Corpus callosum morphology and function in attention deficit hyperactivity disorder and the relationship between the corpus callosum and cognitive functioning in healthy adults

Amanda D Hutchinson

School of Psychology

University of Adelaide, SA, Australia

Institute of Cognitive Science

University of Colorado, Boulder, CO, USA

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Abstract

The corpus callosum (CC) is the largest fiber[1] tract in the brain and connects homological regions of the two cerebral hemispheres. Research with split-brain patients, whose CC has been surgically severed, and neurologically intact groups has shown that the CC is important for sustained and divided attention. Due to its role in attention, the CC is of interest to clinical conditions in which attention is affected, such as attention deficit hyperactivity disorder (ADHD).

Although the size of the CC has been examined in children and adolescents with ADHD, the results have been inconsistent. Therefore, the first of three studies in this thesis synthesized the current research in a meta-analysis, which analyzed the data from 13 studies that examined CC area in children and adolescents with ADHD, when compared to healthy controls. This study found that the splenium, the most posterior region of the CC, was smaller in ADHD and the rostral body, an anterior region, was smaller in boys with ADHD compared with controls. Thus, there is evidence for differences in area in both the anterior and posterior regions of the CC in ADHD.

It was not known whether these differences persist into adulthood, however, because CC size had not been examined in adults with ADHD. Therefore, the second study examined CC area and structural integrity in young adults with ADHD compared with healthy controls using magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), respectively. The difference in the size of the splenium was not present in this adult sample,

[1] American spelling is used throughout the thesis in order to be consistent with the published papers which have been published or prepared using American spelling.

although the genu (an anterior region of the CC) was smaller and two mid-posterior regions were larger in adults with ADHD when compared with controls. In addition, a reduction in the integrity of the genu and greater integrity in the splenium was found in ADHD.

The relationship between CC morphology and measures of attention and IQ was also examined in young adults with ADHD and controls in order to assess the functional significance of differences in the CC. The integrity of the splenium was correlated with performance on the Stroop task, which requires attentional control. Hence, this study indicated that the morphology of the CC is atypical in young adults with ADHD and that these differences in the CC may impact on cognitive functioning. Interestingly, an estimate of performance IQ was negatively correlated with CC area in controls. This result conflicts with previous research on the relationship between IQ and the CC in healthy adults although the literature has yielded inconsistent findings.

The third study, therefore, examined the relationship between IQ and both CC area and integrity in more detail in a larger sample of young adults. A negative correlation was found between the area of posterior regions of the CC and an estimate of performance IQ, while an estimate of verbal IQ was associated with decreased structural integrity in the genu. This study supports the hypothesis that differences in CC size and or integrity may have cognitive consequences.

In summary, this thesis confirms the view that the development of the CC is atypical in children and young adults with ADHD. In addition, differences in CC integrity were associated with cognitive functioning in

young adults with ADHD. Finally, the morphology of the CC is related to cognitive performance in healthy adults.

Declaration

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* Published Works

Hutchinson, A. D., Mathias, J. L., & Banich, M. T. (2008). Corpus callosum morphology in children and adolescents with Attention Deficit Hyperactivity Disorder: a meta-analytic review. *Neuropsychology*, 22(3), 341-349.

Hutchinson, A.D., Mathias, J.L., Jacobson, B.L., Ruzic, L., Bond, A.N., & Banich, M.T. Corpus callosum size and composition in adults with attention deficit hyperactivity disorder. Manuscript submitted for publication.

Hutchinson, A.D., Mathias, J.L., Jacobson, B.L., Ruzic, L., Bond, A.N., & Banich, M.T. (2009). Relationship between intelligence and the size and composition of the corpus callosum. *Experimental Brain Research,* 192(3), 454-464.

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I am thankful that I have two places I call home. It is bittersweet to return to Australia and leave Boulder. I will miss Colorado life but I know that this is a beginning as well as an ending. Colorado holds a special place in my heart and I know I will return soon.

"Every new beginning comes from some other beginning's end"

Closing Time, Semisonic

Statements of the contributions on jointly authored papers

Chapter 2

Title: Corpus callosum morphology in children and adolescents with attention deficit hyperactivity disorder: a meta-analytic review.

Co-authors: J.L. Mathias, M.T. Banich

Contributions: Both co-authors acted in a supervisory capacity during all stages of this research and manuscript preparation. I was responsible for this study's inception and design, data-collection, statistical analyses, data interpretation, and manuscript preparation, under the supervision of J.L. Mathias and M.T. Banich.

Chapter 3

Title: Corpus callosum size and integrity in adults with attention deficit hyperactivity disorder

Co-authors: J.L. Mathias, B.L. Jacobson, L. Ruzic, A.N. Bond, E. Willcutt, L.C. Bidwell, Y.P. Du and M.T. Banich

Contributions: B.L. Jacobson developed the semi-automated algorithm that was used to trace the corpus callosum from the MRIs performed on study participants. L.T. Ruzic processed the imaging data using FSL and ascertained measures of FA from the DTI data. A.N. Bond conducted traces of the corpus callosum in order to allow the inter-rater reliability of the tracing technique to be evaluated. E. Willcutt and L.C. Bidwell were involved in participant recruitment, screening and neuropsychological data collection. Y.P. Du helped with Magnetic Resonance acquisition, writing the pulse

sequence for data acquisition, and initial analyses. J.L. Mathias and M.T. Banich acted in a supervisory capacity and guided all stages of this work, including manuscript preparation. I was responsible for this study's inception and design, completed all traces of the corpus callosum (excluding those completed by A.N. Bond for the analysis of inter-rater reliability), conducted all statistical analyses and data interpretation, and was the primary author on this paper.

Chapter 4

Title: Relationship between intelligence and the size and composition of the corpus callosum.

Co-authors: J.L. Mathias, B.L. Jacobson, L. Ruzic, A.N. Bond and M.T. Banich

Contributions: B.L. Jacobson developed the semi-automated algorithm used to trace the corpus callosum. L.T. Ruzic processed the imaging data using FSL and ascertained measures of FA from the DTI data. A.N. Bond conducted traces of the corpus callosum in order to allow the inter-rater reliability of the tracing procedure to be evaluated. J.L. Mathias and M.T. Banich acted in a supervisory capacity and guided all stages of this work, including manuscript preparation. I was responsible for this study's inception and design, completed all traces of the corpus callosum (excluding those completed by A.N. Bond for the analysis of inter-rater reliability), undertook all statistical analyses and data interpretation, and was the primary author on this paper.

The undersigned agree that the statements made regarding author contributions are accurate and true.

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Chapter 1: Introduction

This thesis examines differences in corpus callosum (CC) morphology in children and young adults with attention deficit hyperactivity disorder (ADHD). In addition, it explores the relationship between CC morphology and IQ in healthy adults. The current chapter will describe the CC, its measurement, and its involvement in attentional processes. A broad overview of ADHD will then be provided, before examining the literature on CC differences in ADHD. Evidence for a relationship between CC morphology and IQ will be examined. It will conclude with a final summary and statement of aims.

1.1 The Corpus Callosum

The CC is the largest white matter structure in the human brain (Hoptman & Davidson, 1994; Hynd et al., 1991; Innocenti & Bressoud, 2003). Although the anterior, hippocampal and posterior commissures also connect the hemispheres, the CC is the main connecting pathway between the left and right hemispheres of the brain (Hoptman & Davidson, 1994; Myers & Sperry, 1985; Seymour, Reuter Lorenz, & Gazzaniga, 1994; Yazgan, Wexler, Kinsbourne, Peterson, & Leckman, 1995). The CC consists of fibers that mediate sensory-motor coordination and fibers that connect equivalent association areas in the two hemispheres (Yazgan et al., 1995), and is considered critical in the integration and communication of high-level information, such as the precise information that is required to identify an item (Banich, 2003; Hoptman & Davidson, 1994).

In general, the anterior regions of the CC, the rostrum and genu, connect the left and right prefrontal cortical areas (see Figure 1) (Witelson, 1989). Posterior to these regions, the rostral body connects homologous prefrontal, premotor, and supplementary motor regions. The anterior midbody connects the motor cortices, and the posterior midbody connects somatosensory and posterior parietal areas. The isthmus connects the superior temporal and posterior parietal regions. Finally, the splenium, the most posterior section of the CC, connects homologous occipital and inferior temporal regions (Giedd, Castellanos, & Rapoport, 1995; Giedd et al., 1994; Steere & Arnstein, 1995; Witelson, 1989). Disruption to the functioning of the CC, such as impaired interhemispheric transfer of information, can result either from abnormalities in the cortical sources of the fibers crossing the CC or from problems in interhemispheric connectivity (i.e. in the CC itself) (Giedd et al., 1994).

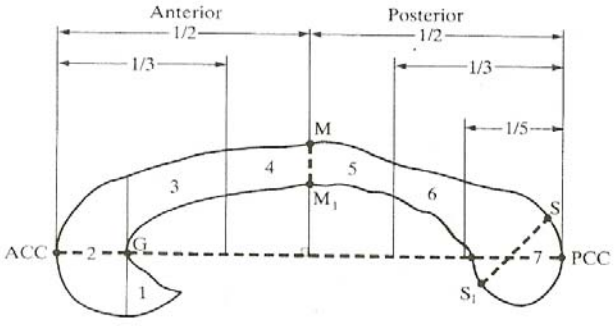


Figure 1: Witelson's divisions of the corpus callosum

Witelson, S.F., Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study, Brain, 1989, 112 (Pt 3), 799-835, by permission of Oxford University Press. 1 = rostrum, 2 = genu, 3 = rostral body, 4 = anterior midbody, 5 = posterior midbody, 6 = isthmus, 7 = splenium. ACC and PCC = the most anterior and posterior points of the corpus callosum respectively, M and M1 = superior and inferior points of the corpus callosum at its midpoint, S and S1 = superior and inferior points of the splenium, G = the most anterior point of the inner convexity of the anterior corpus callosum.

1.1.1 Measurement of the corpus callosum.

Due to the anatomical and functional significance of the CC, differences in its size, as measured by area, have been of interest to researchers. The area of the CC is typically measured at the midsagittal slice of the brain (midline slice that divides the brain into the left and right halves) (Jancke & Steinmetz, 2003). It is not possible to accurately determine the volume of the CC because CC fibers project into the cortex making the boundary between the CC and cortex difficult to define. Some studies have calculated volume by examining the midsagittal slice and several slices on either side of the midsagittal slice (Fine, Semrud-Clikeman, Keith, Stapleton, & Hynd, 2007; Rotarska-Jagiela et al., 2008). However, these measurements are somewhat arbitrary and, like the midsagittal measurements alone, provide only an estimate of CC size. These volume measurements may introduce additional error and may not, therefore, provide better estimates of CC size than area measurements (Fine et al., 2007).

A number of factors affect the area of the CC, namely the degree of myelination of the fibers (Yakolev & Lecours, 1967) or the number of myelinated fibers traversing the CC (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). The diameter of CC fibers and their degree of myelination varies between regions. The largest fibers are found in the midbody of the CC with a progression to smaller fibers in both an anterior and posterior direction towards the genu and splenium, respectively (Aboitiz et al., 1992). In addition, myelination of the CC is a process that continues throughout childhood and adolescence (Giedd et al., 1996; Yakolev & Lecours, 1967). Therefore, the size of the CC is dependent upon degree of myelination, the

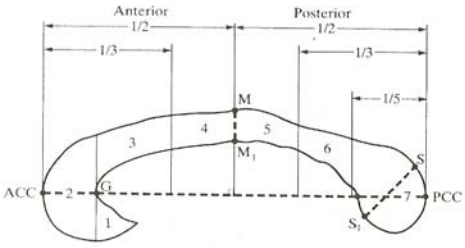
number of fibers and their diameter, and age. The speed with which information is transferred is also thought to be related to the number of fibers, and a fiber's size and degree of myelination (Aboitiz et al., 1992; Hagelthorn, Brown, Amano, & Asarnow, 2000). Therefore, the area of the CC is likely to be related to the rate of interhemispheric transfer of information.

In addition to measuring the total area of the CC, the CC has been divided into anatomical regions to determine whether there are more localized differences between clinical groups and healthy controls. Regional differences are of interest because fibers passing through different parts of the CC project to different areas of the cortex. A range of different methods have been used to divide the CC into regions because there are no visible anatomical landmarks to guide the division of the CC (Peterson et al., 2001). Four methods of dividing the CC will be described, all of which measure CC area at the midsagittal slice of the brain.

Witelson's (1989) method for dividing the CC is arguably the most commonly used approach by researchers. This method involves drawing a line between the most anterior and posterior points of the CC. Another set of lines are then placed perpendicular to this horizontal line, dividing the CC into halves, thirds, and fifths (see Figure 2A). This results in seven regions: namely, from anterior to posterior, the rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and the splenium. These divisions are somewhat arbitrary, although they are based on research with monkeys (Witelson, 1989). However, they have been widely applied due to their simplicity and the absence, until recently, of more accurate techniques.

Three other methods have been used to divide the CC into regions, although these are less commonly used than Witelson's scheme and its variations. One of these techniques is the radial method in which a horizontal line is drawn along the base of the CC connecting the most anterior and posterior points of the CC (see Figure 2B). Five lines are drawn from the centre of this line so that they intercept the CC at 30 degree intervals, dividing the CC into five regions (Bishop & Wahlsten, 1997). Another method, the tangent method, also involves drawing a horizontal base line connecting the most anterior and posterior points of the CC. Lines are then drawn perpendicular to the baseline, dividing it into quarters. However, at the point at which this line meets the boundary of the CC, a division is placed perpendicular to the tangent of the CC wall (see Figure 2C). These regions are simply referred to as the first through to the fourth quartile, although the first quartile is also named the genu and the fourth quartile is labeled the splenium. The rationale for the radial and tangent methods is unclear. A fourth method identifies a curved central line that bisects the CC lengthwise. Divisions are then placed perpendicular to this line at fifths along the centerline, resulting in five regions (Bishop & Wahlsten, 1997) (see Figure 2D). This method was proposed in order to better account for individual variation in the shape of the CC, and more specifically, its contour.

A: Witelson's CC divisions



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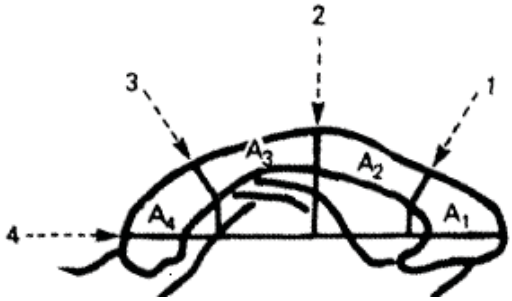
B: Radial method

C: Tangent method



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D: Curved line method

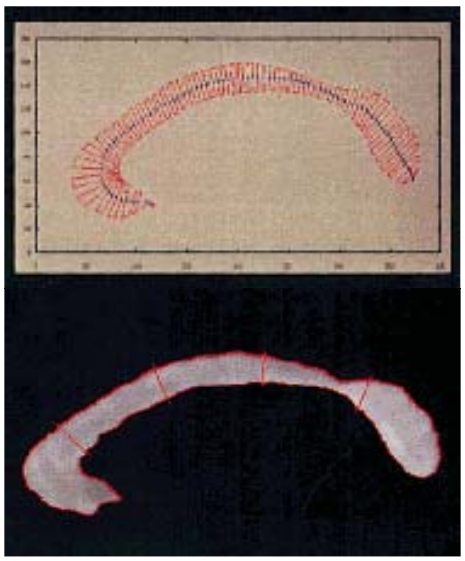

Figure 2: Corpus callosum measurement techniques

A: Witelson, S.F., Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study, Brain, 1989, 112 (Pt 3), 799-835, by permission of Oxford University Press. 1 = rostrum, 2 = genu, 3 = rostral body, 4 = anterior midbody, 5 = posterior midbody, 6 = isthmus, 7 = splenium. ACC and PCC = the most anterior and posterior points of the corpus callosum respectively, M and M1 = superior and inferior points of the corpus callosum at its midpoint, S and S1 = superior and inferior points of the splenium, G = the most anterior point of the inner convexity of the anterior corpus callosum.

B: From Hynd, G.W., Semrud-Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., Lyytinen, H. (1991): Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. *J Learn Disabil* 24:141-6. Copyright (1991) by PRO-ED, Inc. Reprinted with permission. 1 = genu, 5 = splenium. Regions 2, 3 and 4 not specified.

C: Reprinted from Biological Psychiatry, 26, Hauser, P., Dauphiniais, I.D., Berrettini, W., DeLisi, L.E., Gelernter, J., and Post, R.M. Corpus callosum dimensions measured by magnetic resonance imaging in bipolar affective disorder and schizophrenia, 659-668, 1989, with permission from Elsevier. 1 = first quartile (genu), 2 = second quartile, 3 = third quartile, 4 = fourth quartile (splenium).

D: Reprinted from Human Brain Mapping, 12, Peterson, B.S., Feineigle, P.A., Staib, L.H., and Gore, J.C. Automated measurement of latent morphological features in the human corpus callosum, 232-245. Copyright (2001), with permission from Wiley Interscience. Regions not specified.

More recently, Hofer and Frahm (2006) have suggested a set of divisions of the CC that are functional because they are based on the cortical sources and projections of CC fibers observed in a diffusion tensor imaging (DTI) study, which was designed to map CC fibers using tractography. This approach places a line between the most anterior and posterior points of the CC and a number of divisions perpendicular to this line. However, in this case, divisions are placed 1/6, 1/2, 2/3 and 3/4 along the line dividing it into five regions (see Figure 3). From anterior to posterior, these regions connect left and right (I) prefrontal regions, (II) premotor and supplementary motor regions, (III) primary motor cortices, (IV) primary sensory cortices, and (V) parietal, temporal, and occipital cortices. This method reflects the cortical connectivity of the CC observed in humans. Therefore, this method is more likely to reflect regional differences in anatomy and function than the techniques for dividing the CC described earlier. This approach will be used in this thesis because regional differences can be more accurately related to the cortical projections of the CC and potential consequences of differences in CC morphology can be identified.

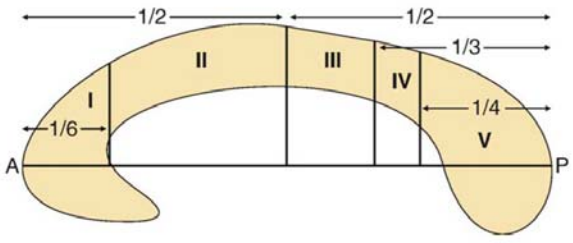

Figure 3: Hofer and Frahm's proposed corpus callosum divisions.

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1.1.2 Gender differences.

Gender differences in CC size have been well researched in order to determine whether the gender differences that have been found in total brain size (Lenroot et al., 2007) are reflected in the CC. However, existing research has yielded inconsistent results. A meta-analytic review by Bishop and Wahlsten (1997) found a larger CC in males but this gender difference disappeared when results were adjusted for total brain size because males typically have a larger total brain size than females. In addition, one study failed to find gender differences in the growth rates of the CC, as measured by CC area, during development (Lenroot et al., 2007). In contrast, some individual studies have found that males have a larger CC even after controlling for brain size (Sullivan et al., 2001) and increased relative anisotropy, a measure of structural integrity, in the CC (Westerhausen et al., 2004; Westerhausen et al., 2003). There are also inconsistencies in research of the shape of the CC, with one study finding gender differences (Dubb, Gur, Avants, & Gee, 2003) and another finding differences in the distance between specific points of the CC but no differences in general shape (Ozdemir et al., 2007). Therefore, the extent to which gender may impact on CC size is unclear.

1.1.3 Role of the corpus callosum in attention.

Although a lot of research has examined the anatomical size of the CC, the function of the CC has also been demonstrated, particularly in relation to the functional consequences of compromise to the CC. The relationship between the CC and attention has been particularly well researched due to evidence from research with split-brain patients, who have had their cortical

commissures surgically severed (commissurotomy) for the treatment of intractable epilepsy and who exhibit deficits in attention compared to healthy controls. Firstly, split-brain patients have difficulty sustaining attention (Dimond, 1976; Ellenberg & Sperry, 1979). For example, Dimond (1976) examined sustained attention using a vigilance task with six commissurotomy patients. Participants looked at a display with four lights, with two located to the left and two located to the right of a central fixation point. When one of these lights was turned off, participants were required to respond by pressing a button that corresponded to the specific light. Participants used their left hand to respond to the lights on the left and their right hand to respond to those on the right. Dimond (1976) found that the performance of the split-brain patients deteriorated over time. Specifically, accurate detection of the stimulus (extinction of a light) dropped to 30% of the initial task performance over a period of half an hour, leading the author to conclude that sustained attention is supported by the CC.

Second, although one study has found enhanced dual-task performance in commissurotomy patients (Holtzman & Gazzaniga, 1985), other studies have found deficits in these patients (Holtzman & Gazzaniga, 1982; Kreuter, Kinsbourne, & Trevarthen, 1972; Teng & Sperry, 1973) with increased complexity leading to increased interference and poorer task performance (Kreuter et al., 1972; Teng & Sperry, 1973).

Third, and in contrast, commissurotomy patients have demonstrated quicker performance on visual search tasks, which require sustained and focused attention, than healthy controls (for a review refer to Gazzaniga, 2000). In general, the time taken to complete a visual search task increases

with each additional item that is added to a display. However, in split-brain patients, the additional reaction time is half of that in controls. Visual search is thought to be quicker in commisurotomy patients because each hemisphere can complete half of the task independently of the other hemisphere (for a review refer to Gazzaniga, 2000). Therefore, it is thought that the CC is involved in maintaining a cohesive attentional system by forcing the hemispheres to work together in the healthy brain (Ellenberg & Sperry, 1980). Furthermore, research examining attention in participants with a partial commisurotomy has demonstrated that an intact splenium alone is capable of unifying attention emphasizing the importance of this posterior region in particular for attentional processes (Ellenberg & Sperry, 1980).

In addition to research with split-brain patients, the role of the CC in attention has been examined more recently in neurologically intact samples. In particular, research on interhemispheric interaction has been informative. Interhemispheric interaction refers to the integration of information between the left and right hemispheres of the brain and the CC is the main conduit for the interhemispheric transfer of information. Therefore, a number of studies have examined the nature of interhemispheric interaction and the conditions under which it benefits or impedes task performance. This research has been integrated into a model described by Belger and Banich (1992) and later by Banich and Brown (2000). These authors have argued that there are three factors that determine whether interhemispheric interaction is beneficial or detrimental for task performance (Banich & Brown, 2000). The first factor is the degree to which the callosal transfer of information increases the time taken to process information. The second factor is the extent to which a task's

complexity taxes the processing resources of one hemisphere and the third factor is the capability of the individual's CC to transfer information between the hemispheres (Banich & Brown, 2000).

This model is largely based on studies that used an experimental paradigm in which participants are required to determine whether a target item matches either of two probes (see Figure 4). In the Left Visual Field/Within Hemisphere Trial in the top left of Figure 4, participants are required to recognize that the target 'A', located below the fixation cross ('+'), matches one of the probes located above the fixation cross ('A'). Performance on within-hemisphere trials, in which the target and the probe are presented to the same visual field, is compared with across-hemisphere trials, in which the target and the matching probe are presented to opposite visual fields.

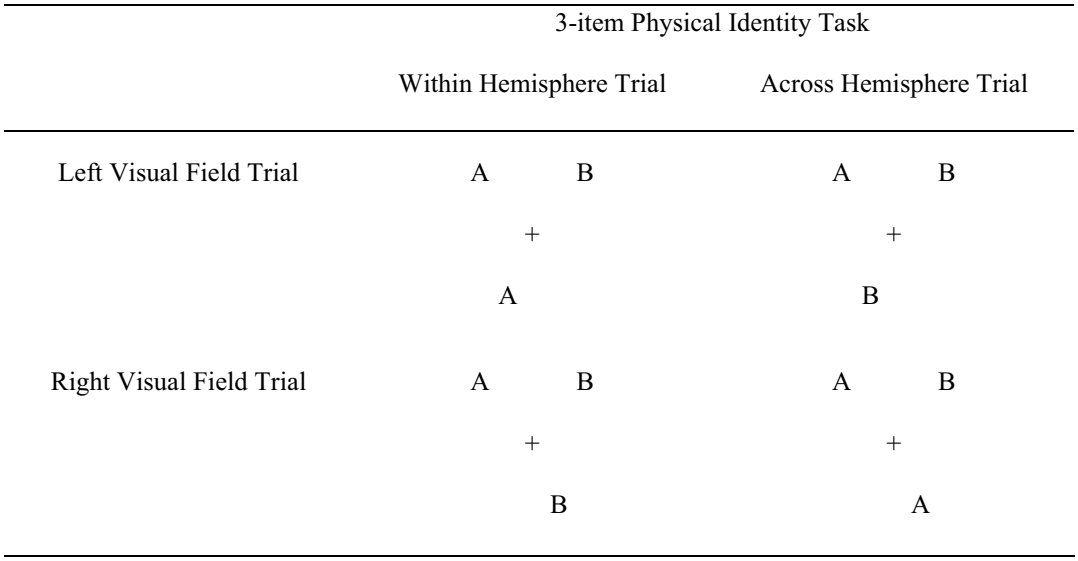

Figure 4: The interhemispheric interaction paradigm used by Banich and colleagues.

N.B. + = a fixation cross, upper letters = probes, lower letter = the target.

For the within-hemisphere trials, no interhemispheric interaction is necessary to identify the match because the matching items are presented to the same visual field and, therefore, the same hemisphere. However, for the across-hemisphere trials, interhemispheric interaction is necessary to integrate the information presented to the two visual fields (or two hemispheres). In general, the research findings suggest that, for simple tasks, it is beneficial for information to be processed by a single hemisphere (e.g. Banich & Belger, 1990; Banich, Passarotti, & Chambers, 1994; Belger & Banich, 1992; Passarotti, Banich, Sood, & Wang, 2002). In contrast, interhemispheric interaction leads to better task performance for complex tasks that have higher attentional demands (e.g. Banich & Belger, 1990; Belger & Banich, 1992; Passarotti et al., 2002). This is thought to result from the time cost associated with callosal transfer. When a task is relatively simple, this cost outweighs the benefit of recruiting the other hemisphere to increase computational power. However, when a task is complex and is more attentionally demanding, the benefit of recruiting additional resources by using both hemispheres outweighs the time cost of callosal transfer, making it advantageous compared to within-hemisphere processing (for a review refer to Banich, 1995, 1998, 2003; Banich & Brown, 2000). Therefore, interhemispheric interaction appears to benefit performance under attentionally demanding conditions. These studies provide further evidence for a relationship between the CC and attention.

To summarize, the CC appears to play a role in attentional processing in both neurologically intact samples and split-brain patients. However, split-brain patients are not the only clinical group who experience problems with attention. Thus, the morphology of the CC is of interest in other clinical

groups due to the possibility that compromise to the CC may underlie their difficulties with attention. One of these conditions is attention deficit hyperactivity disorder (ADHD). A broad review of ADHD will be presented before discussing research conducted on CC morphology in ADHD.

1.2 Attention Deficit Hyperactivity Disorder

ADHD is well established as a childhood disorder affecting inattention and/or hyperactivity (American Psychiatric Association [APA], 2000). However, adulthood ADHD has been controversial due to the difficulties associated with the retrospective diagnosis of ADHD, disagreement about the characteristics of the disorder in adulthood and comorbid psychiatric and learning disorders (APA, 2000; Biederman, 2005). Although interest in adult ADHD has increased in recent years (Hervey, Epstein, & Curry, 2004), most ADHD research has focused on children.

1.2.1 Diagnosis of childhood ADHD.

According to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV-TR), ADHD in children is characterized by persistent inattention and/or hyperactivity-impulsivity (APA, 2000). In order for a diagnosis to be made, either inattention or hyperactivity must have been present for at least six months, and symptoms must cause a clinically significant impairment in functioning in at least two settings (such as school, work, or home). In addition, some of these symptoms must have been present before 7 years of age and symptoms must be inappropriate for the individual's developmental level. There are three subtypes of ADHD: ADHD combined type, where the criteria for both inattention and hyperactivity are met, ADHD

predominantly inattentive type, where only the criteria for inattention are met, and ADHD predominantly hyperactive/impulsive type, where only the criteria for hyperactivity are met (APA, 2000). The combined type is the most common form of ADHD in children (APA, 2000).

