by Hynd et al. (1991); see the figure below. First, the most anterior and posterior

points of the structure were identified. The line between the two represents maximal CC length and was defined as the AC-PC line. The AC-PC line was divided into five equal sections and vertical lines demarking these sections were extended into the CC. Where the vertical lines intersected the CC, radial tangents were constructed from the point of intersection to the midpoint of the AC-PC line and through the image of the CC (Hynd et al., 1991).

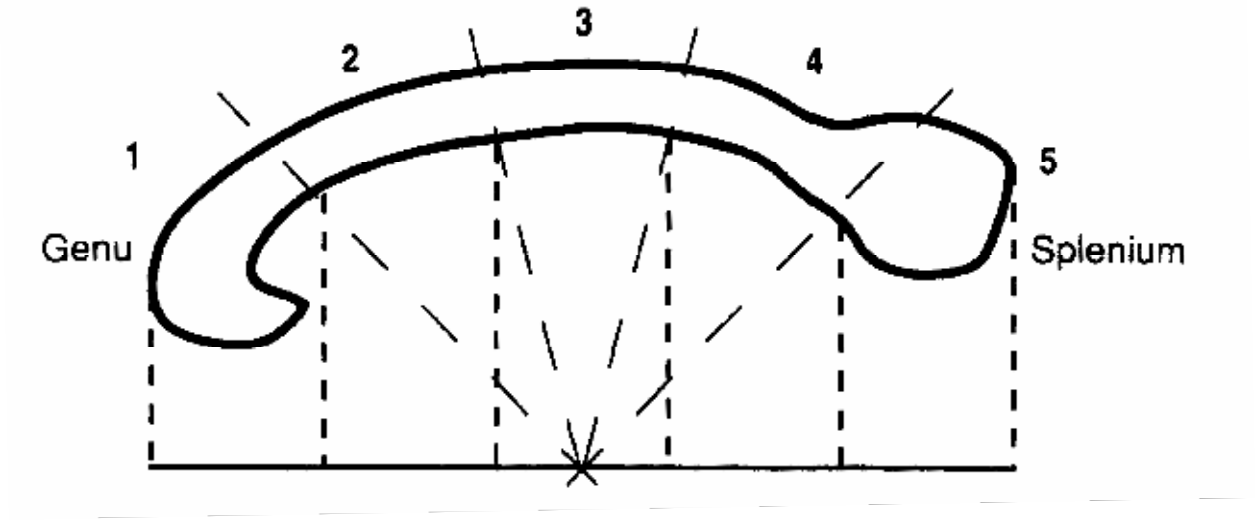

Figure 7. Adapted O'Kusky et al. (1988) five-segment subdivision procedure. *Source:* "Corpus callosum morphology in attention deficit-hyperactivity disorder" by G.W. Hynd, M. Semrud-Clikeman, A.R. Lorys, E.S. Novey, D. Eliopulos, & H. Lyytinen, 1991, *The Journal of Learning Disabilities*, p. 143. Copyright 1991 by PRO-ED, Inc. Reprinted with permission.

Data Analysis

Hypothesis 1: Participants with ADHD (both chronically treated and treatment naïve) will show differential overall CC volume and area and differential subregion areas when compared to healthy controls.

a) Both ADHD groups will have smaller overall CC volume and area than healthy controls. There will be no difference between the two ADHD groups.
b) Both ADHD groups will have smaller areas in the genu (most anterior) and splenium (most posterior) regions of the CC when compared to healthy controls. There will be no difference between the two ADHD groups.

Multivariate analysis of covariance (MANCOVA) was used to test the difference in the dependent variables of overall CC volume and area between the three groups (healthy controls, ADHD chronically treated, and ADHD treatment naïve). Overall brain volume was used as a covariate. A significant F-value was to be followed by tests of between-subjects effects for each dependent variable and multiple comparisons utilizing the Sidak adjustment to examine the nature of the between-group differences.

A multivariate analysis of covariance (MANOVA) was utilized to test the difference in the dependent variables of genu, and spenial mid-sagittal area between the three groups (healthy controls, ADHD chronically treated, and ADHD stimulant naïve). Overall brain size was the covariate. If the multivariate F-value was found to be significant, the analysis was to be followed up by ANCOVA's for each of the dependent variables. Multiple comparisons utilizing the Sidak adjustment would then be employed to examine how the groups differ on each dependent variable.

Hypothesis 2: Level of behavioral symptomotology of ADHD will be related to CC size.

a) Parent reports of hyperactive and inattentive behavior will be inversely related to overall volume and genu and splenium area when data is collapsed across all groups, such that greater symptomatology is related to smaller size.

The scores from the Restless/Impulsive scale on the Conners' Rating Scales-Revised (Conners, 1997) parent form was regressed on overall brain volume, overall corpus callosum volume, genu area, and splenial area in a simultaneous multiple regression. Overall brain volume was included in the regression to statistically control for the effects of these variables on CC size. The regression coefficients, *b*, for the independent variables of overall CC volume, genu area, and splenial area were examined for significance. Because the overall corpus callosum volume may be representative of the genu and splenial area, multicollinearity diagnostics were run. If variance inflation factors (VIF) were equal to or greater than a value of 6, the regression was to be conducted without overall CC volume.

Hypothesis 3: Neuropsychological measures will be related to CC size in both ADHD and control subjects.

a) Planning ability will be related to the overall CC volume, as well as the area of the genu, such that larger size is associated with higher scores on a planning measure.
b) Speed of information processing will be related to larger volumes of the overall CC, such that greater volume is associated with faster performance on a measure of speed of information processing.
c) Sustained attention will be related to the area of the genu and splenium of the CC, such that greater area is associated with higher scores on a measure of sustained attention.

d) Inhibitory control will not be related to the overall CC volume nor the area of any subregion of the CC across groups.

Simultaneous multiple regression were utilized to test these hypotheses. In each of the regressions, overall brain volume was included in the regression to provide statistical control for this variable. For planning ability, the Total Move standard score from the Tower of London was regressed on overall brain volume, overall CC volume, and genu area. The standard score on the Speed of Information Processing test from the DAS was regressed on overall brain volume, and overall CC volume. For sustained attention, the raw TN – E score (total number of items processed minus errors) was regressed on age in months, overall brain volume, genu area, and splenial area. Finally, a composite inhibitory control score was created from the following measures (Stop Signal Reaction Time, Probability of Inhibition, and Stroop Color-Word Interference Score). This variable was regressed on overall brain volume, overall CC volume and the area of each of the five subregions.

