Examining the Relationships Between Anterior Cingulate Cortex Morphology and Behaviour in ADHD

by

Esther Yona Direnfeld
B.Sc., Queen's University, 2007

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in the Department of Psychology

Supervisory Committee

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Abstract

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Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder characterized by increased hyperactivity, impulsivity, and inattention. Some theories propose that ADHD is caused by a deficit in inhibitory control, interacting with other executive functions (e.g., emotional control) to lead to behavioural dysfunction. Furthermore, certain brain regions have been found to be involved in executive functions, and several studies have examined the neural correlates of ADHD at broad-based levels. Increased interest has been placed on the Anterior Cingulate Cortex (ACC), which is known to play a role in attention and other complex cognitive processes. Thus, to further clarify the nature of the behavioural and cognitive deficits observed in ADHD, and to elucidate potential relationships between these difficulties and their neural substrates with more specificity, volumetric analyses of the ACC were conducted. For this purpose, 10 children with ADHD and 10 matched controls underwent magnetic resonance imaging and neuropsychological assessment. Manual tracing of ACC subregions was conducted using ANALYZE 9.0 (Mayo Clinic), followed by between-group statistical comparisons. Correlation analyses were used to investigate whether ACC subregions were associated with performance on executive functions tasks. It was hypothesized that there would be significant volumetric groups differences between the two groups, and that subregions would have a differential relationship with executive function performance. Results indicated the ADHD group has marginally larger right dorsal ACC volumes relative to controls. Further, between the two groups, brain-behaviour relationships were different. These results provide support for the hypothesis of a delay in neuronal maturation of the ACC in children with ADHD from Spain.

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Acknowledgments

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Introduction

Examining morphometric qualities of the brain, such as shape, volume, area, and folding are established methods of studying neural differences between clinical groups and typically developing individuals. Thus, this study will examine the volumes of anterior cingulate cortex (ACC) subregions to attempt to clarify where differences lie in a group of children from Spain diagnosed with attention-deficit/hyperactivity disorder (ADHD). To gain a better understanding of what the volumetric differences mean in terms of the symptom profile of ADHD, relationships between subregions and behaviours will be examined and compared between the ADHD group and a matched control group.

Attention Deficit/Hyperactivity Disorder (ADHD)

ADHD is a developmental disorder typically characterized by impairments in hyperactivity, impulsivity, and attention in children, over and above difficulties expected at the child's age (American Psychiatric Association, 2000). Approximately 5-10% of school-aged children suffer from ADHD (Biederman, 2005), and geographic location does not account for the worldwide variability in prevalence rates (Polanczyk, de Lima, Horta, Biederman, & Rhode, 2007), indicating that it is the most common childhood disorder (Diamond, 2005). To receive a diagnosis of ADHD, core symptoms of hyperactivity-impulsivity or inattention must have been present prior to seven years of age and caused impairment in two or more everyday environments such as academic, familial, or social settings. ADHD is not diagnosed if symptoms can be accounted for by

a mood disorder, and diagnosis is complicated when a child has other comorbid disorders (e.g., mental retardation, FASD, oppositional behaviour, etc).

The Diagnostic and Statistical Manual-IV-TR (DSM-IV-TR: APA, 2000) categorizes ADHD into subtypes based on symptoms of hyperactivity-impulsivity and inattention. Individuals with ADHD Predominantly Inattentive Type (ADHD-PI) tend to have difficulties sustaining attention on a variety of tasks, are easily distracted by stimuli, and are often forgetful. For a diagnosis, individuals must have at least six symptoms of inattention and fewer than six symptoms of hyperactivity-impulsivity. In contrast, individuals with Predominantly Hyperactive-Impulsive Type (ADHD-PHI) have difficulties inhibiting behaviours. Children with ADHD-PHI must demonstrate at least six symptoms of hyperactivity and impulsivity, such as fidgeting with their hands or feet, talking excessively, difficulties waiting for their turn, and interrupting others. Finally, ADHD Combined Type (ADHD-C) is diagnosed when criteria for both the inattentive and hyperactive-impulsive subtypes are met.

Approximately 80% of individuals with ADHD are diagnosed with ADHD-C, whereas 15% are diagnosed with ADHD-PI, and 5% with ADHD-PHI (Rappley, 2005). In addition, ADHD has been observed to be two times more common in boys than girls (Bauermeister et al., 2007); however, more girls are increasingly being identified making gender disparity a questionable issue (e.g., Barkley, 2003; Garcia-Barrera & Kamphaus, 2006). Bauermeister et al. (2007) further explained that girls with ADHD-PI were more likely to be diagnosed with a comorbid anxiety disorder, while boys with ADHD-C have an increased risk for mood disorders.

The most common form of treatment for children with ADHD is stimulant medication. Methylphenidate (e.g., Ritalin or Concerta) is a dopamine and norepinephrine reuptake inhibitor. Most children with ADHD-C respond to low to moderate doses of methylphenidate, and the remaining respond to moderate to high doses (Diamond, 2005). In contrast, many children with ADHD-PI respond to amphetamines (such as Adderall; Diamond, 2005), which act through the same mechanism as methylphenidate but also promote release of both dopamine and norepinephrine.