The ICD-10 criteria are used to diagnose Hyperkinetic Disorder, which refers to a subtype of ADHD (World Health Organization, 2007). The ICD-10 criteria for Hyperkinetic Disorder are similar to those set out for ADHD in the DSM-IV but are more rigorous in terms of inclusion and exclusion criteria (Swanson, Castellanos, Murias, LaHoste, & Kennedy, 1998). Symptoms of inattention, hyperactivity, and impulsivity must have been present to an extent that is maladaptive and inconsistent with the child's developmental level for at least six months in order for a diagnosis of Hyperkinetic Disorder to be made. Like the DSM-IV criteria, onset must occur by the age of seven and symptoms of inattention and impulsivity must cause significant distress or impairment in social, academic, or occupational functioning (World Health Organization, 1993). According to the ICD-10, a different diagnosis is given for cases with significant conduct disturbance; namely, Hyperkinetic Conduct Disorder. Therefore, comorbid Conduct Disorder is less likely to occur with an ICD-10 diagnosis of Hyperkinetic Disorder than it is with a DSM-IV diagnosis of ADHD (Swanson, 1997).

1.2.2 Diagnosis of adult ADHD.

The diagnosis of ADHD in adults is complicated, as there is no gold standard for this disorder, nor is there any consensus regarding the most appropriate methods for diagnosing ADHD in adults. Some studies use DSM-IV criteria, ICD-10 criteria, criteria that were specifically developed for

diagnosing adults with ADHD, such as the Wender Utah diagnostic criteria (Ward, Wender, & Reimherr, 1993), and/or scores on measures developed to assess the presence and severity of symptoms in adults. The latter measures include the Barkley Self, Other and Past ADHD symptom checklists (Barkley & Murphy, 2006), the Adult Self Report Scale (Adler, Kessler, & Spencer, 2004; Kessler et al., 2005), Conners Adult ADHD Rating Scale (Conners, Erhardt, Sparrow, & Conners, 1998), and the Brown Adult Attention Deficit Disorder Scale (Brown, 1996).

A diagnosis of ADHD in adults relies on an individual's recall of childhood events and behavior because the onset of symptoms must have occurred before 7 years of age (Barkley & Biederman, 1997; Faraone, 2000). This requires a shift from parental reports of symptoms to self-report, potentially after a few decades have passed. Although parental recall of symptoms has been shown to be reliable (Faraone, Biederman, & Milberger, 1995), the recall of a precise age of onset of these symptoms may not be (Barkley & Biederman, 1997). Therefore, Barkley and Biederman (1997) have questioned the reliability of the age of onset criterion when diagnosing ADHD in adults. Diagnosis is also complicated because although the DSM-IV indicates that symptoms must be inconsistent with the individual's developmental level to contribute to a diagnosis of ADHD, there is little guidance about how this criterion is established (Faraone et al., 2000). In addition, there is evidence that adults with ADHD tend to under-report the presence of current symptoms or do not indicate their severity, possibly due to difficulties with self-reflection and evaluation (Kooij et al., 2008).

Thus, there are a number of obstacles to accurately diagnosing adult ADHD and determining its prevalence. Faraone and Biederman (2005) found that the combined and predominantly hyperactive subtypes were equally prevalent and more common than the predominantly inattentive subtype in adults who met DSM-IV criteria in both childhood and adulthood. However, when a less stringent set of criteria were utilized, the combined subtype was the most prevalent type of ADHD in adults, consistent with research with children with ADHD.

1.2.3 Prevalence of ADHD.

The DSM-IV-TR (APA, 2000) estimates the prevalence of ADHD to be 3% - 7% of school age children. There has, however, been some confusion regarding prevalence estimates due to the use of different criteria (i.e. DSM-IV-TR, ICD-10 criteria). In particular, ICD-10 criteria for Hyperkinetic Disorder only identify a subset of people classified with ADHD according to DSM-IV. The use of these different sets of criteria in different parts of the world has made international population estimates difficult (Swanson et al., 1998). A recent study reported that the worldwide prevalence of ADHD based on DSM or ICD criteria was 5.29% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, prevalence rates varied according to geographic location, with lower estimates in Africa and the Middle East compared with North America. This may be due, in part, to methodological differences in the studies, as well as cultural differences. In addition, very few studies have been conducted in Africa and the Middle East and therefore, the finding of increased prevalence in North America should be interpreted cautiously (Polancyzk et al., 2007).

ADHD is more common in males than females, with between 2 and 9 times more male children being diagnosed with this disorder (APA, 2000). Although more males are diagnosed with ADHD than females in childhood, this gender bias is less pronounced in adulthood. It has been suggested that this could be because boys with ADHD may be more disruptive than girls and are, therefore, more likely to be referred for assessment as children (Faraone et al., 2000). These gender differences in behavior may be less likely to affect adult referrals.

No estimate of the prevalence of ADHD in adults is provided in the DSM-IV. However, it is stated that a small number of people continue to experience symptoms in adulthood (APA, 2000). Elsewhere, it has been reported that between 1% and 6% of the general population manifest symptoms of ADHD in adulthood (de Graaf et al., 2008; Faraone & Biederman, 2005; Fayyad et al., 2007; Kessler et al., 2006; Roth & Saykin, 2004; Wender et al., 2001). Estimates of the continuation of ADHD symptoms into adulthood range from 30% to 70% of affected children (Castellanos et al., 1996; Durston, 2003; Kessler et al., 2005; Roth & Saykin, 2004; Wender et al., 2001). A meta-analysis of follow-up studies of ADHD diagnoses found that the rate of persistence was as low as 15% at 25 years of age (Faraone, Biederman, & Mick, 2006). However, when using the DSM-IV criteria for ADHD in partial remission (i.e. symptoms were still present but no longer met full criteria) the rate was between 40% and 60% (Faraone, Biederman, & Mick, 2006). Despite the variation in these estimates, it is evident that only a proportion of children with ADHD experience symptoms that persist into adulthood. The difference between these children and those

whose symptoms remit before adulthood is not clear although it is thought that genetic, environmental, and biological factors play a role (Moss, Nair, Vallarino, & Wang, 2007). Overall, differences in diagnostic standards make it difficult to determine an accurate prevalence rate in either children or adults.

Despite difficulties in accurately determining the prevalence of ADHD, this disorder clearly has a significant financial and social impact given that it affects between 3% and 5% of school age children alone. ADHD affects academic and occupational functioning, sleep, self-esteem, self-efficiency, social relationships, family well-being, and individual well-being (Barkley et al., 2002; Biederman & Spencer, 1999; Schredl, Alm, & Sobanski, 2007). In addition, adult ADHD is associated with risk-taking and anti-social behavior, marital difficulties, lower socio-economic status, increased physical injuries, and problems related to driving (Barkley et al., 2002; Faraone, 2000; Jerome, Habinski, & Segal, 2006; Roth & Saykin, 2004). Therefore, ADHD impacts not only the individual, but also their family, friends, and school or work environments. Pelham, Foster and Robb (2007) estimated the cost of illness per child with ADHD at $14, 576 (USD) based on health, mental health, education, and crime and delinquency costs. This amounts to a significant financial burden of $42.5 billion dollars for children with ADHD in the United States, using a prevalence rate of 5% (Pelham et al., 2007).

1.2.4 Comorbidities.

Comorbid psychiatric conditions add to the financial and social burden experienced by people with ADHD. Many people with ADHD also have Oppositional Defiant Disorder, Conduct Disorder, Antisocial Personality Disorder, Mood Disorders, Anxiety Disorders, Learning Disorders,

Communication Disorders, Tourette's Disorder, and/or Substance Abuse Disorders (APA, 2000; Castellanos, Giedd, Marsh, & Hamburger, 1996; Faraone, 2000; Wender, Wolf, & Wasserstein, 2001). Substance Abuse is also more likely in adults with ADHD than in children or adolescents with ADHD (Faraone, 2000). However, substance abuse also increases in adulthood in the healthy population (Faraone et al., 2000). In addition, it is thought that there may be a negative relationship between the use of medications for the treatment of ADHD and substance use, such that adolescents and young adults who have *not* received treatment are at an increased risk of substance abuse (Biederman, Wilens, Mick, Spencer, & Faraone, 1999).

1.2.5 Treatment.

Traditionally, ADHD has been treated with stimulant medications, although long acting stimulants and non-stimulant medications have more recently been used to treat the disorder. There has also been interest in alternative approaches to treatment, such as dietary changes and behavioral interventions.

Stimulant medications, such as methylphenidate (e.g. methylphenidate hydrochloride) and amphetamines (e.g. dexamfetamine sulphate) increase the release of dopamine and noradrenaline (norepinephrine) and block their uptake, thereby enhancing the effects of both of these neurotransmitters (Biederman & Spencer, 1999; Durston, 2003). This treatment is consistent with genetic research because these medications enhance dopaminergic signaling and dopamine genes have been shown to be associated with ADHD (Biederman & Spencer, 1999; Faraone et al., 2000). Although the reason for the efficacy of these medications is unknown, it has been suggested that

dopaminergic and noradrenergic pathways may promote inhibition by frontal regions of subcortical structures, thereby reducing symptoms of ADHD such as hyperactivity and/or impulsivity (Biederman & Spencer, 1999; Quay, 1997).

Research has indicated that these stimulant medications are efficacious, with approximately 70% of children experiencing beneficial effects. In addition, studies have indicated that, on average, 50% of adults with ADHD respond positively to these medications and this increases to over 70% when the doses are equivalent to those given to children (for a review refer to Faraone et al., 2000).

Despite these benefits, the disadvantages associated with stimulant medications include potential abuse or their redirection to illegal markets for recreational drug use (Banaschewski et al., 2006; Kollins, 2007), although it appears that this only occurs in a small percentage of those without pre-existing substance abuse or Conduct Disorder (for a review refer to Banaschewski et al., 2006). In fact, longitudinal studies have indicated that the use of stimulants for the treatment of ADHD may reduce the risk for future substance abuse (Kollins, 2007; Wilens, Faraone, Biederman, & Gunawardene, 2003). The mechanism for this effect remains unclear. However, the reduction of ADHD symptoms may be related to the reduction of substance abuse later in life (Wilens et al., 2003). As with other pharmacological treatments, there is also a range of side effects including insomnia, appetite loss, headache, growth retardation and abdominal pain associated with stimulant medications (Banaschewski et al., 2006; Lopez, 2006; Wolraich, McGuinn, & Doffing, 2007).

Long-acting stimulants and non-stimulants provide an alternative treatment for individuals who experience the side-effects of stimulant medications (Banaschewski et al., 2006; Banaschewski, Roessner, Dittmann, Santosh, & Rothenberger, 2004). Long acting stimulants have been shown to be effective and have the advantage of a single daily dose and, therefore, do not need to be taken at school or work. However, they are also more expensive (Banaschewski et al., 2006). Non-stimulant medications, such as atomoxetine and antidepressants, provide an alternative for children who either do not tolerate or respond to stimulants (Lopez, 2006). In addition, they are not susceptible to abuse (Banaschewski et al., 2004). However, atomoxetine can also cause decreased appetite, vomiting and dizziness (Wolraich et al., 2007). Therefore, there are side-effects associated with both stimulant and non-stimulant medications.

A review by King and colleagues (2006) found no differences between stimulant (methylphenidate, amphetamines) and non-stimulant medications (atomoxetine) in terms of their efficacy, although they noted that few studies directly compared these treatments. Overall, all three treatments were found to be superior to no pharmacological treatment at all. In addition, the benefits of these pharmacological treatments are thought to outweigh their possible adverse effects (Wolraich et al., 2007). However, it is also important to note that the long-term treatment effects are largely unknown as most studies do not extend beyond two years (Hechtman, 2006).

Alternative approaches, such as dietary treatments, have received a lot of interest as a substitute for pharmacological treatments for ADHD or to supplement more traditional treatments (Sinha & Efron, 2005). Dietary

supplementation with omega 3/6 fatty acids is one such approach. One study found that a subgroup of children and adolescents with ADHD experienced a 25% reduction in symptoms on this diet (Johnson, Ostlund, Fransson, Kadesjo, & Gillberg, 2008). However, results were not significant when considering both responders and non-responders, and other studies have failed to find significant effects of omega fatty acids (for a review refer to Cormier & Elder, 2007). Additive-free and sugar elimination diets have also received attention as potential treatments for ADHD. Despite some evidence for a reduction in hyperactivity in children due to an additive-free diet, a quantitative review failed to find a relationship between sugar and hyperactivity (Cormier & Elder, 2007). Gluten-free and casein free diets have also been trialed in a few studies although the results have been inconsistent (Cormier & Elder, 2007). Dietary interventions remain popular among parents and carers of children with ADHD, although evidence for their efficacy is limited (Cormier & Elder, 2007; Sinha & Efron, 2005). Further research is necessary to evaluate these diets due to small sample sizes, the presence of comorbidities, and inconsistent use of conventional criteria for diagnosing ADHD in the current literature.

There is also limited evidence for psychosocial treatments, such as behavior management training, social skills training, academic skills training, family counseling, parent education and training and school behavioral management programs. These treatments show promising effects when used in conjunction with medication, although there does not appear to be a significant benefit in medication combined with psychosocial treatments when compared to medication alone (Hechtman, 2006). However, a meta-analysis of combined psychosocial and pharmacological treatment of ADHD found

large improvements in the core features of ADHD (inattention, hyperactivity, impulsivity) and social skills using combined treatment (Majewicz-Hefley & Carlson, 2007). A small improvement was also noted in academic achievement. However, the extent to which the outcomes of combined treatments differ from those for treatment with medication alone remains unclear.

Thus, treatments are available that have been shown to be efficacious, including stimulant and non-stimulant medications, despite gaps in our understanding of the mechanisms underlying their efficacy. Alternative treatments such as supplementation with omega-3 fatty acids and psychosocial treatment programs have more limited evidence in terms of the improvement of ADHD symptoms.

1.2.6 Causal models of ADHD.

A substantial body of research has searched for the origins of ADHD and several causal models have been proposed. This section will review some of the most prominent models, which consider psychological, biological and anatomical factors. One of the most extensively studied theories of ADHD is that of Barkley (1997), who has proposed that behavioral inhibition is the central deficit. Behavioral inhibition involves suppressing an immediate response to an event, thereby creating a delay before responding to the event. This, in turn, allows executive functioning to take place and the potential for a more suitable response to be chosen and implemented (Barkley, 1997; Sonuga-Barke, 2005; Wodushek & Neumann, 2003). These executive functions are thought to be supported by a circuit between the basal ganglia and the prefrontal cortex. Dopamine, which has been implicated in ADHD

(see section 1.2.5), is one of the key neuromodulators of this circuit (Sonuga-Barke, 2005).

A large number of studies have focused on executive functioning in ADHD, and response inhibition in particular, as a result of Barkley's theory of executive dysfunction in ADHD (Barkley, 1997). A comprehensive review of individual studies is beyond the scope of this thesis, therefore, only quantitative reviews will be considered here. A meta-analysis by Willcutt and colleagues (2005) found evidence of moderate differences for measures of response inhibition and other aspects of executive functioning in children and adolescents with ADHD such that this group demonstrated poorer performance on these measures than their peers. Thirteen measures of executive function were included in the meta-analysis and significant group differences were found on all of them, including measures of response inhibition, vigilance, set-shifting, planning, verbal working memory, and spatial working memory. Overall, moderate deficits in executive functioning were evident. However, the results for individual studies were inconsistent. Moreoever, it is important to note that a moderate effect size equates to around 50% overlap between children with ADHD and controls in terms of their performance on executive tasks (Nigg, 2005). In general, less than half of children with ADHD demonstrate impairment on any one measure of executive functioning, based on the effect sizes seen in meta-analyses (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Therefore, not all children demonstrate impaired executive functions and these deficits cannot fully account for ADHD.

Executive functioning has also been examined in *adults* with ADHD (Boonstra et al., 2005). A meta-analysis found moderate deficits in response inhibition (Continuous Performance Test), verbal fluency (the Controlled Oral Word Association Test), and set-shifting (Trail Making Test, part B). In addition, a large impairment was found for attention and inhibition, as measured by the interference score on the Stroop task, although this was no longer significant when controlling for color naming. Interestingly, similar effect sizes were found for non-executive components of these tasks, such as errors of commission on the Continuous Performance Task, Trail Making Test (part A), and Stroop color naming and word reading tests. In fact, the average effect size for non-executive tasks was 0.43, while the effect size for executive function tests was 0.40. Therefore, these results do not support a specific deficit in executive functioning in ADHD (Boonstra et al., 2005).

Further evidence against a domain-specific impairment in ADHD comes from a meta-analysis by Hervey and colleagues (2004), which evaluated cognitive test performance in adults with ADHD. This analysis included 33 studies and found that adults with ADHD exhibited impaired performance on tests in a number of domains, including attention, response inhibition, executive function, and memory. Similarly, Schoechlin and Engel (2005) conducted a meta-analysis of cognitive test performance in adult ADHD based on 22 studies. Moderate deficits were evident in the domains of verbal memory, focused attention, sustained attention, and abstract problem solving requiring working memory. In addition, a small impairment was found for executive function tasks. These meta-anlayses are difficult to compare given the subjective nature of categorizing tests according to broad

cognitive categories or constructs. However, both demonstrate the presence of a range of cognitive deficits in adults with ADHD.

Frazier et al. (2004) conducted a meta-analytic review in which they compared the magnitude of specific impairments with general ability in children and adolescents with ADHD and controls. Only a few tests of executive functioning showed significantly larger deficits than those for full scale IQ tests. However, the authors did acknowledge that deficits in executive functioning may impact on overall ability scores, such as IQ. Therefore, this study does not eliminate the possibility that executive impairments are central to ADHD. Nevertheless, the results indicated that not all executive abilities are affected equally in ADHD and that other impairments may be associated with ADHD.

In summary, ADHD is associated with poorer performance on a range of different cognitive domains and deficits in executive functioning (including response inhibition) cannot alone account for ADHD because they are not evident in everyone with ADHD (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005; Nigg, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005).

An alternative model of ADHD suggests that motivation and reward mechanisms are disrupted, such that people with ADHD have difficulty waiting for future rewards and will often choose immediate rewards over larger delayed rewards in the future (Sonuga-Barke, 2002, 2005). Interestingly, this difficulty in waiting for rewards is thought to be related to disruptions in another dopamine modulated neural circuit between the frontal cortex and basal ganglia. However, this theory also fails to account for all of the symptoms of ADHD such as inattentiveness, hyperactivity and problems

with the self-regulation of behavior. Therefore, these authors have suggested that a multiple pathway model of ADHD may be necessary to explain ADHD more fully (Sonuga-Barke, 2005). That is, there may be several neurodevelopmental pathways that result in the presentation of ADHD symptoms.

The cognitive-energetic model is another motivational theory of ADHD that integrates the executive dysfunction and delay-aversion observed in children with ADHD (Sergeant, 2000). This model incorporates three areas of cognition that are affected by ADHD: top-down processing (executive functioning), energetic factors (effort, arousal, and activation), and attentional mechanisms (encoding, search, decision, and motor organization). The executive functioning component of the model consists of a top-down management system that involves planning and monitoring behavior and task performance. The energetic factors reflect the energy required to meet task demands (effort), timely task responses (arousal), and changes in physiological activity (activiation). Finally, the attentional mechanisms include four stages of information processing that involve lower level computational processes. Together, these cognitive abilities, state factors, and/or computational processes are thought to affect information processing in ADHD. Although there is some evidence for a relationship between the three areas incorporated in this model, direct measures of the energetic factors are lacking (Sergeant, 2005). Further research is necessary to determine whether the cognitive-energetic model is related to the motivation model (Sonuga-Barke, 2005) and whether it accounts for a particular subtype of ADHD or represents a more general model of ADHD (Pennington, 2005).

Other theories have focused more exclusively on neuroanatomy to explain ADHD. For example, a review by Stefanatos and Wasserstein (2001) posits that many of the diverse findings in ADHD share an involvement of the right hemisphere of the brain. This is consistent with a recent study, which used a visual extinction task in adults with ADHD (Geeraerts, Lafosse, Vaes, Vandenbussche, & Verfaillie, 2008). When a patient with visual extinction is presented with two items, one on the left and one on the right, they will report only the object on the left due to damage to the right hemisphere of the brain. Therefore, this task allowed the authors to examine possible asymmetry of attentional functioning in ADHD. Geeraerts et al. (2008) found that the presence of distractors disrupted attention networks in the right hemisphere but not in the left hemisphere in adults with ADHD. In contrast, Shaw et al. (2007) propose that ADHD is not characterized by specific neuroanatomical differences but instead reflects a delay in brain development. Specifically, this study examined cortical development in ADHD and found that the cortical maturation of children with ADHD lagged behind that of healthy controls. Therefore, these authors suggest that ADHD may be characterized by a delay in neurodevelopment. However, this theory fails to account for those whose symptoms persist into adulthood.

Other researchers have sought more specific neuroanatomical differences in ADHD, although critical processes or structures have not been consistently identified (Stefanatos & Wasserstein, 2001). Neuroimaging studies with children have predominantly used structural imaging techniques, whilst research with adults has largely used functional imaging, making direct

comparisons difficult (Faraone et al., 2000). However, in combination, this research has advanced knowledge about the neurobiology of this disorder.

A meta-analysis of 21 studies of structural imaging findings in ADHD was recently conducted (Valera et al., 2006). This study examined a broad range of brain regions, including the cerebellum, corpus callosum, prefrontal and frontal regions, caudate, globus pallidus, putamen, hippocampus, and amygdala. However, only the cerebellum, splenium, total and right cerebral volume, caudate, prefrontal and frontal regions, and deep frontal white matter were assessed in at least two studies and yielded significant differences between the ADHD and control groups. The area or volume of these regions was smaller in ADHD participants than in controls.

It is important to note that this meta-analysis only included research with children and cannot, therefore, be generalized to adults with ADHD. One study of adults met the inclusion criteria for the meta-analysis but was excluded because it had a small sample and may have confounded the results from studies with children (Hesslinger et al., 2002). However, this study found a smaller orbitofrontal cortex in adults with ADHD. Another structural imaging study of adults with ADHD found smaller total cortical gray matter, smaller anterior cingulate cortex and, consistent with research with children with ADHD, smaller prefrontal volumes in adults with ADHD (Seidman et al., 2006).

Further evidence for neuroanatomical differences in ADHD comes from functional neuroimaging studies. A meta-analysis, which examined the results of functional neuroimaging studies of executive function in children and adults with ADHD, consistently found frontal hypoactivity in people with

ADHD (Dickstein, Bannon, Xavier Castellanos, & Milham, 2006). However, the authors emphasize that one cannot conclude that frontal dysfunction alone underlies ADHD because their study only focused on executive processes. A qualitative review of functional neuroimaging in ADHD concluded that tasks requiring executive or higher level cognition are associated with greater activity in motor, visual and spatial areas in ADHD (Fassbender & Schweitzer, 2006). This may be due to difficulties engaging these executive systems in ADHD, as healthy controls are more likely to engage the prefrontal cortex and the anterior cingulate cortex during cognitive tasks (Fassbender & Schweitzer, 2006).

Electroencephalography (EEG) studies have provided another approach for examining neuroanatomical differences in ADHD. EEG studies examine the brain's electrical activity, usually through electrodes placed on the scalp. A meta-analysis by Snyder and Hall (2006) synthesized EEG studies of ADHD and found an increase in the ratio of theta/beta frequencies in people with ADHD compared to controls. This indicates increased slow wave activity in people with ADHD and provides evidence for developmental differences in central nervous system functioning in ADHD (Clarke, Barry, McCarthy, & Selikowitz, 2001).

Overall, cognitive, structural, functional and EEG studies indicate that there are differences in neuroanatomical structure and function associated with ADHD. However, the cause of ADHD remains unknown.

The genetic contribution to ADHD has been examined in family and twin studies (Barkley et al., 2002; Faraone et al., 2005). Given the efficacy of stimulants and the involvement of the dopaminergic system (see section

1.2.5), dopamine transporter and receptor genes have been candidates for ADHD research and have therefore been studied extensively (for a review refer to Li et al., 2006). For example, various dopamine and serotonin receptor and transporter genes have been shown to be significantly related to ADHD (for a review refer to Faraone et al., 2005; Li, Sham, Owen, & He, 2006). However, these genetic studies have yielded inconsistent results. This is probably due to a complex interaction of numerous genes, which individually produce only a small effect.

Despite various models of ADHD based on extensive research, the etiology of this disorder remains poorly understood. This may be, in part, due to conflicting research findings. The current thesis aims to resolve some of these differences in one area of ADHD research, namely, the morphology of the CC.

1.2.7 Methodological issues.

Several methodological factors, which complicate the interpretation of research on ADHD, may contribute to the inconsistencies in the results of studies examining cognition, neuroanatomy, and genetics in ADHD. For example, a recent meta-analysis found considerable variation between the studies that were included in the analysis in terms of the comorbid conditions that were present in the samples (Hervey et al., 2004). This is problematic because the presence of comorbid learning disabilities or Conduct Disorder in ADHD samples may affect the study findings. In some cases, samples with these comorbid conditions are deliberately included because high rates of comorbidity are present in ADHD in the community, increasing the generalizability of the results. In other studies, these comorbid conditions are

excluded in order to examine processes or symptoms that are specific to ADHD. Finally, in some studies comorbidities are not reported and/or are overlooked. Overall, the different exclusion criteria used by researchers in an attempt to control for comorbidity lead to heterogeneous samples across studies.

The meta-analysis by Hervey and colleagues (2004) also found variation in the extent to which studies employed closely matched control groups and controlled for important variables, such as education or intelligence. However, it has been argued that the underlying causal factors for deficits in intelligence in ADHD and difficulties in other areas of cognition in ADHD may be the same. Therefore, statistically controlling for differences in intelligence, or employing control groups matched on intelligence, may nullify the potential differences on cognitive variables that are of primary interest in ADHD (Hervey et al., 2004).

Additional variation arises from differences in the particular subtypes of ADHD (combined type, predominantly inattentive type, and predominantly hyperactive/impulsive type) that are included in studies and the extent to which studies report the ADHD subtypes represented in their samples (Hervey et al., 2004; Roth & Saykin, 2004; Stefanatos & Wasserstein, 2001). This can be problematic as their may be important differences between the predominantly inattentive, predominantly hyperactive/impulsive, and the combined subtypes. For example, several researchers have found different cognitive profiles for the different subtypes of ADHD in both children and adults (Armstrong, Hayes, & Martin, 2001; Dinn, Robbins, & Harris, 2001; Houghton et al., 1999). Thus, it is not clear whether some previous research

findings generalize to all people with ADHD, regardless of the subtype, or whether they relate more specifically to a particular subtype of ADHD.

A further constraint in ADHD research is that the samples are often limited in size, particularly in brain imaging studies (Roth & Saykin, 2004). For example, one study of anterior cingulate activity in adults with ADHD only included eight adults in both the ADHD and control groups (Bush et al., 1999). As statistical significance is affected by sample size, non-significant results may reflect a lack of power rather than the absence of a meaningful effect (Penberthy et al., 2005).

The developmental nature of ADHD also complicates ADHD research. ADHD has an onset in childhood when the brain is still developing (Yazgan & Kinsbourne, 2003). Therefore, disruption to one neurodevelopmental stage may impact on later stages (Rapoport et al., 2001). For example, it is possible that, in the presence of cognitive limitations such as attention deficits, the brain may develop compensatory mechanisms. Alternatively, the differences observed in children with ADHD may resolve with further development (Shaw et al., 2007). Therefore, research involving children or adults with ADHD must consider the effect that the disorder may have had on development and any consequences that may persist into adulthood.

Despite the importance of development in ADHD, the majority of research has been conducted with children diagnosed with ADHD and has predominantly focused on boys due to the increased prevalence of ADHD in this group. Although there is some evidence that the symptoms, neuropsychological deficits, pathophysiology, and response to treatment in

adults are similar to those in children (Stefanatos & Wasserstein, 2001) more research is necessary with girls and adults with ADHD.

Finally the effect of medication on brain function needs to be considered. The long term effects of ADHD medications on the brain and therefore, cognition and behavior, are largely unknown (Overmeyer et al., 2001). In order to control for potential short term effects, many studies require participants to cease taking stimulant medications for at least 24 hours prior to participating in research. However, this period is not long enough to entirely eliminate the drug or its effects from the individual's system. In addition, task performance during this period of drug withdrawal may not reflect the performance of drug naïve individuals due to adaptive changes over time due to drug exposure (Goodman Gilman, Goodman, & Gilman, 1980).

1.3 ADHD and the Corpus Callosum

As discussed in section 1.2.6, several regions of the brain have been shown to be atypical in ADHD. One of these brain regions is the CC, which has been extensively studied in ADHD because of its involvement in attentional processes. However, there are inconsistencies in the literature regarding the morphology of the CC in children and adolescents with ADHD (Semrud-Clikeman et al., 1994).

Magnetic Resonance Imaging (MRI) has been used to examine the CC in ADHD. An early study found that the genu, the isthmus, and the splenium were smaller in children with ADHD than healthy children (Hynd et al., 1991). The latter finding has been replicated in subsequent studies. Hill and colleagues (2003) found that the total area of the CC and splenium were smaller in children with ADHD than controls in a sample of children with

ADHD that did not include children with learning disabilities or comorbid disorders, except oppositional defiant disorder. Lyoo and colleagues (1996) also found a smaller splenium in children with ADHD. It should be noted that the children in this study were undergoing inpatient psychiatric evaluations due to behavioral disturbances and many had ADHD with Conduct Disorder. Therefore, these children are not representative of children with ADHD without extreme behavioral disturbances (Lyoo et al., 1996).