Hypothesis 4: Using volume as the measure of the corpus callosum will provide no additional data beyond the measure of the mid-sagittal area of the callosum.

The Pearson Product-Moment correlation between overall CC volume and mid-sagittal area was calculated. If this correlation were to be less than .9, the regressions including overall CC volume as a predictor variable (Hypthoses 3a, 3b, and 3d) would be run again, using mid-sagittal area as the predictor variable.

Chapter 5: Results

This chapter reports the results of the analyses proposed in Chapter Four. Prior to reporting the results of the specific research hypotheses, descriptive data for the sample is provided. The final portion of the chapter is devoted to summarizing the results of the statistical tests utilized to test the various research hypotheses.

Descriptive Analyses

Sample

The average age of the 40 participants included in the study was 13 years and 1 month (SD = 23.4 months). Age did not differ significantly between groups (F[2,37] = .961, p = .392). The range of IQ scores was between 84 and 132, with the mean IQ as measured by the DAS being 109 (SD = 12.5). The groups did not differ significantly in overall IQ scores (F[2,37] = 2.11, p = .135). Overall brain volume (excluding the cerebellum and brain stem) ranged from 967,501 to 1,661,860 cubic mm and was not found to differ statistically between groups (F[2,37] = .382, p = .685). It should be noted that corpus callosum (CC) volume was statistically significantly correlated with brain volume (r[38] = .53, p < .001) but not age (r [38] = .30, p = .057). Since there was no difference in age among the groups, age was not included in the research analyses as a covariate. Since overall brain volume was significantly related to CC volume, it was included in the following analyses as a covariate.

Table 1. Means and Standard Deviations for General Conceptual Ability Scores, Age, and Overall Brain Volume Across the Diagnostic Groups

	ADHD-CT (n=12)		ADHD-TN (n=13)		Control (n=15)	
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*
DAS GCA	106.8	10.8	105.5	13.1	114.2	12.4
Age (months)	156.3	26.7	151.2	19.3	163.4	24.0
Brain volume	1,379,226	96,950	1,349,285	143,771.9	1,332,345	161,174

Of the 40 subjects, 27 identified as White, 12 as Hispanic, and 1 as African American. There were 28 males and 12 females. The charts which follow illustrate the relative frequency of ethnicity and gender in each of the diagnostic groups. Although the specific hypotheses tested in this dissertation did not include questions regarding ethnicity and gender, it is important to note that limited representation of minority groups and females in the study sample would limit the generalizability of any secondary analyses addressing these demographic variables.

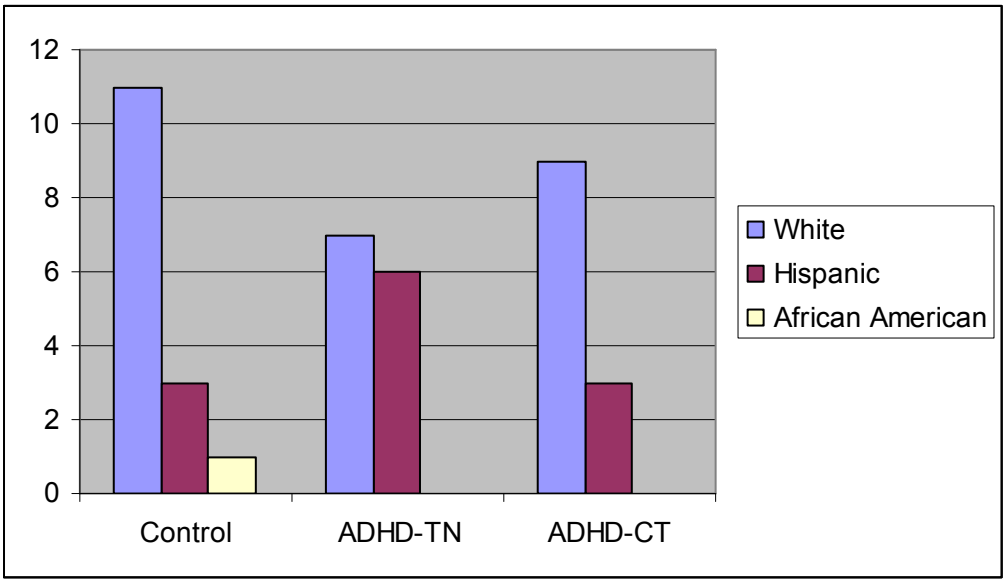

Figure 8: Group comparisons by ethnicity.

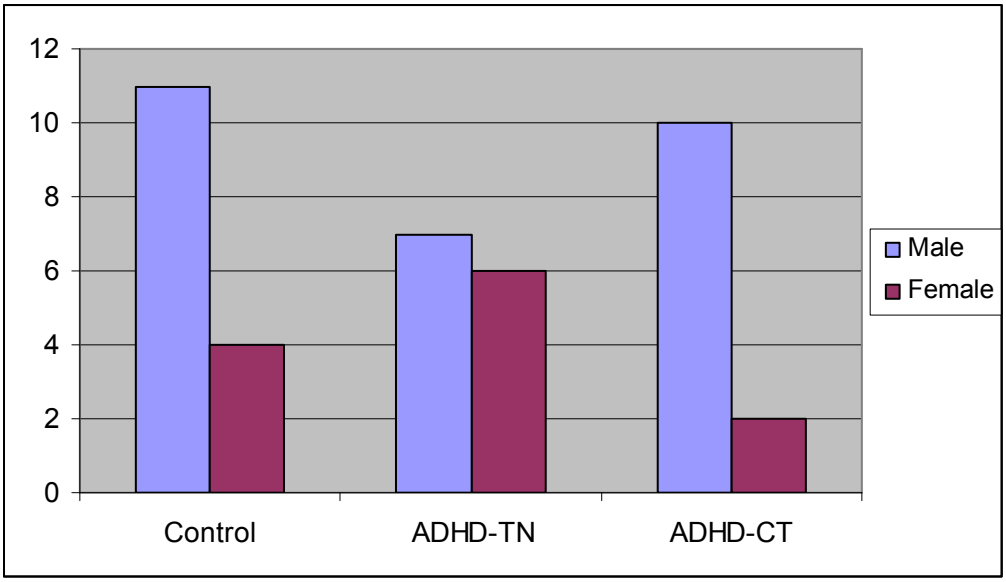

Figure 9: Group comparisons by gender.