Semrud-Clikeman and colleagues (1994) also found a smaller splenium in boys with ADHD. However, the ADHD group only had a significantly smaller splenium than controls when ADHD participants who did not respond to stimulant medications were included in the analysis (Giedd, Blumenthal, Molloy, & Castellanos, 2001). Interestingly, this study also revealed that five out of seven regions of the CC were smaller in children with ADHD who failed to respond to stimulant medications (Semrud-Clikeman et al., 1994), although the samples were very small (5 non-responders to stimulant medications and 10 responders). The finding of a smaller splenium is of particular interest to ADHD research because it has been suggested that sustained attention may be affected by abnormalities in the posterior regions of the CC (Hofer & Frahm, 2006; Semrud-Clikeman et al., 1994).

Smaller anterior regions of the CC have also been found in children with ADHD (Giedd et al., 2001). Specifically, a smaller genu (Hynd et al., 1991) and rostral body (Baumgardner et al., 1996; Giedd et al., 1994) have been reported in children with ADHD. The genu is thought to connect prefrontal regions and the rostral body is thought to contain connecting fibers from the prefrontal cortices, anterior cingulate, premotor and supplementary

motor cortices (Giedd et al., 1995; Steere & Arnstein, 1995). The prefrontal cortex is involved in executive function and the regulation of attention (Funahashi, 2001). Therefore, differences in the genu and rostral body may help explain the difficulties in attention and executive function that are experienced by children with ADHD.

In contrast, a study by Castellanos and colleagues (1996) failed to find significant differences in the total area of the CC, or any of its regions, in a group of 57 boys with ADHD and 55 matched controls. However, Giedd et al. (2001) noted that this study did not control for brain positioning during brain imaging and an unpublished re-analysis of the data, which aligned brain images to a standard orientation, confirmed a smaller rostrum in boys with ADHD (Castellanos et al., 1999, unpublished data, as cited by Giedd et al., 2001). Therefore, this research also suggests that there are abnormalities in the anterior portion of the CC in ADHD.

The CC has also been examined in children with ADHD and their unaffected siblings in order to test the hypothesis that differences in CC morphology are directly responsible for the expression of the disorder (Overmeyer et al., 2000). That is, if there are differences between the CC in children with ADHD and their siblings, these abnormalities may help explain the presence of ADHD. Alternatively, if the CC does not differ between children with ADHD and their siblings, it is likely that ADHD is mediated by alternative mechanisms. This study found no significant differences in the structure or size of the CC between these two groups. Therefore, the authors concluded that differences in the CC do not determine the presence or absence of ADHD. It should be noted that this study did not include a control group of

healthy children without a family history of ADHD. Therefore, it is not known whether the children with ADHD in these studies had smaller CCs than healthy controls without a family history of ADHD.

In summary, both the anterior and posterior regions of the CC have been found by one or more studies to be smaller in children with ADHD compared to controls. However, there is considerable variation in the literature as some studies have found anterior differences (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991), some have found posterior differences (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994), some found an overall difference (Hill et al., 2003; Hynd et al., 1991), and some have not found any differences (Castellanos et al., 1996; Overmeyer et al., 2000). There are a number of factors that may contribute to these disparate findings, including differences in the age of participants, in the method used to partition the CC, the presence of comorbidities, such as learning disorders and Conduct Disorder, and the use of medications to treat ADHD. Moreover, all of these studies have been undertaken with children with ADHD, so it remains to be seen whether differences in CC size persist into adulthood. If there are differences in the size of the CC in children with ADHD, they could be due to a maturational deficit that resolves with age and further development or differences in the size of the CC may reflect a morphological difference that persists into adulthood. Furthermore, the functional consequences of atypical CC morphology in ADHD are unknown. Research with split-brain patients has indicated that damage to the CC has an impact upon sustained, focused and

divided attention. Therefore, one might expect differences in the CC in ADHD to impact upon attention.

1.4 The Corpus Callosum and Cognitive Performance

Although the CC has been linked to attention, the majority of anatomical studies have not discussed their results in relation to general cognitive functioning (Yazgan & Kinsbourne, 2003). Evidence from split-brain patients has demonstrated that the time taken to transfer information between the hemispheres is related to the integrity of the CC (Hoptman & Davidson, 1994). In addition, the size of CC fibers is correlated with the degree of myelination, which is associated with faster neuronal transmission (Aboitiz, Ide, & Olivares, 2003; Aboitiz et al., 1992). Therefore, one might expect the size and number of CC fibers, and hence CC area, to be related to the speed of interhemispheric transfer. However, Banich and Shenker (1994) outline some important cautions about the interpretation of anatomical studies in terms of interhemispheric interaction. Firstly, the implications of abnormalities in the size of the CC are unknown. Although one might assume that a larger CC consists of more nerve fibers, which may be advantageous in terms of interhemispheric interaction, it is also possible that a larger CC has the same number of fibers but that they are more myelinated (Banich & Shenker, 1994).

Second, the relationship between CC size and interhemispheric interaction could go in either direction. For example, the callosal atrophy that is present in Multiple Sclerosis due to the loss of myelin is associated with problems with interhemispheric communication (Banich, 2003). In contrast, there is some evidence that some people with schizophrenia have a larger CC

and impaired interhemispheric interactions relative to healthy controls (Bigelow, Nasrallah & Rauscher, 1983). It is not clear whether the increased size of the CC in this group reflects increased myelination of CC fibers or an increased number of fibers. However, these authors speculate that the larger CC could be due to a viral infection or pathological process, or due to disordered neural organization. Hence, a smaller CC or a larger CC could be associated with impaired interhemispheric interaction (Banich & Shenker, 1994).

Studies on the relationship between the CC and cognitive performance will be reviewed with these cautions about the interpretation of such studies in mind. The effect of compromise to the CC has been examined in research with split brain patients, who have had the CC severed for the treatment of epilepsy, and in people who have agenesis of the CC in which it does not develop fully or is completely absent. As discussed earlier, this research has indicated that the CC is crucial to the interhemispheric transfer of information, which is beneficial to task performance for complex tasks in healthy individuals (for a review refer to Banich, 1995, 1998, 2003; Banich & Brown, 2000). IQ tests involve complex tasks suggesting that optimal performance on these tasks should involve interhemispheric interaction via the CC. Therefore, the relationship between CC morphology and IQ is of interest.

In addition to split-brain patients, studies with clinical populations in which the CC is affected also provide information about the relationship between IQ and CC morphology. A study of two patients with tumors located at the splenium suggests that this part of the CC is related to the performance aspects of IQ because these patients had impaired performance IQ but

relatively intact verbal IQ (Osawa, Maeshima, Kubo, & Itakura, 2006). The splenium connects the parietal, temporal and occipital cortices (Hofer & Frahm, 2006), which are involved in a range of functions including visuospatial processing and memory. Therefore, one might expect the integrity of the splenium to be related to performance IQ in healthy adults. In another study, IQ was examined in two adult males who were diagnosed with lacunar infarction (stroke) and white matter abnormalities (Yamauchi, Fukuyama, Ogawa, Ouchi, & Kimura, 1994). In these case studies, the area of the whole CC was smaller in patients than in controls and was positively correlated with both performance and verbal IQ. The authors concluded that intellectual decline is associated with the atrophy of the CC in this patient group.

The relationship between CC morphology and IQ has also been examined in adolescents with mental retardation and, by definition, low IQ. This research found that adolescents with mental retardation were more likely to have a thinner CC (Spencer et al., 2005) and reduced white matter density in the posterior CC (Spencer et al., 2006). The relationship between IQ and CC morphology observed in these clinical populations indicates that lower IQ may be associated with reduced CC size or density, or atrophy of the CC. However, these results may not generalize to healthy populations.

These studies indicate that there is a relationship between IQ and CC morphology in various clinical groups. Several studies have also examined CC size and IQ in healthy populations with varying results. Nosarti et al. (2004) did not find a significant relationship between IQ and CC area in healthy controls. Similarly, Tramo et al. (1998) did not find a relationship

between CC size and IQ in a group of healthy twins. In contrast, one might expect IQ and CC morphology to be related on the basis of the findings of a twin study by Hulshoff Pol et al. (2006), which examined the genetic and environmental influences on brain regions. The CC was found to be highly heritable and the white matter density of the CC shared a genetic origin with IQ, such that greater density was associated with increased IQ.

Consistent with this hypothesis, Allin et al. (2007) also found evidence for a relationship between the CC and IQ in healthy persons assessed during adolescence and adulthood. Negative correlations were observed between full scale IQ and posterior regions of the CC (posterior midbody and posterior region of the CC in adolescents and the posterior region in adults), such that higher IQ was associated with smaller CC size in these regions. Verbal IQ was also negatively correlated with the size of the posterior midbody in adolescents, and with the most anterior and posterior regions of the CC in adults.

In contrast, a positive correlation has been observed between CC size and IQ in healthy adults (Luders et al., 2007). This group found significant positive correlations between IQ and CC thickness (measured by the distance between the superior- and inferior-most points of the CC in the midsagittal section) across the posterior portion of the CC (posterior body, isthmus, anterior portion of the splenium) and in a portion of the anterior midbody. Interestingly, these relationships were less pronounced when only females were considered, suggesting that there may be gender differences in the relationship between CC morphology and IQ.

Peterson et al. (2001) found that a study-specific measure of the CC, which represented a thinner and more arched anterior portion of the CC, was also associated with higher IQ. However, more conventional measures of CC size (e.g. CC area), were not significantly related to IQ. In addition, two studies, that used voxel based morphometry, a neuroimaging technique that can be used to examine gray and white matter volumes, failed to find a significant relationship between IQ and white matter in the CC (Haier, Jung, Yeo, Head, & Alkire, 2004, 2005). Therefore, the particular measures of the CC that are employed appear to significantly impact on the research findings.

To summarize, existing research on the relationship between CC morphology and IQ in healthy individuals has yielded inconsistent findings. One might expect increased CC size to be associated with higher IQ because an increased number of fibers, or more myelinated fibers, as represented by larger CC size, might allow faster interhemispheric transfer of information in these areas and an increased ability to recruit the other hemisphere to assist task performance. Alternatively, the relationship could be in the opposite direction. That is, higher IQ may be associated with decreased reliance on interhemispheric transfer for task performance because individuals with high IQ may experience less attentional demand due to large cognitive resources. Interhemispheric interaction is beneficial under attentionally demanding conditions (for a review refer to Banich, 1998). Therefore, interhemispheric interaction would be less beneficial in individuals with high IQ compared with those with low IQ. Over time, this may result in a smaller CC due to less use and development of the CC. Therefore, higher IQ would be associated with a smaller CC.

As outlined in section 1.2.8, people with ADHD have been found to perform more poorly on IQ tests than healthy controls (Bridgett & Walker, 2006). In addition, research with children with ADHD has found differences in CC size in this population (Baumgardner et al., 1996; Giedd et al., 1994; Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). However, it is not known whether there is a relationship between differences in CC morphology and IQ scores in ADHD or in the healthy population.

1.5 General Summary

The CC has been shown to play an important role in attention, both in split-brain patients and in individuals in which the CC is intact (Banich, 1995, 1998, 2003; Banich & Brown, 2000; Dimond, 1976; Ellenberg & Sperry, 1979; Holtzman & Gazzaniga, 1982; Kreuter et al., 1972; Teng & Sperry, 1973). Therefore, it is a brain region of interest in ADHD, in which attention, among other cognitive domains, is affected.

The size of the CC has been well studied in children and adolescents with ADHD. Some studies have found anterior differences in the size of the CC, while others have found differences in posterior regions. Despite these inconsistencies, all of these studies have found regions of the CC that are smaller in children with ADHD when compared with healthy controls (Baumgardner et al., 1996; Giedd et al., 1994; Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). However, CC size has not been examined in adults with ADHD.

The implications of differences in the size of CC regions remain unclear. However, the area of the CC may reflect the number of CC fibers, or

their size, and/or their degree of myelination, which is associated with faster neuronal transmission (Aboitiz et al., 2003; Aboitiz et al., 1992). In addition, interhemispheric interaction is beneficial under complex task conditions (for a review refer to Banich, 1998). Therefore, one might expect a relationship between measures of CC morphology and cognitive measures such as IQ. Studies examining these relationships have yielded inconsistent results (Allin et al., 2007; Luders et al., 2007; Peterson et al., 2001).

1.5.1 Gaps in the Current Literature.

Although CC size has been researched in children and adolescents with ADHD there have been inconsistencies in the results. This may be due to differences in the inclusion and exclusion of comorbid conditions, different methods for dividing the CC into regions, or the age of participants. Therefore, there is little agreement about the size of the CC in ADHD. This thesis will address this issue by statistically summarizing the current research findings in children and adolescents with ADHD in a meta-analysis.

Despite a number of studies examining CC size in children with ADHD, CC size has not been researched in adults with ADHD. Therefore, it is not known whether any differences observed in CC size in children with ADHD resolve with further development or persist into adulthood. The current thesis will examine both CC size and integrity in young adults with ADHD.

Finally, few studies have examined the relationship between performance on IQ tests and CC morphology and those that have been conducted have yielded inconsistent results. A meta-analysis is not a practical solution due to the small number of published studies in this area. Therefore,

a study of the relationship between IQ and CC morphology in a group of healthy participants in their late teens and early 20s will be conducted in order to determine if the results of Allin et al. (2007) can be replicated in a sample spanning the two ages assessed in their study. In addition, this research examines the effect of age on CC area and its relationship with IQ.

1.5.2 Aims.

1. To synthesize the research conducted on CC size in children and adolescents with ADHD using meta-analytic procedures in order to (a) reconcile differences in the existing literature, (b) consider differences in CC size in children and adolescents with ADHD and comorbid conditions, and (c) explore gender differences in CC size in ADHD.
2. To examine CC area and integrity in young adults with attention deficit hyperactivity disorder compared with healthy controls in order to (a) determine if the differences in CC size that have previously been reported in children and adolescents with ADHD persist into young adulthood, (b) determine whether there are other regional differences in CC size at this later stage of development, (c) determine whether there are differences in CC integrity, as measured by fractional anisotropy, associated with ADHD, and (d) examine the relationship between CC measures (size and integrity) and performance on the Stroop task, which requires attentional control, and ADHD symptoms in order to explore the possible functional consequences of atypical CC morphology.
3. To examine the relationship between aspects of cognition, as indexed by IQ subtests and CC area and integrity in order to (a) determine

whether there is a relationship between IQ and CC area in healthy young adults, (b) determine whether there is a relationship between IQ and CC integrity in healthy young adults, and (c) examine the influence of age on the relationship between IQ and CC morphology. These three aims will be addressed by the studies outlined in chapters 2, 3 and 4, respectively.

Chapter 2

Corpus Callosum Morphology in Children and Adolescents with Attention Deficit Hyperactivity Disorder: a Meta-analytic Review

The aim of the first study was to provide a quantitative synthesis of the research that has examined CC size in children and adolescents with ADHD using meta-analytic procedures. The published research findings have produced inconsistent results regarding the specific differences in the CC in children and adolescents with ADHD. In addition, these studies have used different techniques to divide the CC into separate regions, making it difficult to qualitatively compare the results of these studies. Therefore, a meta-analysis was conducted to contribute to the literature by providing a quantitative and objective method, by which to integrate existing findings.

When the current study was nearing completion another meta-analysis was published that examined structural differences throughout the brain (Valera et al., 2006). While the study by Valera and colleagues included the CC in its analysis, it only considered two of the methods (Witelson's method, radial method, see Fig 2, p.26) that are used to divide the CC into regions rather than the three different techniques (Witelson's method, radial method, and curved line method, see Fig 2, p. 26) that have been employed in research on the CC in children and adolescents with ADHD. In addition to considering the results of studies that used on of the three techniques to divide the CC, the current meta-analysis extended the work of Valera and colleagues (2006) by considering factors that may impact on the results (e.g. comorbidities, gender).

This study was considered an important first step in understanding the existing research on the CC in children before making predictions about CC morphology in adults with ADHD. The published version of the following paper and the associated supplementary materials can be found in Appendix A and Appendix B, respectively.

Title: Corpus callosum morphology in children and adolescents with Attention Deficit Hyperactivity Disorder: a meta-analytic review

Authors: AD Hutchinson, JL Mathias, MT Banich

Abstract

Several studies have examined corpus callosum (CC) morphology in children and adolescents with attention deficit hyperactivity disorder (ADHD). A meta-analysis of atypical brain morphology in children and adolescents with ADHD by Valera, Faraone, Murray, and Seidman (2006) reported a reduction in the splenium of the CC in this group compared with healthy controls. This meta-analysis undertook a more detailed examination of callosal morphology by also considering comorbid conditions and gender differences. The data from 13 studies were analyzed. Consistent with Valera et al. (2006), the splenium was smaller in children and adolescents with ADHD than in healthy controls. However, this result appears to be the result of a smaller splenium in females with ADHD. In addition, boys exhibited a smaller rostral body. There were no significant differences in CC measurements of studies that included ADHD samples with comorbid conditions. However, comorbidities were not consistently reported, making it difficult to accurately evaluate the impact of comorbidity on CC size. Additional research is needed to investigate whether gender differences reflect different ADHD subtypes. In addition, it is not known if these CC differences persist into adulthood.

Keywords: ADHD, corpus callosum, meta-analysis, comorbidity, gender differences

Introduction

The corpus callosum (CC) is the largest fiber tract in the human brain, consisting of 200 to 800 million nerve fibers that connect homologous areas of the left and right hemispheres (Banich, 2003; Hoptman & Davidson, 1994; Hynd et al., 1991; Innocenti & Bressoud, 2003). It has a critical role in integrating and communicating high level information between the hemispheres, as has been demonstrated in split-brain patients who, as a result of a severed CC, are unable to detect differences in materials that are presented to opposite hemispheres (Sperry, Gazzaniga, & Bogen, 1969). In addition, it has been shown that the CC also plays an important role in certain aspects of attention. Specifically, research with split-brain patients, has demonstrated that the CC is important for sustaining attention and dividing attention between tasks (Dimond, 1976; Kreuter, Kinsbourne, & Trevarthen, 1972). Moreover, there is a large body of work suggesting that the CC plays an important role in attentional control in neurologically intact individuals (see Banich, 2003 for a review). Briefly, these studies suggest that the CC plays a critical role in distributing the processing load across the hemispheres under conditions of high attentional demand so that those high demands can be met.

As the CC appears to play an important role in attentional control, its integrity in clinical populations that suffer from attentional problems is of particular interest. In the current paper we focus on the morphology of the CC in children and adolescents with attention deficit hyperactivity disorder (ADHD). Comorbidity is also considered because many people with ADHD have also been diagnosed with oppositional defiant disorder, conduct disorder, antisocial personality disorder, mood disorders, anxiety disorders, learning

disorders, communication disorders, Tourette syndrome, and/or substance abuse (American Psychiatric Association [APA], 1994; Castellanos, Giedd, Marsh, & Hamburger, 1996; Faraone et al., 2000; Wender, Wolf, & Wasserstein, 2001). Therefore, the current paper also focuses on the morphology of the CC in children and adolescents with ADHD and comorbid conditions as these conditions may confound the findings. Gender is also examined because there has been some disagreement about the effect of gender on CC size in healthy controls. For example, Sullivan, Rosenbloom, Desmond, and Pfefferbaum (2001) found that males have a larger CC size even after controlling for brain size. A meta-analysis by Bishop and Wahlsten (1997) also found a larger CC in males. Although this difference was accounted for by the larger overall brain size of males, these authors argue that a simple ratio measure of CC size to whole brain size is an inadequate method for accounting for this relationship.

Although the morphology of the CC has been examined in children and adolescents with ADHD, the findings have been inconsistent (Castellanos et al., 1996; Lyoo et al., 1996; Overmeyer et al., 2000). For example, some studies report a smaller anterior CC in children and adolescents with ADHD, as compared with healthy controls (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991), some report a smaller posterior CC (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994), some report that the overall CC size is smaller (Hill et al., 2003; Hynd et al., 1991), and others have not found any differences (Castellanos et al., 1996; Overmeyer et al., 2000). It is possible that methodological differences between these studies, such as the participants' demographics (e.g. age,

gender, sample size), the presence of comorbidities (e.g. learning disorders, conduct disorder), the use of medications, and differences in the segmentation schemes that are used to divide the CC into subregions, may have contributed to these inconsistent findings. Direct comparisons of the findings among these studies are therefore difficult.

A recent meta-analysis reviewed the findings of studies that have examined differences in brain morphology via structural imaging in children and adolescents with ADHD compared to controls (Valera et al., 2006). This review included the CC among the many brain structures that it examined, and reported that only the splenium was significantly smaller in children and adolescents with ADHD, when compared to healthy controls. In this meta-analysis, studies were grouped according to two of the three different methods that are used to parcellate the CC into subregions. The goal of the current study was to extend the analysis of Valera et al. (2006) in a number of ways. Thus, in addition to considering the possible influence of co-morbid disorders and gender, we also separately examined data according to the three methods that have been used to divide the CC into subregions in ADHD samples. The method that is most commonly used to subdivide the CC is that of Witelson (1989), which divides the CC into seven subregions: the rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and the splenium (see Figure 1). A second method divides the CC into five equal regions (Baumgardner et al., 1996) (see Figure 2). Finally, the CC can also be divided into five equal sections using a procedure outlined by O'Kusky et al. (1988) (see Figure 3). These three methods were considered separately when

calculating effect sizes for each region of the CC to ensure that the measurements being synthesized were equivalent.

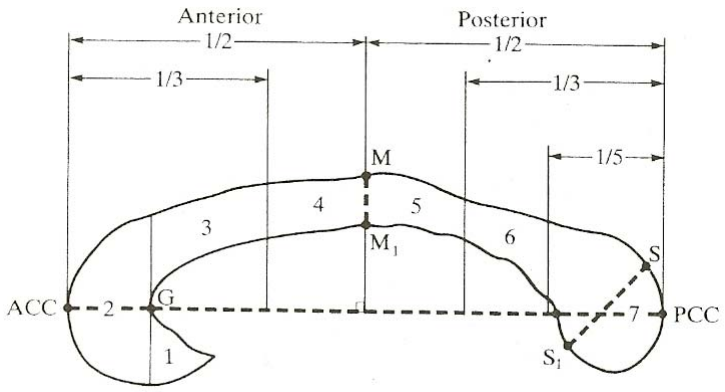

Figure 1. Witelson's divisions of the corpus callosum. From Witelson, S.F., Hand and sex differences in the isthmus and genu of the human corpus callosum: a postmortem morphological study, Brain, 1989, 112 (Pt 3), 799-835, by permission of Oxford University Press. ACC and PCC indicate the most anterior and posterior points of the callosum, M and M_1 are superior and inferior points of the callosum at its midpoint, S and S_1 are superior and inferior points on the posterior bulbous region which is the splenium, chosen such that SS_1 is the length of the maximal perpendicular between two parallel lines drawn as tangents to the superior and inferior surfaces of the splenium, and G is the most anterior point on the inner convexity of the anterior callosum.

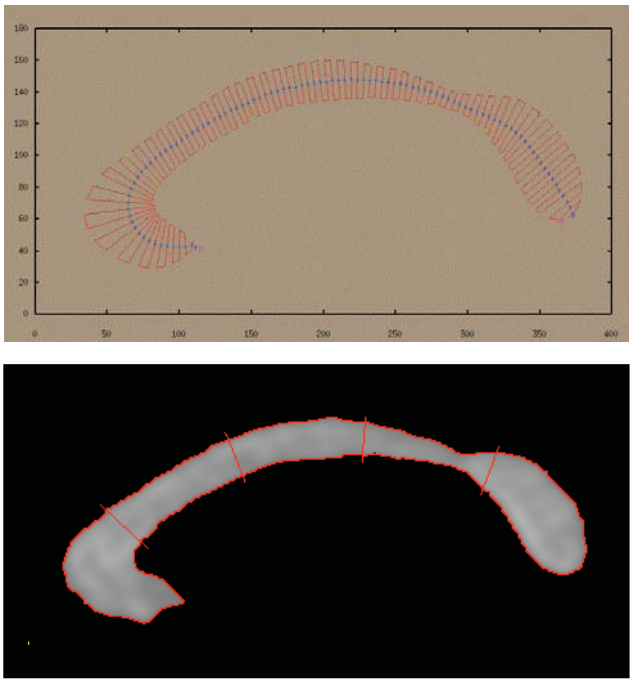

Figure 2. Peterson et al.'s divisions of the corpus callosum (technique used by Antshel et al. [2005], Baumgardner et al. [1996], and Mostofsky et al. [1999]). From Automated measurement of latent morphological features in the human corpus callosum, *Human Brain Mapping,* Vol *12*(4), 2001, 232-245. Reprinted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

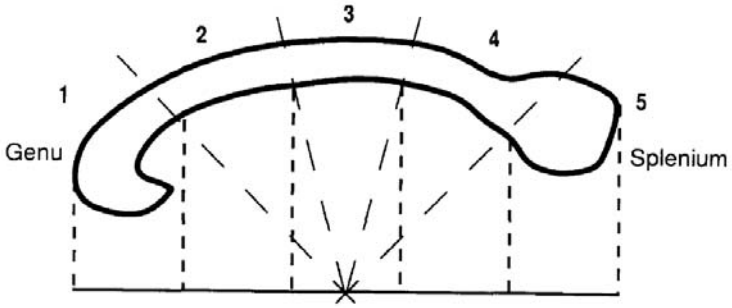

Figure 3. Hynd's division of the corpus callosum. From Hynd, G.W., Semrud-Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., Lyytinen, H. (1991): Corpus callosum morphology in attention deficit-hyperactivity disorder: morphometric analysis of MRI. *J Learn Disabil* 24:141-6. Copyright (1991) by PRO-ED, Inc. Reprinted with permission.

Using Witelson's (1989) divisions of the CC, it has traditionally been thought that the anterior regions of the CC, namely the rostrum and genu, connect the prefrontal cortical areas of the brain. Posterior to these regions, the rostral body connects homologous prefrontal regions, and homologous premotor and supplementary motor regions of the frontal lobes (Giedd et al., 1994; Pandya & Seltzer, 1986). The anterior midbody connects the motor cortices, and the posterior midbody connects somatosensory and posterior parietal areas. The isthmus connects the superior temporal and posterior parietal lobes. Finally, the splenium, the most posterior section of the CC, connects the occipital and inferior temporal lobes (Giedd et al., 1994; Pandya & Seltzer, 1986). However, a recent diffusion tensor imaging (DTI) study, which reexamined the cortical connections of the human CC in healthy adults, suggests that Witelson's divisions may not reflect connectivity as previously assumed (Hofer & Frahm, 2006). They recommend different divisions of the CC into five regions that better reflect the origin of those fibers (see Figure 4). Specifically, they define the most anterior region of the CC as the area that contains fibers that project to prefrontal regions. The second region, which makes up the rest of the anterior half of the callosum, contains fibers projecting to the premotor and supplementary motor regions. The third region contains fibers projecting to the primary motor cortex, while fibers crossing the callosum in the fourth region project to the primary sensory cortex. Finally, the most posterior part of the CC projects to the parietal, temporal, and occipital cortex. This posterior section could not be further differentiated because the fibers projecting to each of these regions overlap.

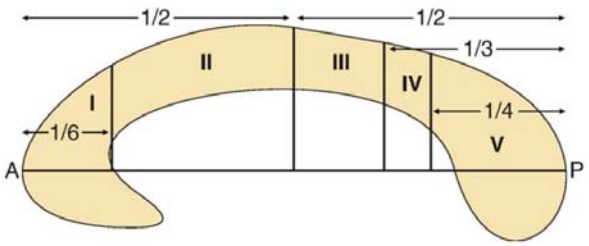

Figure 4. Hofer and Frahm's proposed corpus callosum divisions.

Reprinted from *Neuroimage,* 32, Hofer, S., Frahm, J. Topography of the human corpus callosum revisited--comprehensive fiber tractography using diffusion tensor magnetic resonance imaging, 989-94, Copyright (2006), with permission from Elsevier.

Given the relatively distinct cortical projections of the CC, compromise to the CC would be expected to cause different cognitive problems depending on the location of the compromise. Hofer and Frahm (2006) provide a framework by which to identify which brain regions send projections through different regions of the callosum. If one assumes that the prefrontal and parietal regions are involved in the anterior and posterior attentional systems, respectively (Posner, Inhoff, Friedrich, & Cohen, 1987), then we would expect to see differences in the anterior portion and splenium of the corpus callosum between children and adolescents diagnosed with ADHD and healthy controls. The findings of Valera et al. (2006) are consistent with such a suggestion. We also included studies in our meta-analysis in which the participants with ADHD had comorbid conditions such as Tourette syndrome, velocardiofacial syndrome (a genetic disorder caused by a deletion on chromosome 22q11.2), and neurofibromatosis (an autosomal dominant genetic disorder). In addition to examining group differences, we also examined gender differences. No specific predictions were made about

the impact of comorbidities or gender on CC size due to the lack of research in these areas in ADHD.