Group Comparisons of Performance on Research Measures

In order to determine whether group differences existed on measures of neuropsychological and behavioral performance, one-way ANOVA's were performed

with the scores on the neuropsychological or behavioral measure as the dependent variable. If the ANOVA was statistically significant, post-hoc comparisons among the groups were performed using the Tukey HSD procedure. Means and standard deviations of the various measures by diagnostic group are listed below in Table 2.

Table 2. Means and Standard Deviations for Neuropsychological and Behavioral Measures across Groups

	ADHD-CT (n=12)		ADHD-TN (n=13)		Control (n=15)	
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*
Conner's (Restless/Impulsive Scale) (T-score)	77.8	9.1	84.15	7.5	49.8	8.0
Tower of London Total Move Score (standard score)	89.3	13.7	94.6	14.1	96.7	12.0
DAS Speed of Information Processing (T-score)	57.0	8.3	55.8	7.8	55.1	14.3
d2 TN-E (standard score)	115.8	20.3	102.5	10.6	116.7	14.1
SSRT (time in ms)	793.1	236.5	724.1	139.1	615.5	152.1
Probability of Inhibition (slope)	-.60	.67	-.58	.41	-.84	.71
Stroop (T-score)	48.8	4.7	49.9	7.7	53.9	10.1

The results indicate the groups displayed differential scores on the Restless/Impulsive scale of the parent *Conner's Rating Scale* (F[2,37] = 70.582, p = <.001), with significant differences between the control group and both ADHD groups but not between the two ADHD groups. This finding was expected as scores on this rating scale contributed to the criteria for membership in the diagnostic groups.

Significant between-group differences were also noted on the TN- E (Total number of items processed minus errors) score of the *d2 Test of Attention* (F[2,37] = 3.624, p = .037). Post-hoc analyses revealed that the children in the ADHD-treatment naïve group scored significantly lower than the control group (p = .048). Although the ADHD-treatment naïve group scored lower on the *d2 Test of Attention* than did the ADHD-chronically treated group, the difference was not statistically significant (p = .087). There was no difference on this measure between the control group and the chronically treated subjects (p = .987). Due to technical difficulties in the scanner, the data for 2 of the participants (1 control and 1 treatment naïve) for the Stop Signal Reaction Time (SSRT) and Stop Signal Probability of Inhibition were lost. The difference between groups on the SSRT was approaching significance (F[2,35] = 3.248, p = .051). As displayed in the table above, an examination of the means indicated the chronically treated group had the longest average reaction time. Post hoc tests using the Tukey HSD adjustment found that the ADHD-chronically treated group had a significantly longer SSRT than the control group (p = .043), although there was no difference between the two ADHD groups (p = .619) or the ADHD-treatment naïve and control group (p = .286).

No other neuropsychological variables were found to differ among the groups: *Tower of London* (F[2,37] = .062, p = .356), *Speed of Information Processing* (F[2,37] = .106, p = .900), *Stop Signal* Probability of Inhibition (F[2,35] = .752, p = .479), and *Stroop Color-Word Test* (F[2,37] = 1.579, p = .220).

It should be noted that although protocol dictated all participants were to be tested off medication, five of the chronically treated participants were administered the neuropsychological battery on their prescribed dosage of medication because of difficulty completing the testing while not medicated. No statistically significant differences were noted between those chronically treated participants tested on medication and those tested off medication on any of the neuropsychological measures (see Table 3 below): *Tower of London* (F[1,10] = 1.186, p = .302), *Speed of Information Processing* (F[1,10] = .476, p = .506), *d2 Test of Attention* (F[1,10] = .579, p = .464), *Stop Signal* SSRT (F[1,10] = .013, p = .911), *Stop Signal* Probability of Inhibition (F[1,10] = 1.27, p = .286), and *Stroop Color-Word Test* (F[1,10] = .946, p = .354). Therefore, the medicated subjects were included in the regression of neuropsychological function on measures of CC size. However, the extremely small sample sizes (5 medicated and 7 non-medicated) preclude any assumption that medication effects were nonexistent.

Table 3. Means and Standard Deviations for Neuropsychological Measures for Medicated and Non-medicated Chronically Treated ADHD Participants

	Medicated (n=5)		Non-medicated (n=7)	
Variables	*M*	*SD*	*M*	*SD*
Tower of London Total Move Score (standard score)	94.4	8.4	85.7	16.2
DAS Speed of Information Processing (T-score)	59.0	5.2	55.6	10.1
d2 TN-E (standard score)	121.2	22.1	112.0	19.6
SSRT (time in ms)	783.4	294.1	800.0	211.5
Probability of Inhibition (slope)	-.34	.72	-.78	.62
Stroop (T-score)	47.2	6.8	49.9	2.4

Reliability of Volumetric Measure

Prior to performing analyses utilizing the variable of corpus callosum volume, the obtained measurements were determined to be reliable. On approximately 1/3 of the scans (n = 12), the volumetric measurement of the CC was collected a second time, with the rater blind to the original measurement. The intraclass correlation coefficient was found to be .93, suggesting acceptable reliability of the obtained measurements.

Tests of Hypotheses

Hypothesis 1: Participants with ADHD (both chronically treated and treatment naïve) will show differential overall CC volume and area and differential subregion areas when compared to healthy controls.

a) Both ADHD groups will have smaller overall CC volume and area than healthy controls. There will be no difference between the two ADHD groups.
b) Both ADHD groups will have smaller areas in the genu (most anterior) and splenium (most posterior) regions of the CC when compared to healthy controls. There will be no difference between the two ADHD groups.

Multivariate analysis of covariance (MANCOVA) was utilized to test the difference in CC volume and overall CC area across the three groups (the means and standard deviations for each of the corpus callosum measures are listed below) with overall brain volume as a covariate. The omnibus test using Wilks' Lamba was not statistically significant (F[1,36] = .770, p = .549, η^2 = .042). Furthermore, tests of the between-subjects effects for each dependent variable also were not significant, CC volume (F(2,36) = .498, p = .612, η^2 = .027), overall CC area (F (2,36)= .407, p = .669, η^2 = .022).

In order to test the second part of the hypothesis regarding specific CC subregions of interest, a multivariate analysis of covariance was again performed, with the dependent variables being the areas of the genu and splenium from the midsagittal slice and overall brain volume as the covariate. The omnibus F test was statistically insignificant (F[1, 36] = 1.144, p = .343, η^2 = .061), and individual tests of genu and splenium area were also

statistically insignificant (F[2,36] = .411, p = .666, η^2 = .022 and F[2,36] = 2.319, p = .113, η^2 = .114, respectively). Given the small sample size, exploratory post hoc pairwise comparisons were run for the splenium area. The difference between splenium size in ADHD treatment-naïve and control groups was significant (p = .039), with the treatment-naïve group having the smaller splenium area. No significant differences in splenium size were noted between the chronically treated ADHD and control groups (p = .269) or the chronically treated and treatment naïve ADHD groups (p = .356).

Table 4. Means and Standard Deviations of Corpus Callosum Measures across the Diagnostic Groups

	ADHD-CT (n=12)		ADHD-TN (n=13)		Control (n=15)	
Variables	*M*	*SD*	*M*	*SD*	*M*	*SD*
CC volume	12,566.00	2316.89	11,955.69	1991.73	11,524.93	1799.96
CC area	664.67	119.17	629.38	50.49	641.80	73.22
Genu	177.67	28.81	168.54	10.74	176.07	36.61
Area 2	128.50	28.50	120.38	14.91	114.33	17.26
Area 3	100.33	17.88	97.23	14.04	93.93	16.16
Area 4	110.50	37.17	106.08	14.10	102.47	22.05
Splenium	147.67	32.58	137.15	21.02	155.00	18.82

Hypothesis 2: Level of behavioral symptomatology of ADHD will be related to CC size.

a) Parent reports of hyperactive and inattentive behavior will be inversely related to overall volume and genu and splenium area when data are collapsed across all groups, such that greater symptomatology is related to smaller size.

The standard score from the Restless/Impulsive scale on the *Conner's Rating Scales-Revised* (Conners, 1997) parent form was regressed on overall corpus callosum volume, genu area, splenium area, and overall brain volume in a simultaneous multiple regression. The standardized coefficients for overall CC volume and splenium area (b, beta, and significance are reported in the table below) were found to be significant, whereas the coefficient for genu area was not found to be significant. Larger overall CC volume and smaller splenium area were associated with higher scores on the Restless/Impulsive scale of the *Conners' Rating Scale,* even when the other predictors were taken into account. There was no evidence of collinearity among the predictor variables.

Table 5. b, β, and Significance of the Regression of the Conner's Parent Rating Scale Restless/Impulsive Scale on Measures of Corpus Callosum Size

Variables	*b*	β	Significance
CC volume	.489	.004231	.019*
Genu	-.009	-.00597	.959
Splenium	-.597	-.419	.004*

*significant at the $p < .05$ level

Table 6. Correlation Matrix of Measures of Corpus Callosum Size

	Brain Volume	CC Volume	Genu	Splenium
Brain Volume	1.00	-.424	-.155	.050
CC Volume	-.424	1.00	-.142	-.383
Genu	-.155	-.142	1.00	-.421
Splenium	.050	-.383	-.421	1.00

Hypothesis 3: Neuropsychological measures will be related to CC size in both ADHD and control subjects.

a) Planning ability will be related to the overall CC volume, as well as the area of the genu, such that larger size is associated with higher scores on a planning measure.
b) Speed of information processing will be related to larger volumes of the overall CC, such that greater volume is associated with faster performance on a measure of speed of information processing.
c) Sustained attention will be related to the area of the genu and splenium of the CC, such that greater area is associated with higher scores on a measure of sustained attention.
d) Inhibitory control will not be related to the overall CC volume nor the area of any subregion of the CC across groups.

A series of simultaneous regressions were conducted to test the above hypotheses. All regressions included total brain volume to control statistically for its relationship to CC size. The *b*, β, and significance for each of the following regressions are reported in Table 5 below. To test planning ability, the Total Move standard score from the *Tower of London* was regressed on CC genu area, overall CC volume, and brain volume. Neither overall CC volume nor genu area was found to be related to planning ability.

The *Speed of Information Processing* subtest from the *DAS* was regressed on overall CC volume and brain volume. Overall CC volume did not significantly predict performance on the speed of information processing task.

The raw TN- E (total number of items processed minus errors) score from the *d2 Test of Attention* was regressed on area of the genu and splenium, in addition to brain volume and age in months (age in months was included in the regression because the raw scores were utilized as the dependent variable). The standardized regression coefficient was not significant for the splenium or the genu.

The scores for the three inhibitory control measures were converted into z-scores and a composite inhibitory control variable was created. This composite variable was regressed on overall CC volume, the area of each of the five subregions, and overall brain volume. The regression was not statistically significant ($F [7,30] = .844$, $p = .560$), and none of the regression coefficients for the various CC measures were significant.

Table 7. b, β, and Significance of the Regression of Neuropsychological Function on Measures of Corpus Callosum Size

Variables	B	Beta	Significance
Planning (Tower of London Total Move Score)			
CC volume	.0001	.019	.929
Genu	-.0265	-.055	.770
Speed of Information Processing (DAS)			
CC volume	.0010	.193	.279
Sustained Attention (d2 Test of Attention TN – E)			
Genu	.7000	.253	.105
Splenium	.2750	.089	.557
Inhibitory Control (composite of Stop Signal Task and Stroop)			
Volume	-.00002	-.081	.828
Genu	.0056	.283	.225
Area 2	-.0001	-.006	.984
Area 3	.0151	.430	.167
Area 4	-.0077	-.359	.235
Splenium	-.0026	-.120	.626

Hypothesis 4: Using volume as the measure of the corpus callosum will provide no additional data beyond the measure of the mid-sagittal area of the callosum.