Method and Materials

Literature Search & Inclusion Criteria

A comprehensive search of the PubMed and PsycINFO electronic databases between January 1980 and October 2006 was undertaken in order to identify published journal articles that used magnetic resonance imaging (MRI) with children and adolescents who were diagnosed with ADHD. The key search terms included terms for ADHD (attention deficit hyperactivity disorder, ADHD, attention deficit disorder, ADD) and imaging (neuroimaging, magnetic resonance imaging, magnetic resonance image, MRI). Corpus callosum was not included as a search term in order to conduct a broad search and identify a maximum number of potentially relevant articles. The bibliographies of all relevant papers were also examined for additional references. In order to be selected for the current meta-analysis, a study had to meet the following criteria: (1) the inclusion of participants with ADHD together with a control group, (2) imaging was performed and the CC was measured, (3) the provision of statistical data that would enable the calculation of Cohen's *d* effect sizes was provided (Cohen, 1988) (e.g., means and standard deviations, results of *t* tests or one-way *F* tests), and (4) the studies were published in English.

This literature search yielded a total of 1,066 potentially relevant studies, 11 of which met all of the inclusion criteria. Of the studies that did not meet one or more of the inclusion criteria, 1,022 either did not include participants with ADHD and/or did not measure the CC, 22 were not

published in English, 7 were unpublished dissertations, and 4 did not provide specific measurements of the CC that would enable the calculation of effect sizes. In addition, two of the publications that met the inclusion criteria contained data for separate samples (Antshel, Conchelos, Lanzetta, Fremont, & Kates, 2005; Baumgardner et al., 1996). In each case, data were provided for cases of ADHD that were compared with unaffected controls, as well as data for children who had ADHD comorbid with another clinical condition (e.g. Tourette syndrome or velocardiofacial syndrome) who were compared with controls who had the other clinical condition without ADHD. Each of these publications was treated as two studies because data were provided for independent samples. Therefore, a total of 13 studies were included in the final meta-analysis. Finally, Lyoo et al. (1996) provided results for children who were diagnosed with ADHD on the basis of a clinical chart review as well as results for a subset of these children who were also diagnosed using the Child Version of the Diagnostic Interview Schedule for Children (DISC). The meta-analysis conducted by Valera et al. (2006) only included data from this latter subset of children. However, the current meta-analysis included results for the whole sample because the diagnostic criteria used by Lyoo et al. (1996) (with or without the DISC) were equivalent to those employed by the other studies included in this meta-analysis. This is the only difference between those studies that compared children and adolescents with ADHD and healthy controls that were included in Valera et al. (2006) and those included in the current study. However, whereas Valera et al. (2006) only used two methods of partitioning the CC to group their findings (Baumgardner et al., 1996; Witelson, 1989), the current meta-analysis used three methods (Baumgardner

et al., 1996; Hynd et al., 1991; Witelson, 1989). The most commonly used method was that of Witelson (1989), which was used by seven studies (see Figure 1). Five studies (Antshel et al., 2005; Baumgardner et al., 1996; Mostofsky, Wendlandt, Cutting, Denckla, & Singer, 1999)[2] used a method that divided the CC on the midsagittal slice into five regions (see Figure 2). Finally, one study (Hynd et al., 1991) divided the CC into five regions using a procedure outlined by O'Kusky et al. (1988) (see Figure 3). Separate effect sizes were calculated for each of the regions of the CC that were measured by these three methods.

Statistical Analysis

Cohen's *d* effect sizes (Cohen, 1988) were calculated for each region of the CC that was measured by a study. A small effect size is defined as $d = .2$, a medium effect as $d = .5$, and a large effect as $d = .8$. Each effect size was then weighted by the inverse of the variance using the method outlined by Lipsey and Wilson (2001). This weighting takes into account the effect that sample size has on the reliability of an effect size but is more precise than simply weighting effect sizes by sample size. The effect sizes from all studies that measured a particular region were then aggregated to calculate a mean effect size, standard deviation, and minimum and maximum mean effect size for each region. The CC measurements of the control group were subtracted from those of the ADHD group when calculating effect sizes. Therefore, a negative effect size indicates that the CC was smaller for children and

[2] Antshel et al. (2005) and Baumgardner et al. (1996) each provide data that were treated as two studies, therefore only three references are provided for the five studies.

adolescents with ADHD compared to healthy controls. Whereas mean effect sizes measure the extent (and direction) of the difference between ADHD and controls, the standard deviation (*SD*) shows the degree of variation in the effect sizes for each region of the CC.

Percent overlap (%OL) statistics are also reported. This measures the degree of overlap in the measurements of the two groups (Zakzanis, 2001). These %OL scores vary inversely with mean effect sizes, such that larger effect sizes are associated with less overlap in the CC measurements. For example, an effect size of 0 is associated with 100% overlap, indicating that the CC measurements of the two groups are indistinguishable. A *d* of 1.0, is associated with 45% overlap and, if the effect size is 3.0, the overlap between the CC measurements of the two groups is less than 5%, indicating that the groups are almost clearly distinguishable from each other (Zakzanis, 2001). The 95% confidence intervals (95% CIs) were also calculated in order to determine the statistical significance of an effect size. If a confidence interval does not span zero, the difference in the CC measurements of the ADHD and control groups differ significantly from zero, indicating that there is a statistically significant difference between the size of the CC for the two groups.

It is also possible that studies with statistically significant results are more likely to be published and, therefore, more likely to be included in a meta-analysis. The failure to include unpublished studies with nonsignificant results increases the risk of a Type 1 error, which may result in an effect size being overestimated (Zakzanis, Leach, & Kaplan, 1999). A Fail Safe *N* (*Nfs*) was therefore calculated using the method described by Rosenthal (1995) to

address this possible source of bias. This statistic estimates the number of unpublished studies, with nonsignificant group differences (i.e. small effect sizes), that would be required in order to call the current findings into question. The higher the number, the more confident one can be in a finding.

The potential influence of participants' age on the CC measurements was also examined. The mean age of participants was calculated for each study for this purpose. This was done by combining the age data from the ADHD and control groups for that study (e.g., $M_{ADHD+Control\ age}$) and weighting it by the sample sizes of the ADHD and control groups. In addition, a weighted mean effect size was calculated for the callosal measurements from each study. The mean age for each study was then correlated with the weighted mean effect size for that study using Pearson's *r*. It was also intended that IQ be examined in this way. However, only five studies reported this information, therefore precluding a reliable assessment of the relationship between IQ and callosal size.

Results

Demographic Data

The demographic characteristics for the participants that were included in the current meta-analysis are provided in Table 1. In total, the data from 595 participants were included in this analysis.

Table 1

Demographic Details for the ADHD and Control Groups

	ADHD						Controls (all types combined)					
	N studies	*N* participants	Mean	*SD*	Min	Max	*N* studies	*N* participants	Mean	*SD*	Min	Max
N	13	284	21.8	15.6	7	57	13	311	23.9	12.6	10	55
Age (yrs)	11	241	10.9	1.2	9.1	13.0	11	242	11.6	1.4	9.4	14.5
IQ	7	180	105.8	9.1	92.5	120.3	5	146	111.7	11.9	97.9	124.5
Gender	10	229 (204 males)					10	218 (177 males)				

Note: The N differs between variables because not all studies provided data for each variable

The ADHD and control groups were not significantly different with regard to age (t = - 2.07, df = 10, p = .065), based on the few studies that provided these data, but the ADHD group had a significantly lower average IQ (t = - 2.89, df = 4, p = .045). The latter finding is consistent with previous reports of lower IQ in children with ADHD (Daley, 2006). However, it has been thought that these decrements are likely to be part of the disorder (Hervey, Epstein, & Curry, 2004) and therefore, statistically controlling for these differences in IQ scores may remove variation in cognitive performance or even brain morphology that is related to ADHD. Therefore, IQ was not statistically controlled for in the current meta-analysis. Chi-square tests indicated that there were significantly more males than females in both the ADHD and control groups. In addition there were significantly more females in the control group than in the ADHD group ($p < .05$ level). Therefore, if gender differences are found in the morphology of the CC, they may be confounded by this significant difference in the composition of the samples. However, any differences in CC size are unlikely to be attributable to age differences, as the ADHD and control groups did not significantly differ in this regard. Whole brain size was measured in most studies and was often included as a covariate in order to ensure that differences in CC size were not simply due to a reduction in whole brain size. Only one study did not take this issue into account. The removal of the results from this study did not change the overall findings of this meta-analysis. Therefore, it was included in the analysis.

Diagnostic Criteria, Comorbidities and Medication

All studies based the diagnosis of ADHD on criteria taken from various editions of the Diagnostic and Statistical Manual (DSM) of Mental Disorders (APA, 1980; 1987; 1994). ADHD was assessed through a range of parent, teacher and child questionnaires, and clinical interviews. Therefore, despite changes to the DSM criteria over time, all studies applied comparable rigor to the diagnosis of participants. The ADHD subtypes (i.e. 'combined', 'predominantly inattentive', and 'predominantly hyperactive' subtypes) were introduced to the fourth edition of the DSM (APA, 1994). This information was only provided for two studies, so it was not possible to determine whether there are differences in CC morphology for the different subtypes. In addition, there were some inconsistencies in terms of the inclusion or exclusion of comorbid psychiatric conditions. For example, five studies included participants with ADHD and comorbid conduct disorder (Castellanos et al., 1996; Giedd et al., 1994; Hynd et al., 1991; Lyoo et al., 1996; Overmeyer et al., 2000) and two studies excluded participants with ADHD and comorbid conduct disorder (Hill et al., 2003; Semrud-Clikeman et al., 1994). This information was not provided for the remaining six studies (Antshel et al., 2005; Baumgardner et al., 1996; Kayl, Moore, Slopis, Jackson, & Leeds, 2000; Mostofsky et al., 1999).[3] Moreover, some studies excluded participants with certain comorbid psychiatric disorders, such as depression and anxiety, learning disabilities, neurological disorders, and developmental delay

[3] Antshel et al. (2005) and Baumgardner et al. (1996) each provide data that were treated as two studies, therefore only four references are provided for the six studies.

(Castellanos et al., 1996; Giedd et al., 1994; Hill et al., 2003; Lyoo et al., 1996; Overmeyer et al., 2000; Semrud-Clikeman et al., 1994). However, seven studies did not provide detailed information about the inclusion or exclusion of comorbid psychiatric conditions (Antshel et al., 2005; Baumgardner et al., 1996; Hynd et al., 1991; Kayl et al., 2000; Mostofsky et al., 1999). Due to the inconsistent reporting of inclusion and exclusion criteria, it was not possible to accurately determine whether the inclusion or exclusion of these participants influenced the CC measurements.

Similarly, the amount of information provided about the medications used for the treatment of ADHD varied. Seven studies did not report information about current use of medications (Antshel et al., 2005; Baumgardner et al., 1996; Giedd et al., 1994; Lyoo et al., 1996; Mostofsky et al., 1999)[4]. Four studies indicated that the participants were all taking medications prior to the study but did not indicate whether participants were taking medications at the time of the study (Castellanos et al., 1996; Hynd et al., 1991; Overmeyer et al., 2000; Semrud-Clikeman et al., 1994). One study indicated that participants either had no prior use of stimulants or received a physician's consent to stop taking medications 16 hours prior to participating in the study (Hill et al., 2003) and one study indicated that two thirds of the ADHD participants were taking medications to treat the disorder (Kayl et al., 2000). Due to these inconsistencies, it was not possible to reliably examine the impact of medications on the CC findings.

[4] Antshel et al. (2005) and Baumgardner et al. (1996) each provide data that were treated as two studies, therefore only five references are provided for the seven studies.

Corpus Callosum Morphology in ADHD

The weighted effect sizes (d_w) for subregions of the CC (mean, *SD*, 95% CIs), measured in children and adolescents with ADHD and healthy controls are provided in Table 2. The *Nfs* and the percentage overlap between groups (%OL) are also provided, as are the number of studies, number of participants, and the study references. These statistics were all considered when interpreting the current results.

The effect sizes for the different regions of the CC ranged from a minimum of -0.06 for the midbody, equating to 92% overlap between the measurements for the two groups (Baumgardner et al., 1996 method), to a maximum of -0.94 for region 4 (a region anterior to the splenium), with 48% overlap between ADHD and controls (Hynd et al., 1991 method). The latter result equates to a large difference (Cohen, 1988). In terms of the statistical significance of the effect sizes, as indicated by confidence intervals that do not span zero, only the measurement for the splenium (using Witelson's method) of the ADHD and control groups differed significantly from zero. Thus, there do not appear to be reliable group differences in any region of the CC, other than the splenium. The splenium yielded an effect size of -0.54 indicating that, on average, there is a half a standard deviation difference in the mean measurements between the two groups. Moreover, the *Nfs* for the splenium indicates that seven unpublished findings with nonsignificant findings would be necessary to challenge this result. This is unlikely given the small number of studies that have measured the CC in participants with ADHD.

Table 2

ADHD vs. healthy controls: Weighted Cohen's d effect sizes[a] for subregions of the CC organized by method and from anterior to posterior regions

Region	*N* studies	*N* participants (ADHD + Controls)	Mean Cohen's d_w	*SD* d_w	95% CI		Min d_w	Max d_w	*Nfs*	%OL	Study references
Total CC	5	281	-0.20	0.28	-0.45	0.04	-0.72	0.53	0	85	Antshel et al 2005; Baumgardner et al 1996; Castellanos et al 1996; Hill et al 2003; Semrud-Clikeman et al 1994
Witelson (1989) method											
Rostrum	3	145	-0.15	0.30	-0.48	0.19	-0.72	0.15	0	85	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Genu	4	192	-0.21	0.30	-0.50	0.08	-0.51	0.15	0	85	Giedd et al 1994; Hill et al 2003; Lyoo et al 1996; Semrud-Clikeman et al 1994

Region	*N* studies	*N* participants (ADHD + Controls)	Mean Cohen's d_w	*SD* d_w	95% CI		Min d_w	Max d_w	*Nfs*	%OL	Study references
Rostral body	3	145	-0.16	0.30	-0.50	0.18	-0.93	0.31	0	85	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Anterior midbody	3	145	-0.27	0.30	-0.60	0.07	-0.63	-0.10	1	79	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Posterior midbody	3	145	-0.20	0.30	-0.54	0.14	-0.69	0.32	0	85	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Isthmus	3	145	-0.23	0.30	-0.56	0.11	-0.66	0.24	0	85	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Splenium	4	192	-0.54	0.30	-0.84	-0.25	-0.84	-0.15	7	67	Giedd et al 1994; Hill et al 2003; Lyoo et al 1996; Semrud-Clikeman et al 1994

Region	*N* studies	*N* participants (ADHD + Controls)	Mean Cohen's d_w	*SD* d_w	95% CI		Min d_w	Max d_w	*Nfs*	%OL	Study references
Baumgardner et al (1996) method											
Genu	2	92	0.22	0.33	-0.24	0.68	-0.28	0.68	0	85	Antshel et al 2005; Baumgardner et al 1996
Rostral body	2	92	-0.13	0.33	-0.59	0.33	-0.60	-0.28	0	92	Antshel et al 2005; Baumgardner et al 1996
Midbody	2	92	-0.06	0.33	-0.51	0.40	-0.31	0.17	0	92	Antshel et al 2005; Baumgardner et al 1996
Isthmus/posterior body	2	92	0.42	0.33	-0.04	0.88	0.05	0.77	2	73	Antshel et al 2005; Baumgardner et al 1996
Splenium	2	92	-0.09	0.33	-0.55	0.37	-0.53	0.31	0	92	Antshel et al 2005; Baumgardner et al 1996
Hynd et al (1991) method											
1	1	17	-0.70	0.51	-1.70	0.29			3	57	Hynd et al 1991
2	1	17	0.11	0.49	-0.86	1.08			0	92	Hynd et al 1991

Region	*N* studies	*N* participants (ADHD + Controls)	Mean Cohen's d_w	*SD* d_w	95% CI		Min d_w	Max d_w	*Nfs*	%OL	Study references
3	1	17	-0.27	0.49	-1.24	0.70			0	79	Hynd et al 1991
4	1	17	-0.94	0.52	-1.96	0.08			4	48	Hynd et al 1991
5	1	17	-0.67	0.51	-1.66	0.32			2	57	Hynd et al 1991

Note. *N*=number of studies contributing to the effect size, Mean d_w=mean weighted effect size, *SD* d_w = standard deviation of weighted effect size, 95% CI=95% confidence intervals for means, Max *d*=maximum effect size, Min *d*=minimum effect size, *Nfs*=Fail Safe *N*, % OL=percent overlap between ADHD and Control groups

[a] Effect sizes weighted by the inverse variance

Corpus Callosum Morphology With Specific Comorbid Conditions

Five additional studies compared the CC size of children with ADHD who also had a specific comorbid condition to that of children with the comorbid condition but without ADHD. These studies were not included in the previous calculations but were considered separately. Two of these studies (Baumgardner et al., 1996; Mostofsky et al., 1999) examined CC area in children and adolescents with ADHD and comorbid Tourette syndrome, and compared area measurements with a group of children and adolescents with Tourette syndrome without ADHD, in order to determine whether these conditions had distinct or common differences in CC morphology. This research yielded small (0.02) to moderate (-0.35) effect sizes but these were all nonsignificant (see Table 1, supplementary material).

The remaining three studies looked at different comorbid conditions. Firstly, Overmeyer et al. (2000) compared children and adolescents with ADHD with siblings of children and adolescents with ADHD, although not necessarily siblings of the ADHD participants in the study. This was done in order to examine the relationship between callosal morphology and the expression of ADHD symptoms. These results are presented in Table 2 of the supplementary material. Another study by Antshel et al. (2005) examined CC size in children with ADHD and velocardiofacial syndrome and children with velocardiofacial syndrome without comorbid ADHD (see Table 3, supplementary material). Finally, Kayl et al. (2000) researched CC size in children with ADHD and comorbid neurofibromatosis and children with neurofibromatosis without comorbid ADHD (see Table 4, supplementary material) to determine if the structural differences in ADHD extended to

children with neurofibromatosis, given that ADHD occurs more frequently in these children than in the general population. Effect sizes were calculated for these studies although effect sizes based on single studies are considered to be less reliable (Rosenthal, 1995). The effect sizes from these three studies were all small and nonsignificant, indicating that the size of CC regions did not differ between the two groups. The very small *Nfs* for these studies also suggests limited confidence in these results. Thus, on the basis of limited available evidence, there do not appear to be any differences in CC size when the effects of comorbid conditions are controlled for.

Moderator Variables

In order to examine the effect of gender on CC size, effect sizes were recalculated separately for studies that included only males, only females, or a combination of male and female participants. This analysis is available as supplementary material (see Table 5). When studies were separated according to the gender of the participants, the effect size for the splenium (measured according to Witelson's method) was no longer significant when only male samples were examined. However, significant differences in the rostral body (measured according to Witelson's method) were found for males with ADHD compared to healthy controls. Although this effect size was based on only two studies, the fact that the confidence interval did not span zero suggests that this is a statistically significant effect. Another study examined the rostral body exclusively in females with ADHD and comorbid Tourette syndrome compared with females with Tourette syndrome only. However, there was no significant difference in rostral body size in these two groups.

The influence of age on group differences in callosal size was additionally examined using Pearson *r* correlation coefficients. The mean age of those studies that reported this data was correlated with the weighted mean effect sizes for these studies. A small nonsignificant correlation was observed for age ($r = -.06$, $n = 11$, $p = .86$), indicating that age of the samples was not related to the effect sizes calculated for a study.

Discussion

Overall, the results of this meta-analysis indicated that children and adolescents with ADHD had a smaller splenium than those without, consistent with the findings of Valera et al. (2006). In addition, there was some indication that, for males only, children and adolescents with ADHD had a smaller anterior portion of the CC.

To put these findings in perspective, the data for this meta-analysis was obtained from 13 studies that examined the size of the CC of 284 children and adolescents with ADHD and 311 controls. Although the two groups were comparable in terms of age, participants with ADHD had a lower IQ than control participants. As discussed earlier, this may be part of the disorder (Hervey et al., 2004). Therefore, statistically controlling for differences in IQ may remove variation in cognitive performance or even brain morphology that is an integral part of ADHD (Hervey et al., 2004). In addition, IQ was not available for the majority of the studies, preventing an analysis of the impact of IQ on the findings.

In the current meta-analysis, the splenium of ADHD participants compared with healthy controls (measured using Witelson's method) was the

only difference in callosal size that was associated with an acceptable *Nfs*, small overlap between the two groups, and a 95% CI indicating that it differed significantly from zero. Although it was associated with 67% overlap for the callosal measurements for the two groups, only small differences were expected and moreover, differences in the CC are not being proposed as a tool for the diagnosis of ADHD. The significant difference in this region is consistent with the meta-analysis performed by Valera et al. (2006).

According to Witelson (1989), the splenium has connections to temporal regions (Giedd et al., 1994; Pandya & Seltzer, 1986) and may, therefore, be associated with memory. Problems with memory have previously been reported in both children and adults with ADHD (Cutting, Koth, Mahone, & Denckla, 2003; Gallagher & Blader, 2001; Hervey et al., 2004; McLean et al., 2004; Norrelgen, Lacerda, & Forssberg, 1999). The more recent work by Hofer and Frahm (2006) based on diffusion tensor imaging, suggests that the most posterior part of the CC (which included the splenium) projects to parietal, temporal, and occipital cortex. These projections overlapped, preventing further differentiation of this region. Given these connections of the posterior region of the CC, the smaller splenium may provide a potential substrate for some of the problems experienced by persons with ADHD in the areas of sustained attention and divided attention, which are functions supported by the parietal region (Banich, 2004). In addition, the memory problems associated with ADHD may result from poor encoding of information due to attention problems.

Several studies in the current meta-analysis compared children with ADHD and a comorbid clinical disorder to children with that clinical disorder

without comorbid ADHD. These studies consistently yielded only small effect sizes. It is possible that any differences in CC size were common to both ADHD and the comorbid disorder and therefore, not evident when comparing the two clinical groups. Although these studies provide information about the ways in which ADHD and the comorbid conditions vary from one another, they do not provide clear evidence for any differences associated with ADHD compared to healthy controls.

In the current meta-analysis, effect sizes were additionally calculated for males and females separately. The effect size for the splenium (measured using Witelson's scheme) was significant for studies that examined males or both males and females. However, this effect was rendered nonsignificant when males were considered (such an analysis could not be done for females, as there were no studies comparing the size of the splenium in females only). These results raise the possibility that the smaller splenium associated with ADHD is more pronounced in females. However, further research is needed to confirm this gender difference because females have not been examined exclusively and females were generally underrepresented in the studies that were included here. Although these differences may have disappeared due to low power, such an interpretation is made less likely by the fact that an equal number of studies used males and females, but the difference for the splenium remained significant. In addition, a smaller rostral body was associated with males with ADHD compared to healthy male controls. The rostral body was not significantly different in a study comparing ADHD with comorbid Tourette syndrome with Tourette syndrome only in female participants. This

pattern of results suggests that the smaller rostral body is driven by the inclusion of male participants.

The possible influence of the demographic characteristics on the CC measurements was also examined. Although an analysis of age, for those studies that provided this information, indicated that this variable did not significantly influence the group differences in CC size, we cannot be sure of the impact of other variables, such as current medications, IQ and comorbid psychiatric conditions, as they were not consistently reported. Therefore, there is the potential for significant but unreported variation in the samples under investigation. Our inability to account for the influence of these variables may have obscured additional differences in the size of callosal regions between ADHD children and control groups.

Despite significant findings, there are a number of caveats to the current study. First, several studies included samples of ADHD with comorbid conditions. These comorbidities may obscure or confound relevant group differences. For example, learning disabilities, conduct disorder, and mood disorders are commonly comorbid with ADHD (for a review see Daley, 2006). There is also some evidence for larger CC volume in adults with antisocial personality disorder (Raine et al., 2003), which is the adult manifestation of conduct disorder. If conduct disorder is also associated with a larger CC volume, this might offset reductions in CC size associated with ADHD. In addition, major depressive disorder is often found in children and adolescents with ADHD (Busch et al., 2002). A recent study has shown that people with familial major depressive disorder had larger regions of the CC compared to healthy controls (Lacerda et al., 2005). Therefore, larger CC

regions associated with major depressive disorder may be offset by smaller CC regions associated with ADHD in children and adolescents with both conditions. Therefore, comorbid psychiatric disorders have the potential to obscure differences in callosal size driven by ADHD. Unfortunately, comorbidity is not consistently reported, which makes it difficult to disentangle the effects on callosal size that may be driven by ADHD as compared to other disorders. Such information should be included in future publications of primary research on ADHD to allow an accurate and detailed evaluation of the research findings.

Second, the implications of moderate differences in the size of the splenium in ADHD are unclear. From an anatomical perspective, one could assume that a larger callosum is associated with more nerve fibers. If so, then the reduction in callosal size in the splenium of individuals with ADHD might indicate that there are fewer fibers connecting the parietal regions. Another possible interpretation is that there is reduction in the brain regions that typically send those fibers, that is, parietal regions. Although a reduction in parietal volume has been reported (Castellanos et al., 2002), other studies have failed to find significant differences (Durston et al., 2004; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Although reductions for any given parietal region might not be large enough to reach statistical significance, subtle differences across a variety of parietal regions may add up to be reflected in callosal size if they send fibers through similar regions. Still another possibility is that ADHD and controls have equal number of fibers passing through the splenium, but that these are more myelinated in controls, leading to larger callosal size (Banich & Shenker, 1994). This may result in

individuals with ADHD not being able to coordinate processing between the hemispheres in as integrated a manner as controls.

Finally, our meta-analysis was restricted to samples of children and adolescents because CC size has not yet been examined in adults with ADHD. Therefore, it is not known whether any differences, such as a smaller splenium, persist into adulthood or whether the size differences resolve with further development. The CC begins to develop between the 10^{th} and 25^{th} week of gestation (Moutard et al., 2003) and myelination continues throughout childhood (Barnea-Goraly et al., 2005). In addition, there is evidence that the posterior CC continues to change throughout adolescence, whereas anterior regions reach adult levels earlier in childhood (Giedd et al., 1999; Thompson et al., 2000). Although it would be ideal to examine differences in children and adolescents separately, most of the studies included both children and adolescents in their samples. Further research is needed to determine whether differences persist into adulthood, given the developmental changes in myelination of the CC.

In summary, the findings of this meta-analysis suggest that the splenium of the CC of children and adolescents with ADHD is smaller than that of healthy controls. In addition, the rostral body may be smaller in males with ADHD. Further research is necessary to determine whether these differences persist into adulthood and the mechanisms by which such differences are related to the symptoms observed in children with ADHD.

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Chapter 3

Corpus Callosum Size and Integrity in Adults with Attention Deficit Hyperactivity Disorder

The preceding study revealed that the splenium was smaller in children and adolescents with ADHD than healthy controls and the rostral body was smaller in boys with ADHD. Despite increased interest in adult ADHD (Hervey et al., 2004), the CC has not been examined in this older population. Therefore, it is not known whether the differences observed in the meta-analysis in the previous chapter are present in adults with ADHD or whether they resolve with age.

Shaw and colleagues (2007) proposed that ADHD is due to a developmental delay (refer to section 1.2.6). This theory would predict that the differences in neuroanatomy observed in children and adolescents with ADHD may have resolved by young adulthood. However, it fails to account for those who continue to experience symptoms and meet criteria for ADHD in adulthood. Therefore, it is possible that the CC is atypical in adults with ADHD, consistent with the continuation of ADHD symptoms or that the differences in CC area observed in children, resolve with further development, consistent with Shaw et al.'s (2007) theory. This study examines one brain region that is atypical in children with ADHD, in young adults, in order to determine if this difference is present in an older sample.

The following study examined CC morphology in young adults with ADHD (aged 18 to 23). The specific aim of this study was to examine CC

area and integrity in young adults with ADHD compared with healthy controls in order to determine if the differences in CC size that have previously been reported in children and adolescents with ADHD persist into young adulthood and to determine whether there are other regional differences in CC size at this later stage of development. In addition, this study examined CC integrity, as measured by diffustion tensor imaging, as well as CC area. The relationship between CC measures (area and integrity) and performance on the Stroop task, which requires attentional control, and ADHD symptoms were explored to examine the possible functional consequences of atypical CC morphology.

In this study, regressions were conducted in order to examine the extent to which ADHD symptoms, measures of attentional control, and whole brain volume (included as a covariate), predict CC area and integrity. One could argue that CC measures are more likely to predict ADHD symptoms and attentional control (rather than the other way around) because brain structure usually precedes brain function. However, this is not necessarily the case. For example, there is evidence that musicians have larger regions of the CC and greater CC integrity (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995; Schmithorst & Wilke, 2002). These authors propose that the larger CC in these groups is due to musical training and practice during childhood and young adulthood while the CC continues to develop. This suggests that brain function can result in structural changes. Hence, the regressions in the current study could have been conducted to examine the extent to which brain function predicts CC structure, or conversely, the extent to which CC structure predicts brain function. The extent to which ADHD symptoms and attentional

control predicted CC measures was thought to be an appropriate approach because the CC was the focus of this study and thesis.

The following chapter represents a manuscript that has been submitted to a high-impact international journal for peer review. Supplementary materials mentioned in this study can be found in Appendix C.

Title: Corpus callosum size and integrity in adults with attention deficit hyperactivity disorder

Running title: Corpus callosum size in adults with ADHD

Authors: A.D. Hutchinson[1, 4], J.L. Mathias[1], B.L. Jacobson[2], L. Ruzic[2], A.N. Bond[2], E. Willcutt[2], L.C. Bidwell[2], Y.P. Du[3], & M.T. Banich[2, 4]

Affiliations:

[1]School of Psychology, University of Adelaide, Adelaide, SA, Australia

[2]Department of Psychology, University of Colorado, Boulder, CO, USA

[3]Department of Psychiatry, University of Colorado Denver, Denver, CO, USA

[4]Institute of Cognitive Science, University of Colorado, Boulder, CO, USA

Abstract:

Recent meta-analyses have revealed that the splenium of the corpus callosum (CC) is smaller in children and adolescents with ADHD than controls but it is not known whether this difference persists into adulthood. In the current study, we examined the size and structural integrity of the CC in a group of young adults with ADHD compared to healthy controls. We also examined the relationship of these measures to performance on an attentionally demanding task as well as to symptomatology to establish the functional significance of any differences in the CC. Although the splenium was not smaller in this sample of young adults with ADHD, the genu was smaller and mid-posterior regions were larger than controls. Moreover, a larger midposterior region in the ADHD group was associated with increased hyperactivity. Fractional anisotropy, which provides a measure of the

structural integrity of the CC, showed group differences in integrity in both the splenium and the genu. In addition, reduced integrity of the splenium in those with ADHD was associated with poorer attentional control on the Stroop task. As such, our results suggest that CC morphology is altered in adults with ADHD and that these differences may impact on cognitive functioning.

Keywords: attention deficit hyperactivity disorder, corpus callosum, adults, magnetic resonance imaging, diffusion tensor imaging

Introduction

Attention deficit hyperactivity disorder (ADHD) is a well established childhood disorder (American Psychiatric Association, 1994). However, the validity of this diagnosis and its manifestations in adulthood are more controversial due to problems associated with the retrospective diagnosis of ADHD, disagreement about the characteristics of the disorder in adulthood, the existence of comorbid conditions, and its overlap with learning disabilities (Faraone, 2000; Seidman et al., 2004). Nonetheless, interest in adulthood ADHD has increased over recent years (Hervey et al., 2004), with between 1% and 6% of the general population manifesting symptoms of ADHD in adulthood (Roth and Saykin, 2004; Wender et al., 2001) and estimates of the continuation of ADHD symptoms from childhood into adulthood ranging from 30% to 70% (Castellanos et al., 1996; Durston, 2003; Roth and Saykin, 2004; Wender et al., 2001).

One neuroanatomical characteristic of children with ADHD compared to their peers that has repeatedly been observed is a reduction in the area of the

corpus callosum (CC). The CC, which is the largest fiber tract in the human brain, connects homologous areas of the left and right cerebral hemispheres, and serves as the major conduit for the transfer of information between the cerebral hemispheres (Banich, 2003; Hoptman and Davidson, 1994; Hynd et al., 1991; Innocenti and Bressoud, 2003; Sperry et al., 1969). However, the exact region of the CC that is smaller varies between studies. In some studies, children with ADHD have a smaller anterior CC (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991), in others a smaller posterior CC (Hill et al., 2003; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994), and in still others a smaller overall CC area (Hill et al., 2003; Hynd et al., 1991). Moreover, some studies have not found any differences (Castellanos et al., 1996; Overmeyer et al., 2000).

Nonetheless, two recent meta-analyses found differences in CC size in ADHD. First, Valera et al. (2006) used a meta-analytic approach to determine which brain regions, as assessed by magnetic resonance imaging, differ in size between children and adolescents with ADHD compared to healthy controls. With regard to the CC, they reported a significantly smaller splenium in children and adolescents with ADHD. This finding was confirmed in a subsequent meta-analysis by Hutchinson et al. (2008) that specifically focused on CC morphology in children and adolescents with ADHD. In addition, Hutchinson et al (2008) found an additional effect restricted to males with ADHD, who were found to have a smaller rostral body (an anterior portion of the CC) than controls (Hutchinson et al., 2008). Therefore, although there is variability across studies, when the data are combined there appears to be a

significant difference in one region, the splenium, and a possible gender difference in another, namely the rostral body.

The CC is of particular interest to the study of ADHD because its functioning has been linked to attentional control. Specifically, research with split-brain patients has demonstrated that the CC plays a role in sustaining attention over time and dividing attention between tasks (Dimond, 1976; Kreuter et al., 1972). Moreover, a large body of research with neurologically intact individuals has shown that the CC also plays a critical role in distributing the processing load across the hemispheres to meet high attentional demand (see Banich, 2003 for a review). Hence, the atypical morphology observed in individuals with ADHD may have consequences for attentional control.

In the current study, we examined whether the morphological differences that have been observed in children and adolescents with ADHD are also observed in young adults with ADHD. To our knowledge, this issue has not been examined previously, but it is important for a number of reasons. First, the question of what aspects of ADHD continue from childhood into adulthood is relatively poorly understood – both from the perspective of behavior and brain morphology. Second, although the CC was previously thought to be fully developed by adolescence (Yakolev and Lecours, 1967), recent evidence suggests a more extended period of development (Barnea-Goraly et al., 2005; Giedd et al., 1999; McLaughlin et al., 2007; Thompson et al., 2000). Specifically, research indicates that myelination of the CC peaks in young adulthood (McLaughlin et al., 2007) and that there are regional changes in its development, with the anterior regions reaching adult levels earlier than

the posterior regions (Giedd et al., 1999; Thompson et al., 2000). Hence, the current study examined CC area in adults with ADHD, when compared to healthy controls, in order to determine whether the differences previously observed in samples of children and adolescents with ADHD persist.

Most of the prior studies have examined CC size, as indexed by CC area in the midsagittal slice. However, with the advent of newer neuroimaging techniques, it is also possible to investigate the integrity of CC fibers via diffusion tensor imaging (DTI). DTI is an MRI technique that provides information about the diffusion of water in white matter tracts. Fractional anisotropy (FA) measures the strength and directionality of this diffusion, providing a measure of the integrity of white matter (Neil, 2008). Although not used extensively, its potential is suggested by a recent study of adolescents with very low birth weight (Skranes et al., 2007). Those who also had a diagnosis of ADHD or a high level of ADHD symptoms had reduced FA values in the anterior CC compared to those with very low birth weight but without ADHD.

We were also interested in exploring the link between anatomy and function. In particular, we examined how these measures of CC anatomy are related to behavioral performance on a variety of attention tasks as well as their relationship to ADHD symptomatology. A relationship between these measures would help to implicate CC morphology as part of the neutral substrate specifically involved in ADHD.

Finally, our sample was carefully selected to exclude individuals who had a co-morbid psychiatric disorder (e.g. learning disability, substance use disorder) in order to examine the link between CC morphology, attention, and

ADHD symptomatology in a sample of young adults without the potentially confounding effects of these comorbid conditions.

Method

Participants

Twenty-three young adults with ADHD (14 male, 9 female) and 21 healthy controls (12 males, 9 females), aged between 18 and 23 years, participated in this study (mean age = 19.5, SD = 1.4).

Participant Selection

All participants were drawn from a pool of 3913 undergraduates, who completed a battery of self-report measures as part of the research participation requirement of an introductory Psychology course. These measures included the self-report form of the ADHD Current and Childhood Symptom Scales (Barkley and Murphy, 1998). Approximately 70% of these undergraduates also consented to have their symptoms rated by a parent using the Other Report version of the Current and Childhood Symptom Scales. Participants who met DSM-IV criteria for ADHD (American Psychiatric Association, 1994), based on these measures, were invited to come back for more extensive neuropsychological testing and to complete a structured interview concerning DSM-IV ADHD symptoms (Barkley and Murphy, 1998). A group of matched controls, who did not meet current or lifetime criteria for any ADHD subtype, based on parent or self-report, was additionally randomly selected from the sample. Participation was voluntary and participants were reimbursed for their time.

Due to the difficulties associated with diagnosing ADHD in adulthood, four criteria were used to identify participants with ADHD for this study: (1)

retrospective ratings (self-report and/or parent report) indicated that the participant met DSM-IV criteria (American Psychiatric Association, 1994) for the ADHD combined subtype (i.e. both inattention and hyperactivity symptoms) in childhood; (2) the participant either currently met DSM-IV criteria for ADHD (N = 20) or scored above the 90th percentile on the ADHD symptom measures while exhibiting marked impairment in daily functioning (N = 3), consistent with the DSM-IV specification of ADHD in partial remission (i.e. symptoms were still present but no longer met full criteria); (3) the ADHD symptoms led to significant functional impairment across social, occupational and educational domains; and (4) the onset of the ADHD symptoms was prior to 12 years of age. Although the latter criterion is less stringent than the requirement of symptom onset prior to age 7, as specified in the DSM-IV, it has been employed by another study of adult ADHD (Nigg et al., 2005) due to evidence that it may be more reliable and valid than the DSM-IV threshold (e.g., Barkley and Biederman, 1997).

Twenty-two of the ADHD participants had been prescribed stimulant medication during their lifetime and 14 were currently prescribed for mixed amphetamine salts (N = 9), methylphenidate (N = 4), or dexmethylphenidate (N = 1). Participants using stimulant medications refrained from taking the medication for 24 hours prior to study participation.

The exclusion criteria for both the ADHD and control samples included a previous diagnosis of a learning disability, measured by self-report or performance indicative of a learning disability on measures of reading and math ability (refer to the measures section). Research with ADHD is often complicated by a high rate of comorbidity with other psychiatric disorders.

Therefore, individuals with a self-reported history of bipolar disorder, obsessive-compulsive disorder, and substance-use disorder were also excluded. Individuals with a history of depression were included if they no longer met the criteria for major depression and were not taking medication for the condition.

A number of additional exclusion criteria were necessary because this study involved the use of MRI. Firstly, participants who were pregnant or had metal in their body that could not be removed (e.g., a screw for a broken limb, cardiac pacemaker) were excluded for safety reasons. In addition, participants with a Full Scale IQ < 80, a previous history of seizures, a head injury with loss of consciousness, or who were left-handed were not included in the study as this may have affected brain function/organization.

Measures

ADHD symptoms.

During the initial screening, ADHD symptoms (as specified in DSM-IV) were assessed using the Self-Report form of the ADHD Current and Childhood Symptom Scale by Barkley and Murphy (1998). On the *Current Symptom Scale,* the participant indicates how often each of the 18 ADHD symptoms is true on a 4-point likert scale ("Not at All", "Once in a While", "Often" or "Very Often"). The *Childhood Symptom Scale* asks the individual to retrospectively rate ADHD symptoms during their childhood (i.e., 5-12 years of age). Each scale also measures the extent to which the symptoms interfered with the individual's social, academic, and adaptive functioning. Consistent with previous research (Pelham et al., 1992), items rated as occurring "often" or "very often" were coded as positive symptoms.

During the neuropsychological testing session, the Adult ADHD Interview was also administered (Barkley and Murphy, 1998). This interview assesses the 18 DSM-IV ADHD symptoms and the extent to which the symptoms lead to significant impairments in academic functioning, social functioning, job performance, the ability to operate motor vehicles, and the ability to manage daily responsibilities.

All participants completed a range of measures of functional impairment as part of the initial screening in order to determine if ADHD symptoms led to functional significance, as required for a DSM-IV diagnosis. The Current and Childhood Scales and interview include questions about the impact of ADHD symptoms on the individual's social, occupational, educational, and overall daily functioning (Barkley and Murphy, 1998). These items were supplemented with a more detailed impairment questionnaire, which was developed by Willcutt et al. (in preparation). This scale includes a broader range of questions relating to academic functioning (high school and college grade point average, completion of assignments, retention of academic material), interpersonal relationships (both friendships and romantic relationships), and specific aspects of adaptive functioning, such as money management, driving performance, and occupational functioning. Global functioning was assessed by asking the participant and their parents to rate the participant's lowest functioning during the past year on the Global Assessment of Functioning Scale (American Psychiatric Association, 1994). Impaired functioning was defined as the 93rd percentile for composite scores of global, academic, social, and occupational functioning, management of daily responsibilities, and driving impairment derived from this test battery.

Academic achievement.

The Letter Word ID and Calculations subtests of the Woodcock-Johnson Tests of Achievement – Third Edition (WJ-III) assessed academic achievement in order to exclude participants with learning disabilities (Woodcock et al., 2001). Reading or math disabilities were defined by a standard score below 85 on the Letter-Word Identification subtest or the Calculations subtest respectively.

IQ.

Participants also completed the WAIS-III Matrix Reasoning and Vocabulary subtests (Wechsler, 1997). These were used to provide an estimate of performance IQ (PIQ_{est}) and verbal IQ (VIQ_{est}) respectively. The mean of these scores also allowed an estimate of full scale IQ ($FSIQ_{est}$) to be calculated. The Matrix Reasoning subtest is correlated with performance IQ as determined by the full WAIS-III ($r = .79$) and the Vocabulary subtests is correlated with WAIS-III verbal IQ ($r = .89$) (Wechsler, 1997). These correlations indicate that although these subtests are not equivalent to the full PIQ and VIQ measures in the WAIS-III, they provide good estimates of these measures.

Attention.

A variant of the Stroop Color Word Test (Golden, 1978) was included as a measure of attentional control. This task requires participants to respond selectively to one dimension of a multidimensional stimulus. Participants were presented with words printed in one of four ink colors and were required to indicate the ink color in which the words were printed using a manual keypress. There were three types of blocks: congruent in which the word and

the ink color matched (e.g. ‘red’ printed in red ink), incongruent in which the word conflicted with the ink color (e.g. ‘red’ printed in green ink) and neutral trials in which the word was not a color (e.g. ‘bond’ printed in red ink). Within each block, half of the words were block specific (as just described) and half were another set of neutral words that were common across all blocks. These trials were included to keep individuals engaged in the attentionally demanding aspect of the task (e.g., to avoid cheating on congruent blocks). This task was undertaken during functional MRI scanning, the results of which are reported elsewhere (Banich et al., in preparation). Only the behavioral results of the Stroop task were used in the current study.

A facilitation score was calculated by subtracting the RT on the 36 congruent trials (within the congruent block) from RT on the 36 block-specific neutral trials within the neutral block and dividing by RT on the block-specific neutral trials [neutral(RT)-congruent(RT)] /neutral(RT). Increased facilitation is associated with a lack of attentional control as it is thought to index “cheating” by reading the word rather than attending to the ink color (MacLeod and MacDonald, 2000). An interference score was calculated similarly using RT on the 36 incongruent and 36 block-specific neutral trials [incongruent(RT)-neutral(RT)]/neutral(RT). This measure reflects the difficulty individuals have ignoring the incongruent/conflicting word. Data from trials on which an error was made was excluded from the calculation of facilitation and interference scores.

Brain Morphology.

T-1 weighted 3D-SPGR anatomical images were collected on a 3 Tesla GE-Signa MR scanner (repetition time = 9 ms, echo time = 2.0 ms, flip angle

= 10°, inversion time = 500 ms; 220 mm field-of-view, 256 x 256 matrix, 0.86 mm x 0.86 mm in-plane resolution, 124 slices, 1.7-mm slice thickness). Slices were acquired coronally. These images were used to determine the CC area. In addition, DTI images were obtained using single-shot echo-planar imaging sequence with diffusion-sensitizing gradients applied in 25 encoding directions and b = 1000 s/mm^2. The acquisition for each encoding direction was repeated twice for magnitude averaging. Other scan parameters were: repetition time = 10 s, echo time = 85 ms, flip angle = 90°, 280mm field-of-view <correct?>, 20 slices, and 4 mm slice thickness. The acquisition matrix was 128x128 and the images were zero-filled interpolated on the scanner to a matrix size of 256x256. The in-plane resolution was 1.09mm x 1.09mm after interpolation.

The midsagittal slice was determined as the slice in which the cerebral aqueduct was observed most clearly. The CC was then traced and divided into regions using a semi-automated algorithm developed by the third author (BLJ). Hofer and Frahm's (2006) method was utilized to divide the CC into five regions. These authors proposed these divisions based on tractography of the origins and projections of the fibers in the CC. From anterior to posterior, the regions connect the I) prefrontal regions, II) premotor and supplementary motor regions, III) primary motor cortices, IV) primary sensory cortices and V) parietal, temporal, and occipital cortices of the left and right hemispheres. The location of these regions is shown in Figure 1. This method of partitioning the CC allows for better interpretation of the possible functional significance of any group differences in area measurements.

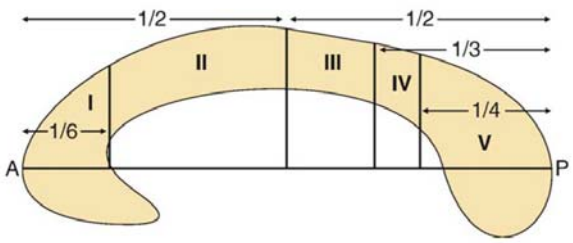


Figure 1: Hofer and Frahm's divisions of the CC

Reprinted from *Neuroimage,* 32, Hofer, S., Frahm, J. Topography of the human corpus callosum revisited-comprehensive fiber tractography using diffusion tensor magnetic resonance imaging, 989-94, Copyright (2006), with permission from Elsevier.

The first author (ADH), who was blind to group membership, conducted the CC traces. Intra-rater reliability was assessed for this method in a sample of 33 healthy controls from a different sample. Intra-rater reliability was 0.98 for overall CC size and ranged from 0.95 for region 3 to 0.98 for regions 1, 2 and 5. Therefore, all traces had very good intra-rater reliability. These measurements and those of another rater (ANB) were then compared to assess inter-rater reliability, which was 0.91 for the whole CC. Inter-rater reliability coefficients for the CC regions ranged from 0.85 for region 4 to 0.95 for region 1. These coefficients are comparable to those of another study of CC morphology in which intra and inter-rater reliabilities were above r = .92 (Johnson et al., 1994). Thus, we achieved acceptable inter-rater and intra-rater reliability using Hofer and Frahm's method to partition the CC.

Whole brain volume (WBV) was additionally calculated to control for differences in CC size that may be related to more general differences in brain size and volume. WBV was calculated using unnormalized volumes from SIENAX in FSL (Smith et al., 2004; Smith et al., 2002).

CC Integrity.

Diffusion Tensor Imaging (DTI) data, measuring fractional anisotropy (FA), was also obtained to examine white matter integrity in the CC. Our approach was to examine two regions that we felt would provide a representative measure of FA within the CC, one located in the genu and one in the splenium. This approach was highly conservative in order to ensure that we were obtaining a measurement from CC tissue that was not influenced by partial volume effects, which can occur if a voxel contains both CC and surrounding tissue. Because our axial slice thickness was 4 mm, we restricted our analysis to FA in the thickest part of the genu and the splenium that contained voxels entirely within the CC.

Regions of interest (ROIs) that encompass the genu and splenium separately were manually defined, based on FA maps. Manual determination was required to define these areas due to the great variation in size and shape of CC morphology across individuals, and, as a result, the ROIs varied in size. These ROIs were square in-plane but varied in the number of slices included. The following constraints were applied when defining the ROIs. Where possible, the ROI was drawn to at least one or two voxels past the obvious border of the CC with non-callosal tissue, which could be easily determined because the FA in the CC is much higher than in the surrounding tissue. In the *y* direction, the ROI was drawn to end at regions in which the CC appeared significantly thinner and/or the FA values for a voxel suggested partial volume effects. In the *x* direction, boundaries were drawn to be centered on the midline of the CC. The sizes of the ROIs for each participant ranged from 2,646 to 9,801 voxels, with an average of 4,932 voxels (SD = 1,756), for the

genu and ranged from 4,375 to 12,960 voxels, with an average of 6,531 (SD = 1,738), for the splenium due to individual variations in CC size and shape.

We created two measures based on FA to examine CC integrity. The first was the number of voxels within each of the ROIs separately (i.e. genu and splenium) that met criteria for being CC tissue. We had three criteria to ensure that the voxels contained callosal white matter. First, we selected only those voxels with an FA of at least .6. This value was selected based on the mean and standard deviation of FA values obtained from controls (mean age 39) in a DTI study of CC morphology (Rotarska-Jagiela et al., 2008). Although the sample in the Rotarska-Jagiela study was older than ours, it represents the values that would be observed in a "mature" CC. Second, we selected only those voxels in which the primary eigenvector did not deviate more than 11.48 degrees from the x-axis as CC fibers at the midsagittal slice are oriented along the x-axis. Finally, voxels in the slice above and below the voxel had to have an FA of at least .35, which would indicate that at least part of the volume in these neighboring voxel represented white matter of the CC. To ensure that these parameters for voxel selection were not driving the results, the threshold for the neighboring voxels and the x component of the primary eigenvector were varied in a subsample of participants to ensure that our results were not driven by the choice of thresholds (Hutchinson et al. 2008, unpublished data). Only results for FA >.35 and x < 11.48 degrees are presented because variations in these thresholds did not affect the results. The voxels identified by the algorithm were checked visually to confirm that they were located in the CC and that no voxels that were obviously part of the CC had been excluded by the algorithm and were not contained in the ROI.

Hence, one of our dependent measures was the number of voxels within the ROI that met the criteria for being midline CC tissue (i.e. FA > .6 and primary eigenvector could not deviate more than 11.48 degrees from the x-axis).

Our second approach was to determine, within each ROI, the peak FA value. Then a standard size slab (3 x 3 x 1 voxels in the *x*, *y* and *z* directions respectively) was drawn around that peak to provide a better estimate of the peak FA within the ROI. Hence, we obtained two measures for each ROI: one that provided an index of how many voxels were likely to meet our criteria for representing midline CC tissue, and one that provided an estimate of the peak FA value within the ROI.

Procedure

This study received ethics approval from the Colorado Multiple Institutional Review Board and the University of Adelaide Human Research Ethics Committee. Participants completed the initial screening as part of an introductory Psychology course. Participants meeting criteria for ADHD and a randomly selected control group were invited to come back for a neuropsychological testing session. A third session was held to acquire MRI and DTI data.

Results

Demographics

Sample characteristics and behavioral data are presented in Table 1. The ADHD group and control group were well matched in terms of gender, although the ADHD group was slightly older than the control group. This was

not expected to impact on the findings, given that the mean difference between the groups was less than one year.

Table 1

Demographics, symptomatology and IQ scores for the ADHD and Control groups

	ADHD (N = 23)		Controls (N = 21)				Effect Size
	Mean	SD	Mean	SD	t	P	Cohen's *d*
Age (years)	20.0	1.6	19.0	0.9	-2.72	.01**	0.81
Gender (% female)	39.1		42.9		0.06 (chi-square)	.80	
DSM-IV Symptoms							
Childhood symptoms							
Inattention	7.4	1.9	0.7	1.0	14.29	<.001***	4.37
Hyperactivity	6.5	2.0	1.1	1.3	10.61	<.001***	3.17
Overall (inattention and hyperactivity)	14.0	2.9	1.8	2.0	15.81	<.001***	4.81
Current symptoms							
Inattention	6.6	2.3	0.9	1.3	10.21	<.001***	3.05
Hyperactivity	5.0	2.2	1.5	1.3	6.54	<.001***	1.95
Overall (inattention and hyperactivity)	11.7	3.7	2.4	2.0	10.44	<.001***	3.11
Lifetime symptoms							
Inattention	8.1	1.3	0.8	1.1	19.72	<.001***	5.99

	ADHD (N = 23)		Controls (N = 21)				Effect Size
	Mean	SD	Mean	SD	t	P	Cohen's *d*
Hyperactivity	6.7	2.0	1.3	1.2	11.01	<.001***	3.36
Overall (inattention and hyperactivity)	14.8	2.5	2.1	1.8	19.37	<.001***	5.88
Attention measures							
Stroop interference (reaction time)	0.14	0.10	0.24	0.11	3.21	.03**	-0.97
Stroop facilitation (reaction time)	0.04	0.05	-0.04	0.06	-4.44	<.001***	1.33
IQ estimates							
Performance	114.4	9.9	113.1	10.9	-0.40	.69	0.12
Verbal	117.8	12.9	112.1	10.2	-1.61	.11	0.49
Full Scale	116.1	8.2	112.6	8.3	-1.39	.17	0.42
WJ-III							
Letter Word ID	100.8	8.0	104.9	9.1	1.56	.13	-0.47
Calculations	103.0	15.1	109.7	13.7	1.33	.20	-0.46

Note. DSM-IV ADHD symptoms assessed by self-report rating scales (Barkley & Murphy, 1998), WJ-III = Woodcock-Johnson Tests of Achievement, Third Edition. *p ≤ .05, ** p ≤ .01, ***p ≤ .001

Symptomatology

The DSM-IV symptom scores indicated that the ADHD group experienced significantly more inattention, hyperactivity, and overall symptoms in childhood, currently, and across their lifetime than controls. These differences represented very large effects (Cohen, 1988) (see Table 1).

IQ and academic achievement

Although the ADHD group met diagnostic criteria for ADHD, their WAIS-III scores revealed that their $FSIQ_{est}$, PIQ_{est} and VIQ_{est} estimates were comparable to those of the control group (refer to Table 1), as was their performance on the Woodcock Johnson III Test of Achievement. Overall, the two groups were equivalent in terms of IQ and academic achievement, which suggests that we were successful in obtaining a sample of individuals with ADHD who did not have comorbid learning disabilities.

Attention

In addition to group differences in ADHD symptoms, there were significant group differences in the Stroop measures of attention, with the ADHD group demonstrating more facilitation on this task. This measure assesses the failure to stay on task, as reading is faster when the participant simply reads the word rather than naming the ink color. Therefore, this result is consistent with the increased inattention reported by those in the ADHD group and represents a large effect size (Cohen, 1988). The ADHD group also demonstrated less interference on the Stroop task than controls. Although this was unexpected, the effect was considerably smaller than the difference on the Stroop facilitation score. Therefore, this result may reflect some fast guesses by the ADHD group.

Thus, the two samples were well matched in terms of gender, $FSIQ_{est}$, and academic achievement, which could independently contribute to group differences on the measures of CC size and integrity. In addition, the symptomatology scores indicate that the ADHD group experienced significantly more ADHD symptoms than controls, making it a suitable sample for examining CC morphology.

Whole brain volume

The two groups did not differ in terms of whole brain volume (WBV) (refer to Table 2). Nonetheless, WBV was used as a covariate in subsequent analyses in order to evaluate regional differences in CC area between ADHD and controls because WBV and CC area were positively and significantly correlated ($r = .32$, $p = .03$).

CC morphology

ANCOVAs were conducted to examine differences in total CC area and regions 1 through 5 with the group factor (ADHD, Control) and whole brain volume as a covariate. These analyses revealed regional differences in CC area between adults with ADHD and controls (refer to Table 2 and Figure 2). Specifically, region 1 was significantly smaller and regions 3 and 4 were significantly larger in adults with ADHD when compared to controls.

There were no significant differences in CC area between ADHD and Controls when males and females were considered separately, possibly due to the loss of statistical power resulting from smaller group sizes (see supplementary materials for separate gender data for the ADHD and control groups, and the results of the statistical analyses).