Overall CC volume and mid-sagittal area were found to have a correlation of $r(38) = .82$, $p < .01$. When corrected for attenuation caused by measurement error, a correlation of $r(38) = .88$ was found. Although a high level of correlation, it was below .90 and suggests that utilizing volume as opposed to area may account for more or less of

the variance in the regression equations. Therefore, the regressions described above which utilized overall CC volume as an independent variable were repeated, this time substituting area for volume.

This substitution resulted in no difference to minimal difference in the amount of variance accounted for in the overall regression. The table below lists the R^2 using volume and area as the predictor variable for each of the repeated regressions. Only in the regression utilizing the Restless/Impulsive scale of the *Conners' Rating Scale* did substituting area for volume change the results of the regression. When volume was utilized as a predictor variable, the coefficients for both the splenium and overall CC volume were significant (b = -.419, β = -.597, p = .004; b = .0042, β = .489, p = .019, respectively); however, when area was utilized, only the splenium measure was significant (splenium: b = -.456, β = -.650, p = .007; overall CC area: b = .0962, β = .457, p = .086).

Table 8. R^2 for the Volume and Area of the Regressions of Behavioral and Neuropsychological Measures on Corpus Callosum Measures

Regression	Volume	Area
Conner's (Restless/Impulsive Scale) (T-score)	.272	.216
Tower of London Total Move Score (standard score)	.046	.097
DAS Speed of Information Processing (T-score)	.182	.182

Inhibitory Control (composite score)	.165	.163

Summary

Descriptive analyses revealed the three diagnostic groups were similar in age, overall brain volume and IQ with no statistically significant difference between the groups on any of these variables present. CC volume was significantly correlated with total brain volume but not age; therefore, total brain volume, but not age, was included in the research analyses as a covariate or entered into the regressions. The sample consisted predominantly of white males, and there was not enough representation of other ethnicities or females to perform separate analyses with these demographic data as the variables of interest.

Analysis of variance conducted on the behavioral and neuropsychological measures revealed relatively few differences in performance on the instruments utilized to collect data on executive functioning ability. As would be expected, both ADHD groups were found to have significantly higher T-scores on the Restless/Impulsive scale of the *Conner's Rating Scale* than the control group. The ADHD-treatment naïve group obtained a significantly lower score on the neuropsychological measure of sustained attention, the TN – E score on the *d2 Test of Attention*, than the control group. The only other performance measure suggestive of diagnostic group differences was that of the SSRT variable from the *Stop Signal Task.* The omnibus *F* showed a trend toward significance and follow up comparisons revealed the chronically treated ADHD group displayed a longer reaction time than the control group. It should be noted that there were

no statistically significant differences between the medicated and non-medicated chronically treated participants on measures of neuropsychological function.

No differences were found between groups on measures of planning or information processing speed or on the inhibitory control variable of the Stroop and Probability of Inhibition variable of the *Stop Signal Task*. It is important to note that the volumetric measures of CC volume were found to be reliable, allowing for their use in the research analyses. Results of the research hypotheses will be addressed and interpreted in the following chapter.

Chapter 6: Discussion

Because of its prevalence and potential to interfere with key developmental tasks, Attention Deficit/Hyperactivity Disorder is perhaps one of the most frequently studied childhood psychiatric disorders (Wolraich, 1999). The prevalence of ADHD is estimated to be between 3 and 7% of the school-aged population (APA, 2000), making it one of the most common childhood disabilities. Furthermore, the list of secondary difficulties which often accompany the disorder include academic failure, social impairment, antisocial activity and drug use (e.g. Barkley, 2000; Gentschel & McLaughlin, 2000; Fischer et al., 1990; Mannuzza et al., 1991). In addition, ADHD is comorbid with many other forms of childhood psychopathology, including learning disabilities, other disruptive behavioral disorders, and internalizing disorders (e.g. Biederman et al., 1991; Butler et al., 1995; Semrud-Clikeman et al., 1992). Therefore, ADHD represents an important and frequently disabling condition.

Given that ADHD is commonly treated with the use of stimulant medication, some have expressed concern regarding the long-term neurological consequences of chronic stimulant treatment (e.g., Hyman, 2003). However, the majority of previous neuroimaging studies have not controlled for extended stimulant usage. Therefore, examining the effects of chronic stimulant treatment for ADHD on the developing brain is an important area of investigation for a number of reasons. First, it is important to determine whether the neuroanatomical differences that have been observed in ADHD samples are indeed related to the disorder or instead merely an "artifact" of long-term stimulant usage, as highlighted by Pliszka and colleagues (under review). The age at

which children are generally diagnosed with ADHD certainly coincides with the continuing myelination process of a multitude of brain structures, including the corpus callosum (Giedd et al., 1999; Kolb & Fantie, 1989; Njiokiktijin et al., 1994; Schaefer et al., 1992; Yakovlev & Lecours, 1967), which reinforces the concern that psychotropic medications may alter the trajectory of brain development. Additionally, the literature has reported neuroanatomical changes resulting from chronic administration of medication, specifically the antipsychotics, in both animals (Andersson et al., 2002) and humans (Chakos et al., 1994, Doraiswamy et al., 1995; Keshavan et. al., 1994). It should be noted that changes in brain structure could be either adaptive or maladaptive. For example, in a recent functional neuroimaging study, chronically treated children with ADHD showed a trend, although nonsignificant, toward normalized brain activation during an inhibitory control task, even when off their stimulant medication (Pliszka et al., under review). Therefore, it is essential that neuroimaging studies, both structural and functional, include groups of children who have never received psychostimulants in order to address this question of whether protracted psychopharmacological therapy does indeed affect brain anatomy.

Second, it has been argued that the structural differences noted between individuals with ADHD and healthy children are meaningless unless an association can be made between neuroanatomical variation and cognitive and behavioral clinical presentation (Hill et al., 2003; Hynd et al., 1991). It has been documented that the corpus callosum exhibits a significant amount of individual variation in both adults (Byne et al., 1988; Clark et al., 1989) and children (Giedd, 1999; Njiokiktjien et al., 1994). Therefore,

determining whether this variation has any real meaning in terms of practical functioning is an important question.

The purpose of the current study was to investigate the concerns listed above as related to the corpus callosum (CC). Previous anatomical studies regarding this structure have reported differences between control and ADHD groups (generally either composed entirely of children treated by stimulants or a mixture of treated and stimulant-naïve subjects). However, the nature of these reported differences has been somewhat inconsistent, with reports of both smaller genu area (Baumgardner et al., 1996, Giedd et al., 1994; Hynd et al, 1991) and smaller splenium area (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). Some studies have found smaller overall CC size (Hill et al., 2003; Hynd et al., 1991) while others have not (Castellanos et al., 1996; Giedd et al., 1994; Semrud-Clikeman et al., 1994). The current study was designed to extend this work through the addition of clearly defined groups of chronically treated and treatment naïve ADHD participants.

Additionally, the relationship between corpus callosum size and behavioral and executive functioning measures commonly thought to differentiate ADHD from non-ADHD children was investigated. In particular, the functions of processing speed, sustained attention, inhibitory control, and problem solving were examined. With one exception (Giedd et al., 1994), neuroanatomical studies of the CC in participants with ADHD have failed to examine this structure-function relationship.

Furthermore, all previous studies have utilized the mid-sagittal area of the CC as the unit of measurement. While many research groups have turned to utilizing volumetric

data as opposed to area to characterize the size of various brain structures (e.g. Castellanos et al., 1994, 1996; Hill et al., 2003, Filipek et al., 1997; Semrud-Clikeman et al., 2000), this has not yet been the case for the CC. It has been argued that area of the CC as calculated on the mid-sagittal slice is an accurate estimate of overall CC size (e.g. Rilling & Insel, 1999); however, this remains to be empirically tested. Therefore, an additional purpose of this study was to determine whether employing the volume of the CC as a unit of measure yields more information than the traditional area measures, especially given the significant outlay of time required in obtaining volumetric measures.

In this chapter, the specific findings of the investigation are discussed. After presenting the relevant demographic data and the results of the analyses, the findings will be discussed in light of the current body of literature regarding the corpus callosum in ADHD. The limitations of the current study will also be addressed. Finally, information regarding the unique contribution of this study to the knowledge base, as well as future directions for research, will be provided.

Sample Characteristics and Findings

The sample utilized in the current study was well-matched to age and IQ, as these variables were not found to differ significantly across the three diagnostic groups: control, ADHD-stimulant naïve, and ADHD-chronically treated. Furthermore, brain volume was not found to differ significantly among groups. In contrast, corpus callosum volume was significantly related to total brain volume, and therefore brain volume was included as a covariate in the analyses to increase the power of the statistical tests. The correlation between age and corpus callosum size was nearly significant. Longitudinal

studies indicate that the CC increases in size throughout the sampled age range (Giedd et al., 1999; Njiokiktijien et al., 1994; Rakic & Yokovlev, 1968). However, the restricted age range in the current sample may have resulted in this relationship not being clearly demonstrated in the current study, as has been the case in previous studies with this age group (e.g. Semrud-Clikeman et al., 1994).

It was also of interest to note that, contrary to what has been suggested in the literature, very few of the neuropsychological measures were sensitive in distinguishing ADHD participants from nonclinical participants. Although the sample size represented in the current study is consistent with samples frequently reported in neuroimaging study designs, the number of participants is somewhat smaller than previous research examining only neuropsychological measures and therefore may suffer from limited power. Additionally, potential participants were excluded if they met diagnostic criteria for any comorbid psychiatric disorder, with the exception of Oppositional Defiant Disorder in the ADHD groups. Therefore, the groups in the current study were likely more homogenous than some of the previous studies examining neuropsychological function in children with ADHD.

Only the TN-E (total number of items processed minus errors) variable of the *d2 Test of Attention* was found to differ among groups. It should be noted that this particular metric is considered the most reliable and commonly used score to measure sustained attention from the *d2 Test of Attention* (Brickenkamp & Zillmer, 1998). The results indicated that the ADHD-treatment naïve group performed significantly worse on this measure than the control group, and the mean score for the treatment naïve group was

lower than that of the ADHD-chronically treated group, although not significantly so. There was no difference between the chronically treated and control group. Several of the chronically treated participants had taken their stimulant medication on the day of testing. Therefore, further research is required to clarify whether the enhanced performance of the chronically treated participants is reflective of a medication effect or a potential normalization of performance by the chronically treated group when off of their prescribed medication, reminiscent of Pliszka and colleague's (under review) findings.

More puzzling was the finding of a nonsignificant trend toward increased Stop Signal Reaction Time (SSRT) in the ADHD-chronically treated children. The SSRT metric is thought to measure deficits in the inhibitory process and has been shown to be sensitive in distinguishing children with ADHD from normal controls (Oosterlaan, Logan, & Sergeant, 1998), with ADHD subjects generally showing longer SSRT. However, it should be noted that there was no observed difference in the slope of the probability of inhibition among the three groups. One hypothesis which could be proposed to explain this finding is that the longer SSRT in the ADHD-chronically treated participants is a reflection of a compensation, or in this case overcompensation, process. In order to avoid making a mistake and responding to a stop signal in error, these participants could have delayed responding to all targets in order to increase their probability of successful inhibition. However, a follow-up analysis of the mean reaction time revealed that there was no statistically significant difference between the three groups in overall reaction time ($F[2,35] = 1.066$, $p = .355$) Therefore, further study utilizing designs with larger numbers of chronically treated and treatment naïve

participants, both on and off stimulant medication, are necessary to determine if indeed a significant difference on the metric of SSRT does exist between ADHD groups.

Research Hypotheses

One important aim of the study was to determine whether corpus callosum volume could even be reliably measured. Because it is a connective fiber tract, delineating the structure on three-dimensional MRIs is challenging. As one begins to move laterally from the mid-sagittal slice, the corpus callosum becomes difficult to distinguish from the other white matter tracts running through the brain. However, the results of the intra-rater reliability check conducted in the current investigation demonstrated that when strict boundaries are specified through the use of more easily identified neuroanatomical features, the volume of the CC can be reliably obtained. Furthermore, CC volume and area were found to correlate at $r = .82$. Therefore, the assumption that the fibers coursing through the CC maintain relative consistency throughout the structure (e.g. Rilling & Insel, 1999; Ringo et al., 1994) received support in the current study.