Table 2

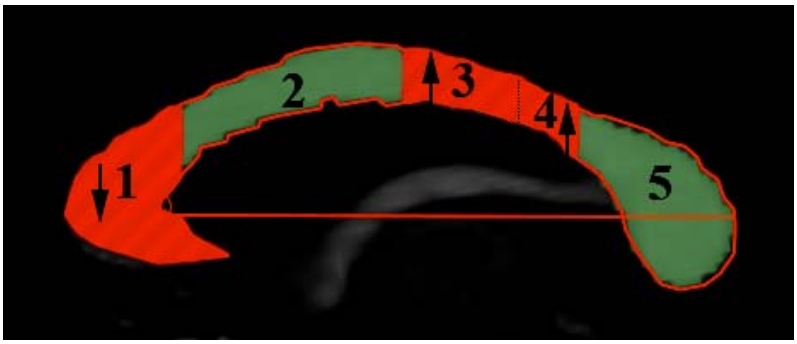
Area measurements of the corpus callosum and whole brain volumes for the ADHD and Control groups

	ADHD		Controls		F	p	Effect Size
Region	Mean	SD	Mean	SD			Cohen's *d*
Total corpus callosum	6.18	0.86	6.07	0.89	2.42	.10	0.13
1	1.48	0.23	1.57	0.19	6.61	<.01**	-0.46
2	1.79	0.31	1.76	0.25	1.96	.15	0.09
3	0.81	0.13	0.75	0.11	3.80	.03*	0.46
4	0.41	0.08	0.38	0.08	3.34	.05*	0.44
5	2.32	0.27	2.23	0.39	0.93	.40	0.25
WBV	1.21	0.12	1.19	0.10	-0.53	.60	0.16

Note: WBV = Whole brain volume. WBV was entered as a covariate in all F tests, * $p \leq .05$, ** $p \leq .01$

Figure 2

CC difference between adults with ADHD and Controls



Note. ↑ indicates that the region was significantly larger in adults with ADHD than controls. ↓ indicates that the region was significantly smaller in adults with ADHD than controls. Hofer and Frahm's CC regions – 1: projects to prefrontal regions, 2: projects to premotor and supplementary motor regions, 3: projects to primary motor cortices, 4: projects to primary sensory cortices, and 5: projects to parietal, temporal and occipital cortices.

Diffusion Tensor Imaging

In order to examine CC integrity, we calculated the number of voxels that met the specified criteria (directionality: <11.48 degrees from the x-axis, FA > .6, neighbouring voxels FA > .35), using area (of the genu or splenium) as a covariate to account for differences in the number of voxels that make up that region (see Table 3). These analyses revealed that the number of voxels in the genu was significantly greater for the control group [$F(1, 43) = 7.92$, $p = .001$], indicating that a greater proportion of the fibers in the genu have more myelination and/or structural integrity in the control than ADHD group. However, no group differences were found in the peak FA value within the ROI in the genu. In contrast, the number of voxels that met the criteria in the

splenium was significantly greater for the ADHD group [$F(1, 43) = 12.71$, $p < .001$], when the area of the splenium was entered as a covariate, suggesting that the fibers in the splenium are more myelinated and/or have greater structural integrity compared with controls. Like the genu, there was no difference in the peak FA between the groups for the splenial ROI.

Table 3

Fractional anisotropy measurements of the corpus callosum for the ADHD and Control groups

	ADHD		Controls		F	p	Effect Size
FA Measure	Mean	SD	Mean	SD			Cohen's *d*
Genu: # voxels	26.70	16.15	36.24	20.48	7.92	<.01**	-0.52
Genu: mean FA	0.77	0.06	0.77	0.05	0.19	.83	0.02
Splenium: # voxels	69.74	27.92	69.00	31.39	12.71	<.01**	0.02
Splenium: mean FA	0.83	0.06	0.82	0.08	0.13	.88	0.11

Note: WBV = whole brain volume, FA = fractional anisotropy, # voxels represents the number of voxels in the ROI that met our criteria for being considered CC tissue; Mean FA represents the mean FA of the voxels so identified as callosal tissue. The area of the genu was entered as a covariate in all F tests for FA measures of the genu and the area of the splenium was entered as a covariate in all F tests for FA measures of the splenium, ** $p \leq .01$

Lastly, we tested variations in the directionality criterion, reducing it to 8.11 degrees or increasing it to 18.19 degrees, and variations in the minimum FA of neighbouring voxels to ensure that these results were not specific to the

parameters we employed. None of these changes altered the results, suggesting that the criteria applied to analyze CC integrity were appropriate.

Relationship between CC morphology and measures of attention

The correlations between CC morphology and the measures of attentional control were computed for each group separately to examine the functional significance of differences in the CC. After Bonferroni corrections were applied, the partial correlations between CC area and performance on the Stroop task were not significant (see Table 4). Similar correlations were performed using DTI measures of CC integrity (for the genu and splenium separately) and measures of attentional control. The area of the genu and the splenium were used as covariates, respectively in these analyses. In the ADHD group, the reaction time measure of facilitation on the Stroop task was positively correlated with the peak FA in the splenium ($r = .49$, $p = .02$) but negatively correlated with the number of voxels meeting our criteria in the splenium ($r = -.54$, $p = .02$). Although these correlations represent large effects, they were not significant after Bonferroni corrections. There were no significant correlations in either the control group or ADHD after correcting for multiple comparisons.

Relationship between the CC and IQ

The relationships between total CC area and IQ estimates ($FSIQ_{est}$, $PIQ_{est,}$ and VIQ_{est}) were examined by separately calculating partial correlations for the ADHD and control groups, controlling for WBV (see Table 4). Interestingly, negative correlations were found between the PIQ_{est} and the area of the total CC and each CC region for controls. Although these correlations were not significant after Bonferroni corrections, the magnitude of the

correlation in controls represents a large effect size (Cohen, 1988). A Fisher's z test indicated that the correlations between total CC size and PIQ_{est} differed significantly between the ADHD and control groups ($z = 2.17$, 95% CI = 1.71 - 2.64, $p < .05$), suggesting that the lack of an association in ADHD individuals is atypical. We also examined the relationship between DTI measures of the CC and IQ, controlling for WBV. There were no significant correlations after correcting for multiple comparisons.

Table 4

Partial correlations between CC area and integrity measures and symptomatology, measures of attention and IQ, controlling for whole brain volume

		CC Area (MRI measures)						CC Integrity (DTI measures)			
		Whole CC (area)	Region 1 (area)	Region 2 (area)	Region 3 (area)	Region 4 (area)	Region 5 (area)	Genu FA	Genu voxels	Splenium FA	Splenium voxels
Attention Measures											
Stroop interference (reaction time)	ADHD	.13	.21	.15	.26	.12	-.08	-.16	.25	-.20	.28
	Controls	-.28	-.11	-.25	-.29	-.42	-.28	-.23	-.08	-.11	-.04
Stroop facilitation (reaction time)	ADHD	.13	.21	.15	.26	.12	-.08	-.34	-.23	.49	-.54
	Controls	-.05	-.13	-.12	.04	.02	.05	.10	.16	-.15	.32
IQ estimates											
Full Scale IQ	ADHD	.04	.20	-.21	-.12	-.15	.25	-.23	-.21	-.03	-.13
	Controls	-.34	-.11	-.33	-.43	-.28	-.30	.35	-.17	.23	-.37
Verbal IQ	ADHD	.05	.10	-.16	-.03	-.09	.30	-.18	-.17	-.08	-.37
	Controls	.04	.15	.09	-.06	.03	-.01	.21	-.57	.22	-.20
Performance IQ	ADHD	< -.01	.21	-.13	-.15	-.12	.02	-.14	-.12	.05	.25
	Controls	-.54	-.30	-.57	-.58	-.44	-.44	.35	.26	.14	-.38

Note. The area of the genu or the area of the splenium used as a covariate in correlations with integrity of the genu and splenium respectively. CC = corpus callosum

The relationship between ADHD symptoms, attention and CC area in ADHD

Stepwise regressions were conducted to examine the extent to which ADHD symptoms and performance on the Stroop task, a measure of attentional control, predict CC area in regions 1, 3 and 4 (the most anterior region, and posterior midbody of the CC) as these regions differed between the ADHD group and controls (see Table 5). The dependent variable was the area of the CC. The independent variables were a) lifetime symptoms of hyperactivity, b) lifetime symptoms of inattention c) Stroop facilitation and d) Stroop interference, with WBV included as a covariate. Table 5 indicates that the only significant predictor of the area of region 1 in ADHD participants was WBV, which accounted for 31% of the variance. In contrast, the area of the posterior midbody (regions 3 and 4) was significantly predicted by symptoms of hyperactivity, which accounted for 22% of the variance in the area of this region in the ADHD group. Greater area was associated with greater hyperactivity. Neither the size of the anterior CC region nor the posterior midbody was predicted by any of these variables in the control group, probably due to the reduced range, at least with regard to ADHD symptoms.

The same variables were entered in a regression with the DTI measures of CC integrity. In the ADHD group, the number of voxels in the genu was predicted by WBV alone. Interestingly, FA in the splenium and the number of voxels in the splenium that met our criteria were both predicted by Stroop facilitation. This was the only factor that predicted these measures, accounting for 24% in both cases. Similar analyses were performed for the control group excluding symptom scores. In the control group, the FA of the

genu was predicted by WBV alone. None of the variables predicted the number of voxels in the genu or the FA or number of voxels in the splenium.

Table 5: Prediction of CC size and integrity (stepwise linear regression)

Dependent variable	Independent variable	B Coefficient	t	p	R Square	F	p
Region 1							
ADHD	WBV	1.12E-006	3.116	0.005			
	Model Summary				0.316	9.712	.005
Controls	-	-	-	-	-	-	-
Region 3+4							
ADHD	Hyperactive Symptoms	0.197	2.455	0.023			
	Model Summary				0.223	6.027	.023
Controls	-	-	-	-	-	-	-
Genu FA							
ADHD	-	-	-	-	-	-	-
Controls	WBV	1.95E-007	2.105	0.049			
	Model Summary				0.189	4.430	.049
Genu voxels							
ADHD	WBV	6.57E-005	2.483	0.022			
	Model Summary				0.227	6.164	.022
Controls	-	-	-	-	-	-	-
Splenium FA							
ADHD	Stroop facilitation (reaction time)	0.558	2.599	0.017			
	Model Summary				0.243	6.754	.017
Controls	-	-	-	-	-	-	-
Splenium voxels							
ADHD	Stroop facilitation (reaction time)	-266.786	-2.570	0.018			
	Model Summary				0.239	6.607	.018
Controls	-	-	-	-	-	-	-

Discussion

The results of the current study are notable in that they demonstrate differences in the size and integrity of the CC between young adults with ADHD, who were screened for comorbid psychiatric disorders, and their healthy peers, who were of equivalent age and intellectual ability. Furthermore, these measures of CC structure were found to relate to aspects of ADHD symptomatology as well as performance on the attentionally-demanding Stroop task.

CC size

The current study is the first to demonstrate differences in CC area and composition between young adults with ADHD and controls. Our results indicate that the most anterior region of the CC was smaller in individuals with ADHD than controls and that the mid-posterior regions (regions 3 and 4 using Hofer and Frahm's method for partitioning the CC) were larger in ADHD compared with controls. In addition, FA measures in two ROIs, one in the genu and one in the splenium, suggest differences in white matter integrity and/or myelination, in young adults with ADHD. Since our ADHD sample was carefully selected to rule out comorbid conditions and did not differ in measures of intellectual ability from the controls, these differences are likely to be associated with neural processes specific to ADHD.

With regard to the differences in CC size, our findings of a smaller anterior section of the callosum in young adults with ADHD is consistent with prior reports of decreases in this area in children and adolescents with ADHD (Baumgardner et al., 1996; Giedd et al., 1994; Hynd et al., 1991). Although these differences were not confirmed in meta-analytic reviews of the research

literature (Hutchinson et al., 2008; Valera et al., 2006), these analyses did not take into account all of the methodological differences across the studies (e.g., in terms of comorbid conditions, gender, and ADHD subtypes), which may account for the null results.

Because the anterior section in Hofer and Frahm's (2006) segmentation method connects the prefrontal regions involved in executive functioning (see Funahashi, 2001 for a review), this decrement in size may be related to the compromise in executive function in children and adults with ADHD (refer to Boonstra et al., 2005; Willcutt et al., 2005 for meta-analytic reviews). In contrast, the midposterior regions (regions 3 and 4) in individuals with ADHD was significantly larger than in controls. Although one might assume that a larger area is associated with more nerve fibers or more myelinated nerve fibers and therefore faster interhemispheric transfer of information, research on individuals with schizophrenia provides an alternative interpretation. While individuals with schizophrenia have a larger CC than controls (Jacobsen et al., 1997) they nonetheless show impaired interhemispheric interaction (Barnett et al., 2007; Lohr et al., 2006). It has been suggested that larger CC area may reflect inefficient axonal pruning during development, when excess axons are eliminated while stronger connections are preserved (Low and Cheng, 2005). Thus, the larger posterior CC area may reflect a disruption in neuronal development.

Our findings support this interpretation with a larger CC size in these regions being associated with greater hyperactive symptoms in individuals with ADHD (see below for a detailed discussion). The link with hyperactivity, rather than inattentive symptoms, seems reasonable when one

considers that region 3 contains fibers that project to the primary motor cortices that are involved in motor control and voluntary movement. Other evidence suggests atypical development of motor regions in individuals with ADHD. For example, Shaw et al. (2007) found that the maturation of the motor cortex in children with ADHD, as measured by cortical thickness, may be atypical, reaching its peak four months ahead of controls. It is possible that this difference in the motor cortex is reflected in larger midposterior regions of the CC in adulthood. In addition, region 4, which contains fibers connecting the primary sensory cortices, was also significantly larger in adults with ADHD than controls. A recent event-related magnetoencephalography (MEG) study found that detection of tactile stimuli differed in adults with ADHD compared with controls, suggesting altered somatosensory processing (Dockstader et al., 2008). Therefore, our findings are consistent with those from other studies, which suggest that this mid-posterior region of the CC may be associated with atypical development in ADHD resulting in increased size relative to controls.

One region where we did not observe group differences was in the splenium. This finding stands in strong contrast to that of previous meta-analyses of CC morphology in children and adolescents, which have indicated that the splenium is smaller in children with ADHD than controls (Hutchinson et al., 2008; Valera et al., 2006). There are a number of potential explanations for this discrepancy. One possibility may be sample selection. Due to the high comorbidity between ADHD and learning disabilities (Friedman et al., 2003), the previous reported differences in splenial area may be linked to this co-morbid disorder. Our sample, in contrast, was carefully selected to exclude

comorbid learning disabilities and psychiatric disorders. However, at least one of the prior studies reporting a smaller splenium in adolescents with ADHD excluded both comorbid learning disorders and Conduct Disorder (Semrud-Clikeman et al., 1994). Therefore, learning disorders cannot fully account for this inconsistency. Another potential explanation for this discrepancy is that this effect is limited to younger individuals with ADHD. Although the anterior regions of the CC reach maturation in childhood, the posterior regions of the CC continue to change through adolescence (Barnea-Goraly et al., 2005; Giedd et al., 1999; Thompson et al., 2000). Given recent suggestions that ADHD is related to a delay in normal brain development (Shaw et al., 2007), the difference in the splenium may be due to a developmental delay of this region in children with ADHD, which is no longer present by the time the CC reaches maturation in early adulthood.

Integrity of the CC

In addition to differences in CC size, DTI measures revealed that the structure of representative areas within the genu and the splenium differed between adults with ADHD and controls. We observed that fewer voxels in the genu of our ADHD sample compared to controls had characteristics similar to those observed in a somewhat older healthy sample (Rotarska-Jagiela et al., 2008). This suggests that, compared to controls, individuals with ADHD have less myelinated fibers, a reduced number of fibers, or fibers with less structural integrity traversing this portion of the CC. Hence, this anterior area appears both to be smaller in area and to have a different composition than in controls. A difference in CC integrity was also observed between individuals with ADHD and controls in the splenium, even though

there was no group difference in size. Hence, these results provide the possibility that the integrity of fibers across the entire extent of the CC may be affected in individuals with ADHD. However, as our ability to clearly measure FA of the callosum was restricted to only the thickest regions (i.e., the genu and splenium) further research is needed to address this question. Nonetheless, our results suggest that differences in CC integrity can exist in the absence of differences in CC area.

The relationship between the CC, ADHD symptoms and attention

CC morphology was associated with behavioral measures of attentional control, suggesting that these aspects of CC morphology are related to the manifestation of ADHD in our sample. Most noteworthy, the area of regions 3 and 4, which were significantly larger in our ADHD and control group were predicted by hyperactivity symptoms. More specifically, larger regions were associated with greater hyperactivity. As these regions connect the primary motor and somatosensory cortices, their association with symptoms of hyperactivity further suggests that CC structure may be important in the etiology of ADHD.

Characteristics of splenial structure were also associated with behavior, namely facilitation on the Stroop task in ADHD even though we did not replicate differences in splenial size, as has been found in children and young adults. Greater facilitation was associated with a higher peak FA and a fewer number of voxels meeting our criteria as being typical CC tissue. Hence, multiple measures of structure of the posterior section of the callosum were associated with attentional control.

Study Limitations

Although our study found differences in CC structure between individuals with ADHD and controls and those differences were related to behavior, the current study had a number of limitations. Specifically, the participants were all college students and, consequently, high functioning adults with ADHD. Furthermore, they were selected to preclude comorbid learning or psychiatric disorders, which coexist with some frequency in samples of individuals with ADHD. Hence, our sample may not be representative of the adult ADHD population in general. This limitation is also one of the strengths of this study, as the ADHD sample was carefully selected to rule out comorbid disorders and was matched in terms of general intellectual abilities, making it more likely that the group differences we observed are attributable to ADHD.

A second limitation is that the average age of participants was limited in range, being between 19 and 20. Since brain development continues through young adulthood (Barnea-Goraly et al., 2005), our findings may not be representative of brain morphology in individuals with ADHD in later adulthood. This is especially true as some theories suggest that ADHD is associated with a maturational lag in brain development (Shaw et al., 2007) and CC structure continues to change until the late 20s (McLaughlin et al., 2007). In order to determine whether the differences we observed persist, a longitudinal study or a sample with an average age approximately 10 years older than in the current sample would be needed.

Third, our study was limited to participants with the 'combined' subtype of ADHD and may not generalize to those with either the

predominantly inattentive or predominantly hyperactive subtypes. In addition, most of the participants with ADHD were either taking or had taken stimulant medication during their lifetime. It is not known what effect these medications have on CC size or integrity. However, it is extremely difficult, if not impossible, to find a sample of adults with ADHD in the United States who have not been medicated if they have met the clinical criteria for ADHD since childhood, as was the case in our sample.

There were also limitations in some of the measures used in the current study. We could only obtain measures of FA in regions of the genu and the splenium due to the thickness of the slices that were obtained. This precluded us from being able to look at integrity in other CC regions that are linked to ADHD symptomatology, namely the midbody regions. In addition, we have had to infer the brain regions that are connected by these sections of the CC based on the prior work of Hofer and Frahm (2006), rather than being able to do so directly via tractography.

Finally, a large number of analyses were undertaken relative to the number of measures and participants in the current study. Although this increases the likelihood of type 1 errors, we used statistical procedures to correct for this possibility. Practically, it is difficult to obtain large samples with young adults with ADHD without comorbid conditions and whose intellectual abilities match those of a control group. We believe our analyses are warranted because of the rich data set available, but they will need to be confirmed by subsequent research.

Implications

The results of this study have a number of important implications. First, they provide additional evidence that ADHD in young adulthood is associated with atypical brain morphology, as has been observed for children and adolescents with ADHD. These results provide additional evidence that ADHD in adulthood is a true syndrome and that, if ADHD is associated with a developmental lag in brain development (see Shaw et al., 2007), it is not resolved by the late teens or early 20s. Second, it adds to a consistent body of evidence that the CC is affected in ADHD. Such a finding is consistent with the large body of research suggesting that interaction between the hemispheres is important for attentional control (see Banich, 2003 for a review). Future research that links measures of CC anatomy to CC functioning and measures of attentional control would help to clarify the role that interhemispheric interaction may play in the etiology of ADHD. Third, our results suggest that models of ADHD need to consider anatomical differences in white matter as well as differences in grey matter. Given that the CC is the largest nerve fiber tract connecting disparate regions of the brain, atypical CC morphology suggests that interactions between brain regions may be compromised in adults with ADHD. This is consistent with recent findings that suggest that functional connectivity, which occurs via white matter tracts, is atypical in adults with ADHD (Castellanos et al., 2008). In sum, our results provide evidence that the CC of young adults with ADHD varies in size and structure from controls, and that these anatomical characteristics are linked to symptomatology and attentional control.

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Chapter 4

Relationship Between Intelligence and the Size and Composition of the Corpus Callosum

Research examining CC morphology often fails to consider the contribution of the CC to cognitive function in addition to its structure. This is important in order to understand the role of the CC in healthy individuals as well as the potential consequences of atypical CC morphology, such as that observed in ADHD. The CC is involved in the interhemispheric transfer of information necessary for higher-order cognitive processes (Banich, 2003; Hoptman & Davidson, 1994). Therefore, general cognitive ability may be associated with the size and composition of the CC. IQ is of particular interest because it reflects a range of cognitive abilities that are integrated via the CC and it involves attentional processes that have been shown to be affected by compromise to the CC (Dimond, 1976; Ellenberg & Sperry, 1979; Holtzman & Gazzaniga, 1982; Kreuter, et al., 1972; Teng & Sperry, 1973). However, as discussed in section 1.4, the investigations of the relationship between CC morphology and IQ have found conflicting results (e.g. Allin et al., 2007; Luders et al., 2007).

The previous paper examined the relationship between CC morphology and ADHD symptoms, measures of attentional control and IQ in young adults with ADHD and healthy controls. The relationship between IQ and CC area was negative in healthy persons such that smaller CC area was associated with higher performance IQ. Although these correlations were not significant after correcting for multiple comparisons, they were of a large

magnitude (Cohen, 1988). A Fisher's z test also indicated that the correlation between CC area and performance IQ was significantly different in ADHD participants and controls. However, a subsequent power analysis indicated that a sample size of 49 participants would be a necessary to find a significant correlation ($p < .05$) of magnitude -.39 (the median correlation between CC area measurements and FSIQ and PIQ) with a power of 0.8. Therefore, an increased sample was necessary to determine the reliability of this finding.

The following study explores the relationship between CC size and IQ observed in the previous paper in more depth by increasing the sample of healthy controls in late adolescence and young adulthood. Specifically, the aim of this study was to examine the relationship between aspects of cognition, as indexed by IQ subtests, and CC area and integrity in healthy young adults in order to determine whether there is a relationship between IQ and CC area or integrity in healthy young adults, and to examine the influence of age on the relationship between IQ and CC morphology.

The relationship between both CC area and integrity and performance on two IQ subtests was examined separately for males and females due to some reports of gender differences in CC size (refer to section 1.1.2). However, this data was not presented in the paper due to the reduced power of these analyses and space limitations in the journal. The results of these analyses can be found in Appendix E.

It should be noted that the controls from the previous study were included in the following study. Therefore, the two samples are not independent. However, when the results were re-analyzed without the participants from study 2, it was demonstrated that the significant relationship

between the integrity of the genu and verbal IQ from the previous study (whole sample: $r = -.35$, $p = .003$) remained significant when the controls from the previous study were removed (reanalysis: $r = -.46$, $p = .05$). In addition, the significant relationship between the area of the midbody (region 3) and performance IQ (whole sample: $r = -.37$, $p = .002$) demonstrated a trend when the participants from study 2 were excluded (reanalysis: $r = -.25$, $p = .08$). Therefore, the inclusion of the control participants from the previous study was not thought to bias the results of study 3. The published version of the following paper can be found in Appendix D.

Title: Relationship between intelligence and the size and composition of the corpus callosum

Authors: A.D. Hutchinson[1, 2], J.L. Mathias[1], B.L. Jacobson[3], L. Ruzic[3], A.N. Bond[3], & M.T. Banich[2, 3]

Affiliations:

[1]School of Psychology, University of Adelaide, Adelaide, SA, Australia

[2]Institute of Cognitive Science, University of Colorado, Boulder, CO, USA

[3]Department of Psychology, University of Colorado, Boulder, CO, USA

Abstract

We investigated the relationship between the morphology of the corpus callosum (CC) and IQ in a healthy sample of individuals in their late teens and early twenties. The relationship between the area of the CC, measured at the midline, and IQ showed regional differences. We observed that a higher estimated performance IQ was associated with smaller area in the posterior regions of the CC, a finding that differs from a positive association previously observed in a somewhat older adult sample. In contrast, higher estimated verbal IQ was associated with decreased fractional anisotropy of the genu, an anterior portion of the CC. Age effects were also observed such that older age was associated with larger CC area. Our results suggest that CC morphology is related to cognitive performance, which may have implications for clinical populations in whom CC morphology is atypical.

Keywords:

Corpus callosum, intelligence, age, gender differences, DTI

Preface

In this paper we examine the relationship between intelligence, as measured by a brief IQ test, and the morphology of the corpus callosum (CC), which connects homologous areas of the left and right hemispheres of the brain and is the largest fiber tract in the human brain (Hynd et al., 1991; Hoptman and Davidson, 1994; Banich, 2003; Innocenti and Bressoud, 2003). An examination of the structure of the CC and its relationship to behavior is particularly apt for this special issue in honor of Prof Giovanni Berlucchi, who has been a pioneer in describing the functions of the CC. In his early work, Prof Berlucchi conducted ground-breaking research that characterized the function of the CC in cats (Berlucchi, 1965, 1966) and demonstrated its importance in binding together two halves of the visual world (Berlucchi and Rizzolatti 1968). He eloquently reviewed how the anatomy and physiology of the CC supports visual function (Berlucchi, 1972) and has shown how interhemispheric integration influences the processing of information in other brain regions, such as the superior colliculus (Antonini et al., 1979). This work was extended by looking at the larger role of the CC in learning in cats (Berlucchi et al., 1979) and examining issues of interhemispheric transmission in humans (Tassinari et al., 1983). The implications of such transmission in humans have also been considered, such as in work noting that the visuo-motor transfer of information is the longest lasting sign of callosal disconnection after traumatic brain injury (Peru et al., 2003). Finally, with his keen appreciation for the history of science, he considered how the work of Roger Sperry on the CC and that of David Hubel and Torsten Wiesel on visual processing, all three of whom received the Nobel prize in 1981, fits into the

tradition of neuroscientific research dating back to Cajal (Berlucchi, 2006). We are honored to be able to contribute a paper to this special issue in honor of Prof. Berlucchi's retirement as his work has informed both this particular article and the larger program of research in the Banich laboratory for years.

Introduction

Research with split brain patients, who have had the CC severed for the treatment of epilepsy, and those with agenesis of the CC, where the CC does not develop fully or is completely absent, has indicated that the CC is crucial to the interhemispheric transfer of information (Dimond, 1976; Kreuter et al., 1972; Sperry et al., 1969). In addition to binding together the two halves of the sensory world that are represented in opposite hemispheres, the CC also appears to play a role in attentional control (see Banich, 2003 for a review). As initially described by Banich and Belger (1990), interaction between the hemispheres is beneficial to task performance under conditions of high attentional demand but is detrimental to performance under conditions of low demand. Based on a large body of empirical work (e.g., Banich and Belger, 1990; Belger and Banich, 1992, 1998; Weissman and Banich, 1999, 2000), Banich and Brown (2000) argued that three factors determine whether interhemispheric interaction is beneficial or detrimental to task performance. One factor is the degree to which the callosal transfer of information increases the time required for processing information. A second factor is the extent to which a task's computational complexity taxes the processing resources of a single hemisphere. The third factor is the capacity of an individual's CC to transfer information between the hemispheres.

According to this model, it is generally beneficial for information to be processed by a single hemisphere when a task is computationally simple. Because the transfer of information between the hemispheres engenders a cost in time, it will be faster for a single hemisphere to perform the task when it has the capacity to do so. However, when tasks are more demanding, interhemispheric interaction leads to better task performance because the processing load can be divided between the hemispheres. Hence, the benefit of recruiting additional resources by using both hemispheres outweighs the time cost of CC transfer, making it advantageous compared to within-hemisphere processing (for a review refer to Banich, 1995, 1998, 2003; Banich and Brown, 2000). However, atypical morphology of the CC, which can occur with multiple sclerosis (Pelletier et al., 2001), schizophrenia (Shenton et al., 2001), Alzheimer's disease (Wang et al., 2005), traumatic brain injury (Mathias et al., 2004), and attention deficit hyperactivity disorder (Hutchinson et al., 2008; Valera et al., 2006), may compromise the ability of the CC to effectively distribute the processing load. As a result, interhemispheric interaction may be less advantageous in boosting task performance on complex tasks.

Given this model, one might expect a relationship between performance on cognitive tasks and CC structure. In fact, there is evidence supporting such a relationship between IQ and CC morphology in studies of clinical populations in which the CC is affected. For example, two patients with tumors located in the splenium of the CC have been found to have impaired performance IQ but relatively intact verbal IQ (Osawa et al., 2006). In another study, the area of the CC in males who were diagnosed with lacunar

infarction (stroke) and white matter abnormalities was positively correlated with both performance and verbal IQ (Yamauchi et al., 1994). In addition, CC area was smaller in these patients. The authors concluded that intellectual decline is associated with atrophy of the CC after stroke.