The results also provided partial support for Hypothesis One, in that the ADHD-treatment naïve group displayed a smaller splenium area than the control group, although there was no difference between the control group and the ADHD-chronically treated group in splenium size. Reductions in splenium size in ADHD groups have been among the more robust findings regarding CC anomalies in ADHD (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). These previous studies have not controlled for chronic stimulant medication; therefore the current study offers greater

specificity as to the nature of these reported abnormalities. However, the interpretation is complicated somewhat because the ADHD groups in a few of these previous studies (Hynd et al., 1991; Semrud-Clikeman et al., 1994) consisted of only medicated participants. However, in the Semrud-Clikeman study, the minimum amount of stimulant treatment was 6 months, whereas it was at least one year in the current study. The minimum length of stimulant treatment is not reported in the Hynd study. Therefore, it will be important for future research to determine if the length of stimulant usage has any effect on corpus callosum size. It is important to note that the greatest growth of the CC is witnessed in the posterior areas, including the splenium, in the age range sampled as part of the current study (Giedd et al., 1999; Rakic & Yakovlev, 1968). Therefore, the splenium abnormalities noted in children with ADHD may be reflective of a developmental difference in these children. Future research may help determine whether stimulant usage offers some protection against such developmental neuroanatomical differences.

Contrary to what was proposed in Hypothesis One, the results indicated that no difference existed among any of the diagnostic groups in terms of total corpus callosum size, whether measured as area or volume, consistent with some of the previous literature (Castellanos et al., 1996; Giedd et al., 1994; Lyoo et al., 1996; Semrud-Clikeman et al., 1994, but not all (Hill et al., 2003; Hynd et al., 1991). No difference in genu area among the diagnostic groups was noted, which again has previously had mixed research support, with some finding smaller genu area (Baumgardner et al., 1996, Giedd et al., 1994; Hynd et al, 1991) and others not (Castellanos et al., 1996; Semrud-Clikeman et al., 1994).

Hypothesis Two was also partially supported. It was hypothesized that parent reports of hyperactive and inattentive behavior would be inversely related to total CC volume and genu and splenium area, in that greater symptomatology would be related to smaller size. Higher scores on the Restless/Impulsive Scale of the Conners' Parent Rating Scale were found to be related to smaller splenium area. This is understandable given the relatively robust finding of reduced posterior CC area in ADHD participants documented in the literature and the indications that this portion of the callosum appears to be involved in tasks of sustained attention (e.g. Rueckert et al., 1999). However, unlike previous studies (Giedd et al., 1999), there was no relationship between the genu and ADHD symptomatology. Furthermore, although an inverse relationship between overall CC volume and ADHD symptomatology was predicted, actually the opposite was found in the current study. However, this relationship was not found for total area of the CC, which will be addressed below when discussing the results related to Hypothesis Four.

Hypothesis Three, which predicted a relationship between various measurements of corpus callosum size and performance on neuropsychological measures, was not supported. However, using a more liberal alpha of .10, there appears to be a trend toward a relationship between sustained attention and genu area, in that greater genu area was related to better scores on the *d2 Test of Attention*. However, this is cautiously interpreted as some of the chronically treated participants had taken their medication on the day of testing, which may confound the results. It is also important to note that the TN – E score on the *d2 Test of Attention* was the only neuropsychological measure noted to be different among the groups. Therefore, it is possible that the lack of observed relationship between

CC size and planning and speed of information processing is a reflection of a restricted range of scores on the neuropsychological measures. As predicted in the initial hypotheses, it was expected that measures of inhibitory control would not be related to CC size as the inhibitory control function has been suggested to be mediated by networks localized primarily in the right frontal region (Pliszka, 2001). Although never studied in an ADHD sample, previous research has found the CC to be related to reaction time (Jaenck & Steinmetz, 1994) and that individuals with callosal agenesis have difficulties with problem solving and planning (Brown & Paul, 2000; Paul et al., 2003). However, it stands to reason that individuals participants in these studies presented with significantly more CC involvement than the relatively mild differences noted in children with ADHD. As indicated above, the results of the current study were likely affected by a restriction in range as there were few differences between groups on the neuropsychological measures. In attempts to match the groups on IQ, it is possible the sample was biased toward a somewhat higher functioning ADHD group, as lower IQs have been reported as a secondary deficit in this population (Barkley, DuPaul, & McMurray, 1990; for a recent meta-analysis, see Frazier, Demaree, & Youngstrom, 2004). That said, an examination of mean IQ scores do reveal an 8 to 9 point difference between the ADHD groups and the control group, which may have been statistically significant had the sample size had been larger.

Although the results revealed that CC volume can be reliably measured, it is of great practical significance to determine whether doing so yields a worthwhile return on the additional time invested as the process of volumetric measurement is significantly

more time consuming than simply calculating CC area via a single mid-sagittal slice. Hypothesis Four addressed this question and was worded as the null, stating that volume would provide no further explanation for the variance in the regression of neuropsychological and behavioral measures on overall CC size. This hypothesis was generally supported in that the CC volume was not found to provide any additional data in terms of predictive power for the neuropsychological measures.

Only on the behavioral measure, the Restless/Impulsive scale of *Conners' Parent Rating Scale,* was a difference noted between the two measures of CC size. When volume was utilized as a predictor variable, smaller splenium area and larger total CC volume were found to predict higher scores on the Restless/Impulsive Scale. This latter finding of larger CC volume as a predictor was actually counterintuitive and contrary to previously reported findings (Giedd et al., 1994). When area was used in the place of volume, total CC area was not found to be related to the score on the Restless/Impulsive scale, which is more consistent with the literature. Therefore, it is possible that a greater degree of error is introduced when attempting to calculate volume because of the inherent difficulties in defining the limits of the CC in three-dimensional space. The CC is easily viewed in the mid-sagittal plane, and therefore, the single slice area can generally be obtained with great reliability. However, in the current study, intra-rater reliability for the area of the CC was high (average intra-class correlation of .94), but only slightly higher than the reliability of the overall CC volume (.93). Given that this is one of the first attempts to measure CC volume, it is certainly possible that the parameters identified may not produce the most useful measure of CC size, either accounting for too little or too much

of the structure. Therefore, although volume was measured reliably, it is possible that some degree of "error" was also reliably measured. Future research comparing the predictive power of different techniques for boundary identification may shed additional light on this issue.