A similar relationship has been observed in a number of developmental studies. Adolescents with mental retardation, and by definition low IQ, are more likely to show thinning of the CC (Spencer et al., 2005) and reduced white matter density in the posterior CC (Spencer et al., 2006). Other studies have found a relationship between CC size and IQ in children and adolescents who were born pre-term, such that a smaller CC was associated with a lower IQ (e.g., Allin et al., 2007; Caldu et al., 2006; Narberhaus et al., 2007; Peterson et al., 2000). Similarly, in individuals with epilepsy, a larger posterior CC area has been associated with higher IQ (Strauss et al., 1994). Therefore it is possible that IQ and CC morphology are related, particularly for posterior regions of the CC.

Not withstanding these findings, the evidence for an association in neurologically intact individuals is generally equivocal. In a large sample of healthy individuals ranging in age from 6 to 88 years, a measure related to CC morphology (which was interpreted to represent a thinner and more concave anterior body of the CC) was associated with higher IQ, while conventional measures of CC size were not (Peterson et al., 2001). Similarly, other studies have failed to find a relationship between CC area and IQ, including a study by Nosarti et al. (2004) of neurologically intact 14- to 15-year olds and one by Tramo et al. (1998) who examined this issue in monozygotic twins. Moreover, two studies that used voxel-based morphometry to examine white/gray matter

volume failed to find a significant relationship between white matter in the CC and intelligence (Haier et al., 2004, 2005)

In contrast, other studies have found a relationship between IQ and the CC in healthy individuals. In a twin study, Hulshoff Pol et al. (2006) examined which brain regions show a high degree of heritability and are related to IQ, a trait which is also known to be heritable (Plomin and Spinath, 2004). They examined monozygotic and dizygotic twins and found that the structure of the CC was highly heritable (0.82) and that CC white matter density shared a genetic origin with IQ, such that greater white matter density was correlated with higher IQ. However, they also found that environmental influences were associated with white matter density of the anterior callosum, suggesting that not all portions of the CC have equal genetic influence.

Moreover, Luders et al. (2007) found significant positive correlations between IQ and the thickness of the CC across the posterior portion of the CC (posterior body, isthmus, anterior portion of the splenium) and across a portion of the anterior midbody in healthy adults. In their study, thickness was measured as the distance between points on the superior and inferior surfaces of the CC on the midsagittal section of the brain. Interestingly, these relationships were less pronounced for females. In contrast, Allin et al. (2007) observed that higher IQ was associated with a smaller posterior section of the CC in adolescents (mean age of 15) and adults (mean age of 22) who were controls for a sample of individuals born pre-term. In this latter study, the CC was divided into quarters (anterior, midanterior, midposterior, posterior). One possible explanation for the differences in the direction of the relationship between the CC and IQ reported by Luders et al. (2007) and Allin et al. (2007)

is that the age of participants varied in these two studies. The CC continues to develop throughout adolescence and into early adulthood (Barnea-Goraly et al., 2005; Giedd et al.. 1999; Thompson et al., 2000). As such, the relationship between CC size and IQ may vary depending on an individual's age.

Given these contradictory findings, the goal of the present study was to examine the relationship between CC area and IQ in a group of individuals aged 14-25. There were two main objectives. First, we wanted to determine whether the results of Allin et al. (2007), which showed a negative relationship between IQ and posterior CC area, could be replicated in a sample whose ages spanned the two ages (age 15, age 22) examined in their study. Second, we investigated the potential influence of age on CC area and its relation to IQ. In doing so, we explored whether the relationships between CC area and integrity differed for estimates of verbal IQ (VIQ_{est}) and performance IQ (PIQ_{est}), given that these aspects of intelligence have been found to be somewhat dissociable, and whether patterns differed for males and females given reports of gender differences in CC size (Bishop and Wahlsten, 1997; Sullivan et al., 2001). This study should improve our understanding of CC development and its relationship to intellectual abilities.

Method

This study was approved by the Colorado Multiple Institutional Review Board and was conducted in accordance with the Helsinki Declaration.

Participants

Thirty-one males and 40 females from the general community, aged between 14 and 25 years (mean age = 19.2, SD = 3.3), participated in this study.

MRI Acquisition and Analyses

T-1 weighted 3D-SPGR anatomical images were collected on a 3 T GE-Signa MR scanner (repetition time = 9 ms, echo time = 2.012 ms, flip angle = 10°, inversion time = 500 ms; 220 mm field of view, 256 x 256 matrix, 0.8594 mm x 0.8594 mm in-plane resolution, 124 slices, 1.7-mm slice thickness). Slices were acquired coronally. These images were used to determine CC area. In addition, DTI images were obtained using single shot echo planar sequence of 25 gradient directions, each with a weighting of b = 1000 s/mm^2 and NEX = 2, along with one volume without diffusion weighting. The acquisition matrix was 128 x 128 and the images were zero-filled to 256 x 256 (repetition time = 10000 ms, echo time = 85 ms, flip angle = 90°, 128 x 128 matrix, 1.09 mm x 1.09 mm in-plane resolution, 20 slices, 4 mm slice thickness).

IQ Measurement

Participants completed the two subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI), consisting of the Matrix Reasoning

and Vocabulary subtests (Wechsler, 1999). Matrix Reasoning provides an estimate of performance IQ (PIQ_{est}) and Vocabulary provides an estimate of verbal IQ (VIQ_{est}).

CC Measurement

The midsagittal slice was defined as that slice in which the cerebral aqueduct could be observed most clearly. The CC in that slice was then traced and divided into five regions, using a semi-automated algorithm developed by BLJ. Hofer and Frahm's (2006) five subdivisions of the CC were utilized because they are based on the origins and projections of the fibers in the CC, as determined by tractography. These regions are defined by drawing a line between the most anterior and posterior points of the CC. Divisions are placed perpendicular to this line, at 1/6, 1/2, 2/3, and 3/4 of its length, thus dividing the CC into 5 regions. These subdivisions connect, from anterior to posterior I) prefrontal regions, II) premotor and supplementary motor regions, III) primary motor cortices, IV) primary sensory cortices and V) parietal, temporal, and occipital cortices.

Although one rater (ADH) conducted all of the CC measurements, intra-rater and inter-rater reliability of the CC measurements were assessed in a subset of 33 participants from the current sample. Intra-rater reliability was assessed by having ADH redo the area measurements for these participants, while being blinded to the original scores. When these measurements were compared, total CC size had an inter-class correlation coefficient of 0.98 and reliability coefficients for the CC regions ranged from 0.95 for region 3 to 0.98 for regions 1, 2 and 5. Inter-rater reliability was calculated for the CC measurements of the first author (ADH) and the fifth author (ANB), yielding

coefficients of 0.91 for total CC size and between 0.85 for region 4 and 0.95 for region 1 for CC regions. Thus, this method had very good intra-rater and inter-rater reliability.

Whole brain volume (WBV) was additionally calculated to control for differences in CC size that may be related to more general differences in brain size and volume. WBV was calculated using unnormalized volumes from SIENAX in FSL (Smith et al., 2002, 2004).

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) data, yielding a measure of fractional anisotropy (FA), was also obtained to examine the white matter integrity of the CC. FA is a measure of the diffusion of water molecules along the direction of the axon and provides a quantitative metric of white matter integrity. Our approach was to examine two regions that we believed would provide a representative measure of FA within the CC, one located in the genu and one in the splenium. This approach was exceedingly conservative in order to ensure that we were obtaining a measurement from CC tissue that was not influenced by partial volume effects, which would occur if a voxel contained both CC and surrounding tissue. Because our axial slice thickness was 4 mm, we restricted our analysis to FA in the thickest part of the genu and the splenium that contained voxels entirely within the CC.

To obtain FA measures in the genu and splenium, regions of interest (ROIs) that encompassed each of these regions separately were manually defined based on FA maps. Manual determination was required to define these areas due to the variation in size and shape of the CC across individuals and, as a result, the ROIs varied in size. These ROIs were square in-plane but

varied in the number of slices that were included. When defining the ROI, the following constraints were applied. Where possible, the ROI was drawn to at least one or two voxels past the obvious border of the CC with non-callosal tissue, which could be easily determined because the FA in the CC is much higher than in the surrounding tissue. In the *y* direction, the ROI was drawn to end at regions in which the CC appeared significantly thinner and/or the FA values for a voxel suggested partial volume effects. In the *x* direction, boundaries were drawn to be centered on the midline of the CC. The sizes of the ROIs ranged from 3,174 to 28,717 voxels, with an average of 8,896 voxels (SD = 4,442) for the genu and ranged from 2,304 to 8,060 voxels, with an average of 4,928 (SD = 1,188) for the splenium.

We then determined the number of voxels within this ROI that met a set of criteria suggesting that they indeed represented CC tissue. First, because CC fibers at the midsaggital slice are oriented along the *x* axis, the primary eigenvector could not deviate more than 11.48° from the *x* axis. Second, based on mean and SD of FA values from controls (mean age = 39) in a DTI study of CC morphology undertaken for other purposes (Rotarska-Jagiela et al., 2008), the voxel had to have an FA of at least .6 in order to ensure that the voxel was CC white matter. Although the sample in the Rotarska-Jagiela study was older than ours, it represents the values that would be observed in a "mature" CC. Finally, it was important that the voxels in the slices above and below the voxel in question had an FA value indicating that at least a portion of it contained white matter of the CC. Therefore, based on FA values from Rotarska-Jagiela et al. (2008), the third requirement was that the neighboring voxels had an FA of at least .35, which would indicate that at

least part of the volume in that voxel represented white matter of the CC. The threshold for the neighboring voxels and the *x* component of the primary eigenvector were varied in a subsample of participants to ensure that our results were not driven by the choice of thresholds (Hutchinson et al., 2008, unpublished data). Only results for FA >.35 and $x < 11.48$ degrees are presented because variations in these parameters did not affect the results. The voxels identified by the algorithm were checked visually to confirm that they were located in the CC and that no voxels that were obviously part of the CC had been excluded by the algorithm and, consequently, were not contained in the ROI. One of our dependent measures was the number of voxels within the ROI that met the criteria for being midline CC tissue (i.e., FA > .6 and primary eigenvector could not deviate more than 11.48 degrees from the *x* axis).

We also took a second approach to obtaining a representative index of peak FA within each ROI. The peak FA value within the ROI was determined and then a standard size slab (3 x 3 x 1 voxels in the *x*, *y* and *z* directions respectively) was drawn around that peak. Hence, we obtained two measures for each ROI: one that provided an index of how many voxels were likely to meet our criteria for representing "mature" midline CC tissue, and one that provided an estimate of the peak FA value within the ROI.

Results

The CC measurements for this sample are presented in Table 1. The total CC area measurements observed were within the range of CC measurements observed in the samples of healthy controls examined by other studies [5.10cm^2 (Zanetti et al., 2007) to 6.51cm^2 (Miyata et al., 2007)].

Therefore, the CC measurements in the current sample appear to be comparable to those in other studies.

Table 1

Midsagittal CC area measurements using Hofer and Frahm's (2006) divisions

	Total CC (cm^2)	1	2	3	4	5	WBV x 10^6 mm^3
Mean	6.29	1.59	1.82	0.85	0.40	2.36	1.20
SD	0.94	0.26	0.27	0.18	0.08	0.36	0.11

Note: CC = corpus callosum, WBV = whole brain volume

Relationship Between CC Area and Age

Our goal was to determine the specific relationship between age and CC area. WBV was associated with increased CC area (r = .29) and modestly associated with age (r = -.06) in our sample. Thus, to determine whether there was any relationship between CC area and age that could not be accounted for by WBV, we calculated partial correlations controlling for WBV. There was a positive relationship between total CC area and age (r = .28, p = .02) (see Figure 1). Interestingly, although regions 1, 2, 4 and 5 showed small to medium positive (albeit non-significant) correlations with age, region 3, which connects the primary motor cortices, was significantly negatively correlated with age. This correlation represents a moderate relationship (Cohen, 1988) and remained significant after correcting for multiple comparisons. However, this relationship may be gender specific, as there was a negative correlation for females (r = -.51, p = .001) but not for males (r = .06, p = .78). Moreover,

this was the only significant correlation between area for any region of the CC and age for female participants. In contrast, the size of regions 1 (r = .36, p = .05) and 2 (r = .39, p = .04) were significantly correlated with age in males, as was total CC size (r = .46, p = .01), such that a larger CC was associated with older age in males. However, these correlations did not remain significant after Bonferonni corrections for multiple comparisons.

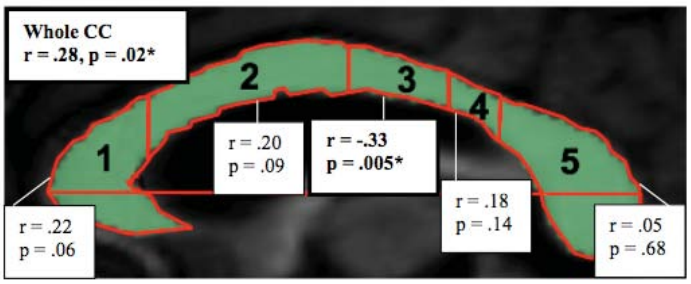

Figure 1: Correlations between CC area and age, controlling for whole brain volume

* = p < .05

Relationship Between FA and Age

Partial correlations were conducted between measures of FA, which serve to index CC integrity, and age with WBV entered as a covariate. There were no significant correlations between FA measures of CC integrity and age for the group as a whole. However, when males and females were considered separately, there was a significant positive correlation between the number of voxels that met the criteria in the genu and age for males (r = .49, p = .008), which remained significant after correcting for multiple comparisons.

Relationship Between CC Area and IQ

In our sample, estimated FSIQ ($FSIQ_{est}$) ranged from 79 to 140 with a mean of 106.9 (SD = 10.8). The Matrix Reasoning subtest scaled score (which was used as an estimate of performance IQ, PIQ_{est}) ranged from 6 to 17, with a mean of 11.9 (SD = 2.2) and the Vocabulary subtest scaled score (which was used as an estimate of verbal IQ, VIQ_{est}) ranged from 3 to 19, with a mean of 10.8 (SD = 2.6).

The relationships between total CC area and IQ estimates were examined in three ways: 1) by simple bivariate correlations, 2) by partial correlations, controlling for WBV because WBV was modestly related to $FSIQ_{est}$ (r= .19), PIQ_{est} (r = .34) and VIQ_{est} (r = .05), and 3) by correlations controlling for both WBV and age due to the relationship between CC area and age discussed above (see Table 2).

Because prior studies have noted a relationship with posterior sections of the CC, we initially focused on this region. To do so we divided the CC in half calculating the anterior half as the sum of areas 1 and 2, and the posterior half as the sum of areas 3, 4 and 5. This analysis revealed a significant negative correlation between $FSIQ_{est}$ and the posterior half that passed Bonferroni correction both when WBV (r= -.25) and when WBV and age (r= -.24) were considered as covariates. No relationship was observed for the anterior half.

To examine the nature of this relationship in more detail, we investigated the relationship between PIQ_{est} and VIQ_{est} with each of the CC regions (areas 1-5). A negative correlation was observed for the simple bivariate correlation between the area of region 3 and PIQ_{est} (r = -.26, p =

.031). Although this correlation was not significant after Bonferroni corrections, it passed Bonferonni correction when WBV was entered as a covariate ($r = -.37$, $p = .002$) (see Figure 2). Negative correlations (that did not pass Bonferonni corrections) were also found between PIQ_{est} and the area of regions 4 and 5, possibly suggesting a larger relationship between PIQ_{est} and posterior regions of the CC. There were no significant correlations between VIQ_{est} and CC area.

When males and females were considered separately, none of the correlations remained significant after Bonferroni corrections for multiple comparisons, possibly due to reduced statistical power associated with the smaller group sizes.

Table 2

Correlations between PIQ and VIQ estimates and CC area and fractional anisotropy (FA) with no covariates, WBV alone, and WBV and age entered as covariates

	No covariates		Covariate: WBV		Covariate: WBV and age	
	PIQ	VIQ	PIQ	VIQ	PIQ	VIQ
CC Area						
Total CC	.01	-.04	-.10	-.05	-.21	-.12
1	.12	.01	.02	-.01	-.06	-.06
2	.00	-.01	-.11	-.03	-.19	-.08
3	-.26	-.19	**-.37***	-.20	-.30	-.15
4	-.06	-.03	-.18	-.05	-.25	-.09
5	-.15	-.13	-.25	-.15	-.28	-.16
CC FA						
Genu: # voxels	.05	-.27	-.08	-.30	-.15	**-.35***
Genu: Mean FA	.04	-.24	-.06	-.26	-.08	-.27
Splenium: # voxels	-.05	-.01	-.07	-.01	-.15	-.05
Splenium: Mean FA	-.07	.09	-.06	.09	-.04	.11

WBV = whole brain volume, CC = corpus callosum, FA = fractional anisotropy, # voxels represents the number of voxels in the ROI that met our criteria for being considered CC tissue; Mean FA represents the mean FA of the voxels so identified as callosal tissue, * = significant after Bonferroni corrections for multiple comparisons

Relationship Between Fractional Anistropy and IQ

The relationships between CC integrity, as indexed by our two FA measures, in the genu and splenium and estimates of IQ were examined in the same manner as CC area (see Table 2). Lower VIQ_{est} was associated with increased integrity, as indexed by both measures of FA for the genu. These correlations were also present when controlling for WBV alone and both WBV and age. However, after corrections for multiple comparisons, the only effect that remained significant was the relationship with the number of voxels identified in the genu when controlling for both WBV and age (see Figure 3). There were no significant correlations between PIQ_{est} and FA.

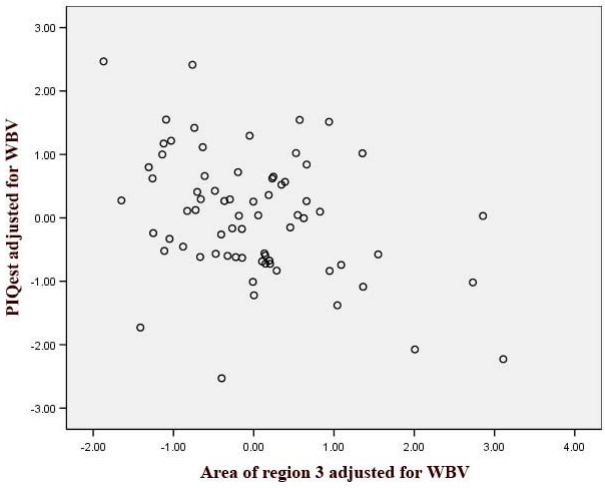

Figure 2: The relationship between PIQ_{est} (adjusted for WBV and age) and the size of region 3 (adjusted for WBV and age)

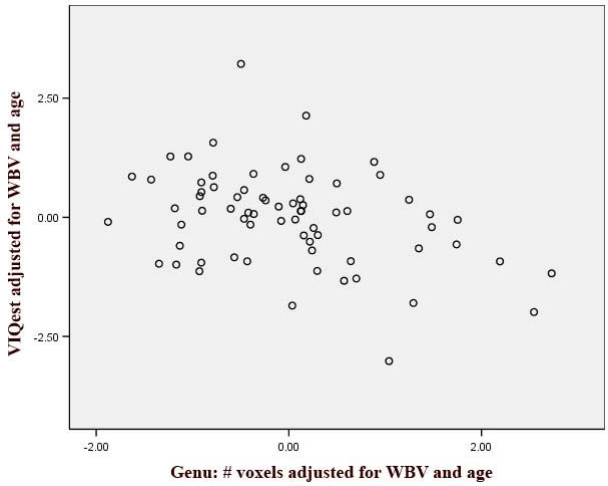

Figure 3: The relationship between VIQ_{est} (adjusted for WBV and age) and FA (number of voxels) in the genu (adjusted for WBV and age)

Discussion

The present study provides insight into some of the factors that are associated with CC morphology. Consistent with the findings of Allin et al. (2007), our data suggest that smaller areas in posterior regions of the CC are associated with higher intelligence. This effect was significant for region 3 with a trend for regions 4 and 5, and appears to be mediated by PIQ_{est} (rather than VIQ_{est}), an issue which we discuss in more detail below. In our study, participants' ages ranged from 14 to 25 with a mean age of 19, spanning the two developmental time points – ages 15 and 22 – examined by Allin et al. (2007). Although our results and those of Allin et al. (2007) are in accord, they conflict with the findings of Luders et al. (2007) who reported that higher IQ was associated with a thicker posterior CC in healthy adults with a mean age of 28. Our study differed from that of Luders et al. (2007) who examined CC thickness, rather than CC area and integrity (as was done in the current study). However, this difference seems unlikely to account for the conflicting

results, especially given that our results are consistent with those of Allin et al. (2007).

A more likely explanation for the difference in findings is that they arise from developmental factors. Although it had been traditionally thought that the CC reached maturity by early adolescence (Yakolev and Lecours, 1967), more recent work suggests a maturational gradient that extends into young adulthood (Giedd et al., 1999; Thompson et al., 2000; Barnea-Goraly et al., 2005). We propose, based on prior work done in our laboratory (for a review refer to Banich, 1995, 1998, 2003; Banich and Brown 2000), that during adolescence and early adulthood, the negative relationship between CC measures and IQ relates to the processing capacity of each hemisphere. By this account, when an individual has a high IQ, there is less need to recruit the other hemisphere to increase the computational power available to complete complex tasks than in lower IQ individuals. Therefore, if youth and young adults with a high IQ have had less need and therefore less experience in requiring interhemispheric interaction to meet task demands, their CC fibers may not have needed to become as myelinated as in less intelligent individuals.

There is precedent for the idea that individual differences in experience can affect the myelination of the CC. For example, adults who began musical training before the age of 7 have been reported to have a larger anterior half of the CC (Schlaug et al., 1995) and musicians display a significantly greater FA in the genu of the CC (Schmithorst and Wilke, 2002). Moreover, individuals who are illiterate have been shown to have a thinner posterior midbody, which is thought to contain fibers connecting parietal regions that are involved in

reading (Castro-Caldas et al., 1999). In a similar manner, less of a requirement to integrate information between the hemispheres in adolescents and young adults with higher IQs may result in less myelination.

However, an explanation is also needed for the findings of Luders et al. (2007) who found that, in an older sample, a larger posterior CC area was associated with higher IQ. Considering that as one ages the repertoire of abilities to be performed becomes more demanding, our account would suggest that it is likely that within-hemisphere resources will become less able to meet task demands. Under such conditions, there will be an increased benefit from the recruitment of the other hemisphere through interhemispheric interaction. If individuals with a higher IQ can handle more cognitively demanding tasks, with time there may be a switch to increased reliance on interhemispheric interaction. The net result would be the relationship observed by Luders et al. (2007): a larger CC is associated with a higher IQ. This hypothesis could be effectively examined in future studies that take a longitudinal examination of the relationship between CC area and IQ during young adulthood.

We also found that integrity of white matter (as measured by FA) in the genu, but not the splenium, was related to IQ. More specifically increased FA in the genu, which connects prefrontal regions, was associated with lower VIQ_{est}. This finding demonstrates the value in examining both CC area and integrity because the relationship with different aspects of IQ (VIQ_{est}, PIQ_{est}) varied for these different measures. What is notable is the consistency in that both relationships with area and FA are negative, such that larger CC size or increased FA (which is thought to index myelination among other aspects of

CC morphology), are each associated with decreased IQ, most likely for the reasons described above.

It is not clear in the present study why there is an association of PIQ_{est} with aspects of posterior CC morphology and an association of VIQ_{est} with aspects of anterior CC morphology. One possible explanation is that the processes tapped by each subtest used to provide estimates of VIQ and PIQ rely on different brain regions and hence show different relationships with regions of the CC. For example, the Matrix Reasoning subtest, requires spatial processing that relies on parieto-temporal areas of the brain, connected through more posterior regions of the CC. In contrast, the Vocabulary subtest may rely on temporal and more importantly frontal regions involved in language and semantic processing, which do send fibers through the splenium but may send some fibers through the genu. But as noted in the limitations below, the different associations of VIQ_{est} and PIQ_{est} with CC morphology must be interpreted cautiously.

The limitations of our study should be considered as well. The current sample size is relatively modest and will need to be replicated with a larger sample. Furthermore, although our findings were consistent across CC regions and whether covariates were included or not, they did not always reach significance when taking multiple corrections into account. Our FA measures were also restricted to the genu and the splenium preventing an examination of the potential relationship between IQ and FA of the CC midbody. In addition, our estimates of IQ were not drawn from the WAIS but rather we used the two subtest version of the WASI, which is a short form of the WAIS intended for use in screening, research or reassessments (Alexrod,

2002; Psychological Corporation, 1999). Hence, our measure of $FSIQ_{est}$, VIQ_{est}, and PIQ_{est} provide a quick estimate of intellectual abilities. We should note that because of the limitations of the WASI, the fact that PIQ_{est} seemed to be a better predictor of posterior CC area than VIQ_{est} and that VIQ_{est} was a better predictor of FA in the genu should be interpreted cautiously.

Conclusions

The present study found some evidence for a relationship between IQ and CC size, with smaller posterior regions of the CC size being associated with higher PIQ_{est}. This finding is consistent with prior research of Allin et al. (2007) who, although it was not the focus of their study, found a similar relationship with IQ in individuals whose age was comparable to that of the current sample. Although our finding is at odds with that of Luders et al. (2007), who report that a larger posterior CC is associated with higher IQ in a sample whose mean age was about 10 years older than ours, we propose that it may reflect continued development of the CC. We also found a relationship between estimated VIQ and the integrity of the genu, once again negative in direction. These findings emphasize the need to consider the regions of the CC separately, as they not only connect different brain regions but they also appear to have different relationships with IQ and age. They also highlight the importance of measuring both CC size and integrity. Finally, this study suggests that differences in CC size can have consequences for cognitive processing. As such, it raises the possibility that atypical CC morphology observed in some clinical populations, such as multiple sclerosis (Pelletier et al., 2001), schizophrenia (Shenton et al., 2001), Alzheimer's disease (Wang et al., 2005), traumatic brain injury (Mathias et al., 2004), and attention deficit

hyperactivity disorder (Giedd et al., 2001) may have implications for the cognitive profile of deficits observed in these groups.

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Chapter 5

Discussion

The findings of three studies were presented in this thesis, each addressing a specific aim, namely:

1. To conduct a meta-analysis on existing research findings on CC size in children and adolescents with ADHD in order to (a) reconcile the inconsistent findings in the literature, (b) consider research on CC size in children and adolescents with ADHD and comorbid conditions, and (c) explore possible gender differences in CC size in ADHD.
2. To examine CC area and integrity in young adults with attention deficit hyperactivity disorder compared with healthy controls in order to (a) determine whether the differences in CC size, observed in children and adolescents with ADHD, are present in young adults with ADHD, (b) examine regional differences in CC size at this later stage of development, (c) determine whether there are differences in CC integrity, as measured by fractional anisotropy, in young adults with ADHD compared with healthy controls, and (d) explore the functional consequences of atypical CC morphology by examining the relationship between CC measures (size and integrity), and performance on the Stroop task, which requires attentional control, and ADHD symptoms.
3. To examine the relationship between aspects of cognition, as indexed by IQ subtests, and CC area and integrity in order to (a) determine

whether there is a relationship between IQ and CC morphology (area and integrity) in healthy young adults, and (b) examine the influence of age on the relationship between IQ and CC morphology.

This discussion will compare the results of the first two studies, which examined CC morphology in ADHD. It will then discuss the findings related to IQ and the CC. Finally, limitations to this research and future directions will be outlined.

5.1 Corpus Callosum Morphology in ADHD

A meta-analysis was conducted to consolidate the findings of existing research that examined differences in the CC of children and adolescents with ADHD when compared to their healthy peers. The second study endeavored to extend this research by examining the CC of young adults with ADHD.

5.1.1 The splenium.

The current meta-analysis concluded that the splenium was smaller in ADHD compared to healthy controls. Therefore, the splenium was of particular interest in the second study. However, this found that there was no difference in the area of the splenium in young adults with ADHD and healthy controls. The latter sample was carefully screened to exclude learning difficulties, along with other comorbidities, which could be the source of the difference in the splenium observed in the meta-analysis. Three of the four studies contributing data to the effect size for the splenium in the meta-analysis included ADHD participants with comorbid Conduct Disorder or Oppositional Defiant Disorder (Giedd et al., 1994; Hill et al., 2003; Lyoo et al.

1996). However, this does not account for the smaller splenium found by Semrud-Clikeman et al. (1994) because they excluded comorbid learning disorders and psychiatric conditions.

Another possibility is that this difference resolves with age. Shaw et al. (2007) examined growth trajectories of cortical thickness in a group of children and adolescents with ADHD and matched controls. These authors found that peak thickness was reached at a later age in the children and adolescents with ADHD compared with controls although there was no difference in peak cortical thickness. Therefore, they argue that ADHD is characterized by a developmental lag in brain development as opposed to atypical development (Shaw et al., 2007).