Limitations

Although the sample size represented in the current study is consistent with "industry standards," as determined by sample sizes reported in published neuroimaging studies, a larger sample size would have allowed for greater power, especially in determining the relationship between the neuropsychological measures and the corpus callosum measurements. As indicated above, the sample may have also suffered from a restricted range of scores on the various neuropsychological measures. Furthermore, because the goal of matching subjects on intellectual functioning was met, it is likely that the current sample represents a relatively high functioning ADHD group, as the mean IQ for the entire sample was 109. Patients with ADHD seen in clinical practice may perform substantially lower on measures of intelligence and executive functioning (Frazier et al., 2004).

Considering that there was no statistical difference in age between the two ADHD groups, it is of interest to consider whether an age-of-onset variable may have been in operation. The treatment-naïve group generally consisted of recently diagnosed children with ADHD, and data was not collected regarding how long these children had been displaying symptoms. Diagnostic criteria requires that at least some of the attentional or hyperactive symptoms are present prior to age seven, although it is possible that the

individuals in the treatment-naïve group did not display as significant symptoms in early elementary school as did the chronically-treated group, perhaps explaining why the chronically-treated children were referred for treatment earlier and are therefore "chronically" treated. This causes one to wonder if there were some difference between the two ADHD groups which enabled the treatment-naïve children to compensate for their inattentiveness and inhibitory control deficits until environmental demands for attention became too taxing. Finally, another important limitation of this study was the relatively small representation of minority groups, which hinders generalizability.

Directions for Future Research

Recent research has suggested that new imaging technologies, Diffusion Tensor Imaging (DTI) in particular, may be better suited to imaging white matter tracts in the brain than traditional MRI sequences. DTI allows for the measurement of the microstructural organization and integrity of white matter fiber through an observation of the alignment of water molecules of the brain. At random, the molecules will be positioned randomly in the brain (anisotropic); however, if they are in white matter tracts or axons, they will point in a single direction (isotropic). The commonly used measurement of anisotrophy is Fractional Anisotrophy (FA) (Basser, 1995), a scalar measure which ranges from 0 (perfectly isotropic diffusion) to 1 (perfectly anisotropic). This technology appears to be highly promising in terms of providing greater sensitivity to white matter abnormalities, and researchers have already begun to employ this technology to examine the corpus callosum. For example, in a study of head injured subjects, DTI scans revealed reduced white matter in the corpus callosum, whereas high

resolution MRI scanning did not (Levine et al., 2005). Therefore, replicating the current study utilizing DTI technology may provide a higher degree of sensitivity to mild corpus callosum abnormalities in subjects with ADHD.

The finding that chronically-treated children showed a trend toward greater similarity to the controls than to the treatment-naïve participants in terms of splenium size argues for the need for prospective studies. Such designs would be longitudinal, with imaging occurring prior to the initiation of stimulant treatment and then periodically throughout the course of treatment. Additionally, comparing the white matter development in children with ADHD to that of typically developing children will be important. As discussed earlier, the corpus callosum is developing throughout the age range when stimulant medications are generally prescribed (Giedd et al., 1999; Kolb & Fantie, 1989; Njiokiktijin et al., 1994; Schaefer et al., 1992; Yakovlev & Lecours, 1967), which reinforces the need for research designs that include serial scans of the participants.

Finally, the question of whether neuroimaging has any utility for the prediction of treatment response if of great interest. This has begun to be addressed by research groups interested in the treatment of depression (e.g. Mayberg et al., 1997). Although stimulant medication has been found to be highly effective in children (Charach, Ickowicz, & Schachar, 2004; MTA Cooperative Group, 1999), certainly not all children are responders, nor do all children respond to the same medications (Biederman, Spencer, & Wilens, 2004). As the understanding of the neurobiology of psychiatric disorders, including ADHD, increases, possibilities for better diagnosis and prediction of treatment

outcomes follow. Considering that mental health services are costly to provide and often in short supply, a biologically-informed understanding of which treatments are most likely to benefit a particular patient would radically change the efficiency and efficacy of service delivery. However, the first step in this line of research is to clearly delineate the neurobiological adaptations associated with various treatment modalities.

Conclusions and Contribution to the Literature

In summary, the results of the current investigation provide important information about the feasibility of measuring corpus callosum volume, and perhaps just as importantly, the practicality of doing so. Corpus callosum volume was reliably measured, but yielded no further information than simply obtaining the area. Therefore, the information gained from volumetric measures may not be worth the significant outlay of time required for its calculation. The finding of reduced splenium area in ADHD treatment naïve subjects, but not in the chronically treated, is of interest considering the recent findings of a trend toward normalization of brain activation pattern in ADHD chronically treated subjects (Pliszka et al., in press).

Also, the current study supports previously reported data suggesting that behavioral measures of attentional difficulties and impulsivity are related to some components of CC size. The attempt to demonstrate a relationship between measures of neuropsychological measures and CC size was less fruitful. However, it tentatively appears that smaller genu area may be related to poorer performance on tasks of sustained attention, which is consistent with the research implicating the CC in sustained attention (Diamond, 1979; Ellenger & Sperry, 1979; Rueckert et al., 1994, 1996). However, given

the importance of the posterior brain regions in vigilance (Posner & Petersen, 1990), it was unexpected that the splenium was not also related to sustained attention. Finally, the predicted absence of a relationship between the corpus callsoum and inhibitory control is consistent with literature implicating a frontal-striatal network as responsible for this function (Pliszka, 2001).

Of great clinical relevance to the mental health providers involved in the treatment of children with ADHD, the results of this study do inform the very important question about whether long-term stimulant usage results in maladaptive brain changes (Hyman, 2003). The current investigation provided no evidence for negative long-term consequences of chronic stimulant treatment, but rather indicated a trend toward normalization of anatomical size in the chronically treated subjects. This is a reassuring finding as the literature indicates that stimulant treatment, especially when coupled with behavioral modification techniques, is the most effective treatment for the symptoms of ADHD (Charach, Ickowicz, & Schachar, 2004; MTA Cooperative Group, 1999). The focus of this study was limited to a single brain structure, and similar designs should be replicated with other neuroanatomical structures as the focus. However, the corpus callosum continues to develop throughout the age range included in the study and would be sensitive to any disruptions in the myelination process which may occur secondary to chronic medication usage or to other factors. Therefore, the corpus callosum serves as a useful model for the effects of chronic stimulant treatment on the neuroanatomy of the developing brain.

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