It is possible that the difference in the area of the splenium is only seen in children and adolescents because it arises from a developmental delay. However, this explanation is complicated by the differences in FA measures in both the genu and the splenium found in adults with ADHD and healthy controls. Despite finding no differences in the area of the splenium in ADHD and controls, differences in the organization of this region were apparent with increased integrity in this region. This may reflect increased myelination, larger fibers or a larger number of fibers in this region. However, a measure of attentional control was predictive of the integrity of the splenium in adults with ADHD. Therefore, the splenium appears to be related to problems in attention.

A recent study demonstrated that in addition to myelin, the organization of fibers, their density and diameter, can affect DTI measures, such as FA (Madler, Drabycz, Kolind, Whittall, & Mackay, 2008). Therefore,

it is possible that although the area of the splenium is the same in adults with ADHD and controls, the fibers may be organized differently, or they may be denser or larger in diameter in young adults with ADHD. Although larger fibers may be assumed to be related to enhanced interhemispheric interaction, it is important to consider Banich and Shenker's (1994) warning that the relationships between the structure and function of the CC could be in either direction (refer to section 1.4).

In sum, there may be a developmental lag in the development of the CC in ADHD but this developmental process may also be atypical, resulting in different composition of the CC in adulthood.

5.1.2 The rostral body.

The meta-analysis of previous research undertaken with children and adolescents with ADHD revealed a *smaller* rostral body in boys. Interestingly, the area of this region, along with other midbody regions, was *larger* in adults with ADHD compared to healthy controls. Like the splenium, the development of the rostral body may "catch up" to that of healthy controls. However, it may develop beyond what is necessary or optimal. Alternatively the larger area may reflect atypical organization of these fibers in this region.

5.1.3 The midbody.

The second study in this thesis found that the regions 3 and 4 were *larger* in adults with ADHD than controls. This difference was not observed in children and adolescents with ADHD. In fact, all of the studies examining CC size in children and adolescents have found regions of the CC to be *smaller* in ADHD. Although future research will need to replicate this

finding, it demonstrates that age related differences in neuroanatomy are evident in ADHD. This is not surprising due to the developmental nature of ADHD. Interestingly, hyperactivity symptoms were found to predict the area of these regions in adults with ADHD. This result suggests that differences in CC morphology are related to the presence of ADHD. This sample was carefully screened to exclude comorbid conditions, making it unlikely that differences in the CC can be attributed to comorbidities. Thus, there appears to be a direct relationship between CC morphology and ADHD symptoms. This result must be interpreted cautiously, however, as it does not mean that differences in the CC cause ADHD. Furthermore, it is not known whether this relationship is present in children with ADHD.

To summarize, the first two papers of this thesis demonstrate that differences in CC morphology, both area and integrity, are evident in children, adolescents and young adults with ADHD. However, these differences may change over time reflecting the developmental nature of ADHD and the fact that CC development continues throughout childhood and young adulthood. This was confirmed in study 3 with increased CC size being associated with older age. However, longitudinal research is necessary to confirm these findings.

5.2 The Relationship Between Corpus Callosum Morphology and IQ

5.2.1 IQ and CC area.

The relationship between IQ and CC area was not examined in the meta-analytic review due to the small number of studies that provided IQ

scores. However, IQ was found to be differentially related to CC size in ADHD and healthy controls in Study 2. Specifically, a negative relationship between CC size and IQ was evident in controls but not in young adults with ADHD. IQ is often found to be lower in ADHD (for a review refer to Hervey et al., 2004). It is possible that atypical brain development in ADHD may affect cognitive development as well as the relationship between IQ and the CC. Therefore, the relationship between CC morphology and IQ was examined in a larger, though not independent, sample of healthy individuals in the third study.

This analysis revealed a negative relationship between performance IQ and the area of mid to posterior regions (regions 3, 4 and 5) of the CC when taking into account individual differences in brain size. In the controls in the ADHD study, this relationship was significant for the total CC and for regions 2 and 3. However, when the sample of healthy individuals was increased this negative relationship was observed in region 3 and 5. Region 4 was also negatively correlated with PIQ when age was included as an additional covariate. These differences highlight the importance of examining the relationship between IQ and the CC in a larger sample with adequate power. This is particularly important due to the large amount of individual variation in CC size and shape.

In the final study on IQ, gender differences were also examined. This analysis demonstrated that the relationship between PIQ and region 3 remained significant in females only, despite the decreased power in these calculations. Therefore, gender differences may contribute to the inconsistent findings in the literature because the extent to which males and females are

represented in research samples has varied. Thus, gender differences should be taken into account in future research.

These results suggest that the area of mid to posterior regions of the CC is associated with PIQ. This may be due to the role the CC plays in attentional control. In these studies PIQ was assessed by Matrix Reasoning, which requires problem-solving skills and sustained attention. In addition, this task increases in complexity throughout the task. Thus, the relationship between CC size and Matrix Reasoning is consistent with a large body of research has indicated that interhemispheric interaction is beneficial for performance on complex tasks, particularly as attentional demands increase (Banich & Belger, 1990; Belger & Banich, 1992, 1998; Weissman & Banich, 1999, 2000).

5.2.2 IQ and integrity of the CC.

Measures of CC integrity were also obtained in Studies 2 and 3, and were correlated with IQ scores. Higher VIQ was associated with less voxels meeting our criteria (reduced CC integrity) in the genu in healthy participants. This may reflect less reliance on interhemispheric interaction in those with high VIQ, leading to less developed callosal fibers. Alternatively, the reduced number of fibers may reflect a more organized CC, leading to more efficient transfer of information. The latter hypothesis is supported by a recent DTI study which found that increased CC integrity, as measured by FA, was associated with improved performance on a range of cognitive tasks in a group of healthy adolescents (Fryer et al., 2008). Finally, this negative relationship between VIQ and the number of voxels meeting our criteria in the genu may be because there were fewer but larger or more myelinated fibers in the genu

in individuals with high VIQ. Functional magnetic resonance imaging may help to distinguish between these possibilities by examining the extent to which interhemispheric interaction is utilized by individuals with high VIQ.

The results from the controls in Study 2 and the extension of this to a larger sample in Study 3 suggest that the CC impacts upon brain function and cognition. Furthermore, both VIQ and PIQ may be affected by damage to or atypical development of the CC. There was also a distinction between anterior and mid-posterior regions of the CC such that the integrity of anterior regions was associated with VIQ, while the area of mid-posterior regions was associated with PIQ.

5.3 Limitations

The research included in this thesis has several limitations. Meta-analyses are inevitably limited by the quality of the primary research studies that they evaluate. There were differences in the extent to which the studies included in the meta-analysis reported comorbid psychological conditions, the use of ADHD medications in their samples, and the inclusion and exclusion criteria used in their studies. These sources of variability may have obscured some differences in CC area in ADHD. In addition, this study included data from research with children and adolescents. Although it would be ideal to consider these developmental periods separately, most studies had both children and adolescents present in their samples, making it impossible to separate the two age groups.

The results of the second study, which examined the CC in adults with ADHD, differed from those found in studies with children and adolescents.

More specifically, no difference was found in the size of the splenium and two sections of the midbody were larger in ADHD than in controls. It is not known whether the differences between studies 1 and 2 are due to the characteristics of the sample (e.g. no comorbid learning disabilities) or alternatively result from changes during development. Therefore, a longitudinal study would provide the most accurate information about changes in the CC during development in ADHD.

The second study was also limited by the fact that it only included people with the combined subtype of ADHD. Thus, it is not known whether the results generalize to those with the predominantly inattentive or predominantly hyperactive subtypes of ADHD. These participants were also screened to exclude people with learning disabilities. ADHD is known to be frequently comorbid with learning disabilities, making it unlikely that this sample was representative of all adults with ADHD. However, this was done in order to examine the CC in ADHD without the possible confounding effects of learning disabilities or other comorbid conditions. Therefore, this aspect of sample selection was both a weakness and strength of this study.

Gender differences were considered in both ADHD studies. However, the adult ADHD sample lacked power when males and females were considered separately. Larger sample sizes are necessary to address gender differences in CC size in adult ADHD. However, these analyses were thought to be warranted for two reasons. Firstly, large sample sizes are difficult to obtain in ADHD research, particularly when participants with a large number of comorbid conditions are excluded from participation in the study. Secondly, gender differences have been found in some studies of CC size

(Bishop & Wahlsten, 1997; Dubb, Gur, Avants, & Gee, 2003; Lenroot et al., 2007; Ozdemir et al., 2007; Sullivan, Rosenbloom, Desmond, & Pfefferbaum, 2001; Westerhausen et al., 2004; Westerhausen et al., 2003), as well as in ADHD research (e.g. Faraone, 2000; Houghton et al., 1999; Liu & Wang, 2002; Rucklidge & Tannock, 2002; Seidman et al., 2005). Therefore, gender may play a role in CC size and/or ADHD and was an important issue to consider despite a limited sample size.

Unfortunately, FA measures were not obtained for the midregions of the CC in the second study. This was dictated by the axial slice thickness of the DTI data, which was determined by a larger, ongoing ADHD study. Therefore, FA measures were obtained for the genu and splenium only, where the results could reliably reflect CC integrity. Appropriate imaging parameters for examining FA throughout the CC should be employed in future studies.

The third study expanded upon a particular result from the study with adults with ADHD, namely, a negative relationship between IQ and CC area in healthy controls. This study examined this relationship with a larger sample size but was limited by the fact that it used the control participants from Study 2. Therefore the samples in studies two and three were not independent. However, the increased number of participants in Study 3 allowed the relationship between the CC and IQ to be examined in a more reliable and detailed manner. In addition, this study used the two subtest version of the WASI to estimate IQ. This relationship should be assessed with the full WAIS so that the relationship between CC area and individual subtests can be examined.

This study also raised questions about the relationship between IQ, CC area, and age. As discussed in Chapter 4, one explanation for the conflicting results of this study and those of Luders et al. (2007) is that the relationship between IQ and CC area changes during adolescence, young adulthood, and adulthood. However, a longitudinal study is necessary to directly examine this hypothesis. An alternative explanation is that the results of Study 3 or the Luders et al. study were erroneous due to relatively small sample sizes. Although the results of these two studies differed, they were based on comparable sample sizes (71 and 62 participants respectively). Type 1 errors may be another source of error in both of these studies due to the number of analyses that were conducted. A longitudinal study with a large sample size is needed to resolve these inconsistent findings.

Finally, the relationships observed between IQ and CC area in Study 3 may reflect a general relationship between white matter throughout the brain and IQ, as opposed to a specific relationship with the CC. Unfortunately measures of white matter were not available in this study. Therefore, this issue needs to be examined in future studies.

5.4 Recommendations for future research

The meta-analytic review was limited by the level of detail provided by the primary research papers in terms of sample characteristics, such as the presence of comorbid conditions, ADHD subtypes and the use of medications. In some cases the age and gender of participants was not reported. This information is not only necessary for a detailed and meaningful synthesis of primary research but also allows the reader to understand the results of the study, its implications, and to more easily compare the results with those of

other studies. Therefore, it is recommended that future studies provide a detailed description of their methods and participants.

As discussed previously, a direct comparison between research in children, adolescents and adults with ADHD is difficult due to differences in research methodology across studies. A longitudinal study would be most appropriate for assessing whether the differences observed in childhood ADHD persist into adulthood. However, longitudinal samples are difficult to obtain and ADHD samples can be particularly difficult to follow-up. ADHD participants can be hard to contact, often do not respond to phone calls or emails, and often do not attend appointments.

This thesis examined CC morphology in ADHD and found that the integrity of the CC differed in adults with ADHD. However, these analyses were restricted to the genu and the splenium. Thus, further research is necessary to determine whether these differences are present in the midbody of the CC. Furthermore, this thesis demonstrated that CC morphology is linked with some aspects of cognitive function. This highlights the potential for research with other clinical populations in which the CC is affected, such as multiple sclerosis, Alzheimer's disease and schizophrenia. These studies should examine differences in CC area and integrity as well as the relationships between these variables and attention, intelligence and other aspects of cognition, dependent on the site of compromise to the CC.

Finally, further research is necessary to explore the relationship between CC morphology and IQ in neurologically intact individuals. If the discrepancies in the literature are due to developmental processes they could be resolved with longitudinal studies. This research should use the full WAIS

to examine IQ. In addition, the relationship between IQ and CC size and integrity implies that a range of cognitive abilities may be associated with the structure of the CC. Therefore, a variety of tests should be used to explore cognitive performance and its relationship with the CC. Research is no longer restricted to studies with split-brain patients due to the availability of brain imaging techniques, such as MRI and DTI, which make it possible for brain structure and function to be explored in healthy individuals. Future advances in brain imaging technology will undoubtedly allow more detailed investigation of the CC, among other areas of the brain, and may help resolve discrepancies in the literature.

5.5 Conclusions

This thesis found that compromise to the CC is present in children, adolescents, and adults with ADHD and that these differences appear to vary for these age groups. This may be due to atypical development of the CC during these time periods. In addition, differences in the development and composition of the CC are likely to have cognitive consequences due to the relationship between CC morphology and IQ. These results emphasize the need for similar research in other clinical conditions in which the CC is affected, such as multiple sclerosis, schizophrenia, Alzheimer's disease and traumatic brain injury to determine the implications of compromise to the CC in these conditions.

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Appendix A

Hutchinson, A.D., Mathias, J.L. and Banich, M.T. (2008) Corpus callosum morphology in children and adolescents with Attention Deficit Hyperactivity Disorder: a meta-analytic review
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Appendix B: Corpus Callosum Morphology in Children and Adolescents with Attention Deficit Hyperactivity Disorder: a Meta-analytic Review.

Supplementary Material

Table B1

Children with ADHD and comorbid Tourette's syndrome vs. children with Tourette's syndrome only: Weighted Cohen's d effect sizes[1] for subregions of the CC, ordered from anterior to posterior

Region	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study references
Total CC	2	56	-0.11	0.38	-0.64	0.42	-0.36	0.38	0	92	Baumgardner et al 1996; Mostofsky et al 1999
Baumgardner et al (1996) method											
Genu	2	56	0.02	0.38	-0.51	0.55	0.00	0.05	0	100	Baumgardner et al 1996; Mostofsky et al 1999
Rostral body	2	56	-0.35	0.39	-0.89	0.20	-0.82	0.52	1	73	Baumgardner et al 1996; Mostofsky et al 1999
Midbody	2	56	-0.08	0.38	-0.61	0.45	-0.35	0.44	0	92	Baumgardner et al 1996; Mostofsky et al 1999
Isthmus/posterior body	2	56	0.11	0.38	-0.42	0.64	-0.04	0.40	0	92	Baumgardner et al 1996; Mostofsky et al 1999
Splenium	2	56	-0.16	0.38	-0.69	0.37	-0.29	0.09	0	85	Baumgardner et al 1996; Mostofsky et al 1999

Note. N = number of studies contributing to the effect size, Mean d_w = mean weighted effect size, SD d_w = standard deviation of weighted effect size, 95% CI = 95% Confidence Intervals for means, Max *d* = maximum effect size, Min *d* = minimum effect size, *Nfs* = Fail Safe N, %OL = percent overlap between ADHD and Control groups

[1] Effect sizes weighted by the inverse variance

Table B2

ADHD vs. siblings of children with ADHD: Weighted Cohen's d effect sizes[1] for subregions of the CC ordered from anterior to posterior

Region	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study reference
Total CC	1	30	0.20	0.37	-0.52	0.92	-	-	0	85	Overmeyer et al 2000
Witelson (1989) method											
Rostrum	1	30	-0.30	0.37	-1.02	0.42	-	-	0	79	Overmeyer et al 2000
Genu	1	30	0.18	0.37	-0.53	0.90	-	-	0	85	Overmeyer et al 2000
Rostral body	1	30	0.11	0.37	-0.61	0.82	-	-	0	92	Overmeyer et al 2000
Anterior midbody	1	30	-0.07	0.37	-0.79	0.64	-	-	0	92	Overmeyer et al 2000
Posterior midbody	1	30	0.25	0.37	-0.47	0.97	-	-	0	79	Overmeyer et al 2000
Isthmus	1	30	-0.39	0.37	-1.12	0.33	-	-	0	73	Overmeyer et al 2000
Splenium	1	30	-0.05	0.37	-0.76	0.67	-	-	0	92	Overmeyer et al 2000

Note. N = number of studies contributing to the effect size, Mean d_w = mean weighted effect size, SD d_w = standard deviation of weighted effect size, 95% CI = 95% Confidence Intervals for means, Max *d* = maximum effect size, Min *d* = minimum effect size, *Nfs* = Fail Safe N, %OL = percent overlap between ADHD and Control groups

[1] Effect sizes weighted by the inverse variance

Table B3

Children with ADHD and velocardiofacial syndrome vs. children with velocardiofacial syndrome only: Weighted Cohen's d effect sizes[1] for subregions of the CC ordered from anterior to posterior

Region	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study reference
Total CC	1	60	-0.14	0.26	-0.65	0.36	-	-	0	92	Antshel et al 2005
Baumgardner et al (1996) method											
Genu	1	60	-0.24	0.26	-0.75	0.27	-	-	0	85	Antshel et al 2005
Rostral body	1	60	0.00	0.26	-0.51	0.51	-	-	0	100	Antshel et al 2005
Midbody	1	60	-0.23	0.26	-0.73	0.28	-	-	0	85	Antshel et al 2005
Isthmus/posterior body	1	60	-0.04	0.26	-0.55	0.46	-	-	0	100	Antshel et al 2005
Splenium	1	60	-0.11	0.26	-0.62	0.40	-	-	0	92	Antshel et al 2005

Note. N = number of studies contributing to the effect size, Mean d_w = mean weighted effect size, SD d_w = standard deviation of weighted effect size, 95% CI = 95% Confidence Intervals for means, Max d = maximum effect size, Min d = minimum effect size, *Nfs* = Fail Safe N, %OL = percent overlap between ADHD and Control groups

[1] Effect sizes weighted by the inverse variance

Table B4

Children with ADHD and neurofibromatosis vs. children with neurofibromatosis only: Weighted Cohen's d effect sizes[1] for subregions of the CC ordered from anterior to posterior

Region	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study reference
Total CC	1	36	0.17	0.35	-0.53	0.86	-	-	0	85	Kayl et al 2000
Witelson (1989) method											
Rostrum	1	36	0.40	0.36	-0.30	1.10	-	-	1	73	Kayl et al 2000
Genu	1	36	0.14	0.35	-0.55	0.83	-	-	0	92	Kayl et al 2000
Rostral body	1	36	0.42	0.36	-0.28	1.12	-	-	1	73	Kayl et al 2000
Anterior midbody	1	36	0.02	0.35	-0.67	0.72	-	-	0	100	Kayl et al 2000
Posterior midbody	1	36	-0.21	0.35	-0.91	0.48	-	-	0	85	Kayl et al 2000
Isthmus	1	36	0.01	0.35	-0.69	0.70	-	-	0	100	Kayl et al 2000
Splenium	1	36	0.05	0.35	-0.64	0.75	-	-	0	92	Kayl et al 2000

Note. N = number of studies contributing to the effect size, Mean d_w = mean weighted effect size, SD d_w = standard deviation of weighted effect size, 95% CI = 95% Confidence Intervals for means, Max *d* = maximum effect size, Min *d* = minimum effect size, *Nfs* = Fail Safe N, %OL = percent overlap between ADHD and Control groups

[1] Effect sizes weighted by the inverse variance

Table B5

ADHD vs. healthy controls: Weighted Cohen's d effect sizes[1] for subregions of the CC separated according to the gender of participants

Region	Method	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study references
Males and Females												
4	Hynd et al 1991	1	17	-0.94	0.52	-1.96	0.08	-	-	4	48	Hynd et al 1991
1	Hynd et al 1991	1	17	-0.70	0.51	-1.70	0.29	-	-	3	57	Hynd et al 1991
5	Hynd et al 1991	1	17	-0.67	0.51	-1.66	0.32	-	-	2	57	Hynd et al 1991
Splenium	Witelson, 1989	2	126	-0.59	0.26	-0.96	-0.23	-0.64	-0.56	4	62	Hill et al., 2003; Lyoo et al., 1996
Isthmus/posterior body	Baumgardner et al 1996	2	92	0.42	0.33	-0.04	0.88	0.05	0.77	2	73	Antshel et al 2005; Baumgardner et al 1996
Genu	Witelson, 1989	2	126	-0.32	0.26	-0.68	0.04	-0.51	-0.21	1		Hill et al., 2003; Lyoo et al., 1996
Rostral body	Witelson, 1989	1	79	0.31	0.24	-0.15	0.78	-	-	1		Lyoo et al., 1996
Isthmus	Witelson, 1989	1	79	-0.29	0.24	-0.75	0.18	-	-	0	79	Lyoo et al., 1996
3	Hynd et al 1991	1	17	-0.27	0.49	-1.24	0.70	-	-	0	79	Hynd et al 1991
Posterior midbody	Witelson, 1989	1	79	-0.26	0.24	-0.72	0.20	-	-	0	79	Lyoo et al., 1996
Genu	Baumgardner et al 1996	2	92	0.22	0.33	-0.24	0.68	-0.28	0.68	0	85	Antshel et al 2005; Baumgardner et al 1996
Total corpus callosum	-	3	139	-0.21	0.32	-0.57	0.15	-0.68	0.53	0		Antshel et al., 2005; Baumgardner et al.,

Region	Method	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study references
												1996; Hill et al., 2003
Anterior midbody	Witelson, 1989	1	79	-0.21	0.24	-0.67	0.26	-	-	0	85	Lyoo et al., 1996
Posterior midbody	Witelson, 1989	3	145	-0.20	0.30	-0.54	0.14	-0.69	0.32	0	85	Giedd et al 1994; Lyoo et al 1996; Semrud-Clikeman et al 1994
Rostrum	Witelson, 1989	1	79	0.15	0.33	-0.31	0.61	-	-	0		Lyoo et al., 1996
Rostral body	Baumgardner et al 1996	2	92	-0.13	0.33	-0.59	0.33	-0.60	-0.28	0	92	Antshel et al 2005; Baumgardner et al 1996
2	Hynd et al 1991	1	17	0.11	0.49	-0.86	1.08	-	-	0	92	Hynd et al 1991
Splenium	Baumgardner et al 1996	2	92	-0.09	0.33	-0.55	0.37	-0.53	0.31	0	92	Antshel et al 2005; Baumgardner et al 1996
Midbody	Baumgardner et al 1996	2	92	-0.06	0.33	-0.51	0.40	-0.31	0.17	0	92	Antshel et al 2005; Baumgardner et al 1996
Males												
Rostral body	Witelson, 1989	2	66	-0.70	0.36	-1.20	-0.20	-0.93	-0.45	5		Giedd et al., 1994; Semrud-Clikeman et al., 1994
Rostrum	Witelson, 1989	2	66	-0.48	0.35	-0.98	0.01	-0.72	-0.22	3		Giedd et al., 1994; Semrud-Clikeman et al., 1994
Splenium	Witelson, 1989	2	66	-0.45	0.36	-0.94	0.04	-0.84	-0.15	3	67	Giedd et al., 1994;

Region	Method	N studies	N participants (ADHD + Controls)	Mean Cohen's d_w	SD d_w	95% CI		Min d_w	Max d_w	Nfs	%OL	Study references
												Semrud-Clikeman et al., 1994
Anterior midbody	Witelson, 1989	2	66	-0.33	0.35	-0.82	0.15	-0.63	-0.10	1	79	Giedd et al., 1994; Semrud-Clikeman et al., 1994
Total corpus callosum	-	2	142	-0.19	0.24	-0.53	0.14	-0.72	-0.06	0		Castellanos et al., 1996; Semrud-Clikeman et al., 1994
Isthmus	Witelson, 1989	2	66	-0.16	0.35	-0.65	0.33	-0.66	0.24	0	85	Giedd et al., 1994; Semrud-Clikeman et al., 1994
Posterior midbody	Witelson, 1989	2	66	-0.13	0.35	-0.62	0.36	-0.69	0.32	0	92	Giedd et al., 1994; Semrud-Clikeman et al., 1994
Genu	Witelson, 1989	2	66	-0.01	0.35	-0.49	0.48	-0.19	0.15	0	100	Giedd et al., 1994; Semrud-Clikeman et al., 1994

Note. N = number of studies contributing to the effect size, Mean d_w = mean weighted effect size, SD d_w = standard deviation of weighted effect size, 95% CI = 95% Confidence Intervals for means, Max d = maximum effect size, Min d = minimum effect size, *Nfs* = Fail Safe N, %OL = percent overlap between ADHD and Control groups

[1] Effect sizes weighted by the inverse variance

Appendix C: Corpus Callosum Size and Integrity in Adults with Attention Deficit Hyperactivity Disorder. Supplementary Material

Table C1

Area measurements of the corpus callosum for male and female ADHD and Controls participants

	ADHD		Controls		F	p	Effect Size
Region	Mean	SD	Mean	SD			Cohen's *d*
Total corpus callosum							
Females	6.27	1.06	5.77	0.89	2.10	.15	0.52
Males	6.12	0.74	6.29	0.86	1.0	.41	-0.21
Region 1							
Females	1.47	0.21	1.50	0.18	2.90	.07	-0.17
Males	1.48	0.26	1.62	0.18	2.07	.13	-0.65
Region 2							
Females	1.81	0.40	1.61	0.20	2.20	.14	0.65
Males	1.76	0.26	1.87	0.22	2.04	.14	-0.44
Region 3							
Females	.81	0.16	0.71	0.12	3.08	.06	0.74
Males	.80	0.11	0.78	0.10	2.51	.09	0.19
Region 4							
Females	.42	0.11	0.36	0.07	2.42	.11	0.59
Males	.41	0.06	0.39	0.08	1.36	.28	0.29
Region 5							
Females	2.37	0.34	2.19	0.44	1.35	.30	0.44
Males	2.28	0.22	2.26	0.37	0.15	.93	0.08

Appendix D

Hutchinson, A.D., Mathias, J.L., Jacobson, B.L., Ruzic, L., Bond, A.N. and Banich, M.T. (2009) Relationship between intelligence and the size and composition of the corpus callosum
Experimental Brain Research, v.192 (3) pp. 455-464, January 2009

Appendix E: Relationship Between Intelligence and the Size and Composition of the Corpus Callosum. Supplementary Material

Table E1

Correlations between CC area and age, controlling for whole brain volume, for male and female participants

	CC Area	CC FA									
	Total CC	1	2	3	4	5	Genu: # voxels	Genu: Mean FA	Splenium: # voxels	Splenium: Mean FA
Age											
Females	.20	.17	.13	**-.51***	.11	-.06	.00	-.15	.19	-.05
Males	.47	.45	.37	.05	.26	.29	.49	.29	.23	-.10

NB: CC = corpus callosum, FA = fractional anisotropy, # voxels represents the number of voxels in the ROI that met our criteria for being considered CC tissue; Mean FA represents the mean FA of the voxels so identified as callosal tissue, * = significant after Bonferonni corrections for multiple comparisons.

Table E2

Correlations between PIQ and VIQ estimates and CC area and fractional anisotropy (FA) with no covariates, WBV alone, and WBV and age entered as covariates for male and female participants

	No covariates		Covariate: WBV		Covariate: WBV and age	
	PIQ	VIQ	PIQ	VIQ	PIQ	VIQ
CC Area						
Total CC						
Females	-.02	.07	-.11	.01	.20	-.04
Males	.02	-.19	-.04	-.14	-.16	-.29
1						
Females	.08	.11	.00	.05	-.07	.01
Males	.12	-.18	.10	-.17	.02	-.28
2						
Females	.00	.04	-.09	-.03	-.15	-.06
Males	-.06	-.12	-.10	-.09	-.21	-.21
3						
Females	-.25	-.07	-.39	-.15	-.26	-.05
Males	-.17	-.38	-.27	-.33	-.29	-.35
4						
Females	-.09	.08	-.18	.03	-.23	.00
Males	-.04	-.18	-.14	-.10	-.23	-.19
5						
Females	-.19	.00	-.29	-.06	-.28	-.05
Males	-.02	-.29	-.10	-.23	-.17	-.32
CC FA						
Genu: # voxels						
Females	.01	-.29	-.10	-.43	.11	-.44
Males	.17	-.24	.06	-.12	-.10	-.26
Genu: Mean FA						
Females	-.16	-.33	-.22	-.37	-.18	-.36
Males	.31	-.19	.22	-.08	.15	-.15
Splenium: # voxels						
Females	.01	.07	-.01	.06	-.08	.02
Males	-.11	-.08	-.14	-.06	-.22	-.11
Splenium: Mean FA						
Females	.09	-.07	-.11	-.09	-.10	-.08
Males	.00	.36	.06	.32	.10	.35

NB: WBV = whole brain volume, CC = corpus callosum, FA = fractional anisotropy, # voxels represents the number of voxels in the ROI that met our criteria for being considered CC tissue; Mean FA represents the mean FA of the voxels so identified as callosal tissue.