Many studies have found evidence for a wide variety of possible etiologies for ADHD (e.g., Barkley, 1997; Mick et al., 2002; Biederman & Faraone, 2005). Birth complications and maternal age have been found to lead to increased risk of ADHD (Claycomb, Ryan, Miller, & Schnakenberg-Ott, 2004). Furthermore, events such as toxin exposure, pre- or peri-natal trauma [e.g., TBI, stroke, particularly in the putamen region (Max et al., 2002)], and cigarette exposure in utero (Mick et al., 2002) may contribute to a greater risk of developing ADHD. However, the most compelling evidence has indicated a strong genetic component in ADHD. Coolidge, Thede, and Young (2000) found that there is a high degree of heritability in ADHD. Specifically, an association between the dopamine transporter gene and ADHD has been observed (e.g., Barkley, Smith, Fischer, & Navia, 2006), and others have suggested that the dopamine D4 receptor, which is prevalent in frontal-subcortical networks, is involved (Biederman & Faraone, 2005). Because of the convergence of biological, genetic, psychosocial, and environmental factors that appear to increase one's vulnerability to developing ADHD, Biederman and Faraone (2005) proposed a multifactorial model of ADHD, in which

combinations of factors additively and interactively increase one's likelihood of being diagnosed with this disorder.

Theories of ADHD: Executive Dysfunction

Recently, neuropsychological theories of ADHD have also been proposed. Barkley (1997) hypothesized that difficulty with inhibitory control is the core deficit in children with ADHD. More specifically, this deficit, likely stemming from an underlying impairment in executive functions, was used by Barkley to create a model of ADHD. Barkley's (1997) model suggests that inhibitory control deficits interact with other executive functions such as reconstitution (behavioural analysis and synthesis), verbal and spatial working memory, self-regulation of affect, motivation, and arousal, and internalization of speech to act as a core cause of ADHD, leading to deficits in these and other executive processes. In particular, components of the model of executive dysfunction have been supported through functional magnetic resonance imaging (*f*MRI) tasks (Rowe, Owen, Johnsrude, & Passingham, 2001) and frontal lesion studies in which similar deficits to those observed in ADHD are detected (Demakis, 2003).

Pennington and Ozonoff (1996) evaluated the three behavioural characteristics seen most commonly in ADHD, inattention, hyperactivity, and impulsivity, and examined their relationship to executive functions. Based on analysis of a number of studies (n = 18) which examined these cognitive abilities, Pennington and Ozonoff hypothesized that ADHD may be caused by a core deficit in an executive function such

as motor inhibition (e.g., as observed in stop-signal tasks), with other general cognitive impairments.

However, although much importance has recently been given to ADHD as a disorder of executive functioning, some researchers have questioned the view that executive dysfunction is the sole and core cause of ADHD (e.g., Willcut et al., 2005; Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2005). Geurts et al. (2005) assessed children with ADHD-C and ADHD-PI on tasks measuring response inhibition, verbal fluency, cognitive flexibility, visual working memory, and planning (based on Pennington & Ozonoff's theory, 1996). Relative to healthy controls but not to those with ADHD-PI, children with ADHD-C performed worse on tasks in which inhibition of both prepotent and ongoing responses were required. However, children with ADHD-C did not perform more poorly on all tasks of executive functioning and were not distinguishable from children with ADHD-PI. As Barkley's (1997) hypothesis states that children with ADHD-C, but not ADHD-PI, suffer from EF deficits due to a lack of inhibitory control, Geurts and colleagues argued that children with ADHD-C did not exhibit the deficits necessary to state that ADHD-C is a disorder of executive functioning.

Cognitive Executive Functions

In a recent meta-review, Willcutt et al. (2005) examined studies in which children with ADHD were measured on tasks consisting of planning, set-shifting, response inhibition, vigilance, as well as verbal and spatial working memory. The authors concluded that although children with ADHD showed significant deficits on all executive functioning tasks, their findings did not support executive dysfunction as the sole cause

of ADHD. This was due to moderate effect sizes and variability in the executive function deficits exhibited among individuals with ADHD. However, Willcutt et al. stressed that many factors such as sampling, methodological, and diagnostic differences could affect clarity and interpretation of the relationship between ADHD and executive functions. In this regard, Pineda, Puerta, Aguirre, Garcia-Barrera, and Kamphaus (2007) demonstrated that traditional neuropsychological tests used in the diagnosis of ADHD show only modest sensitivity and low specificity to identifying cognitive deficits in this disorder (e.g., executive functions, working memory).

Moreover, other researchers have emphasized that the definition of executive functions is quite broad, difficult to define (e.g., Denckla, 1996), and commonly referred to as an "umbrella" term (e.g., Kipp, 2005). A common definition of executive functions is that they are a set of interrelated abilities that combine to produce goal-directed behaviours (Lezak, 1995). Thus, researchers have recently begun to examine specific facets of executive functions and their relation to impairment in ADHD (Frazer & Garcia-Barrera, in prep.). In accordance with Barkley's (1997) view that an inhibitory control deficit is the core impairment in children with ADHD, Goos, Crosbie, Payne, and Schachar (2009) compared performance on a stop signal reaction time task (SSRT) of children with ADHD and their families to controls (children and their families). They found that age and psychopathology group predicted performance on the SSRT task in younger children. More significantly, they found that families with ADHD had significantly worse inhibitory control than families without ADHD, regardless of the parents' own diagnostic status, and that children with ADHD performed more poorly than typically developing children. They concluded that these findings supported their

hypothesis that inhibitory control may be a quantitative trait that indexes an individual's likelihood to develop ADHD (i.e., an endophenotype of ADHD).

Emotional Dysfunction

Another area of functioning in which children experience difficulties is that of emotion regulation. Emotional impairment and dysregulation are considered to load on to the same mechanisms as inhibitory control impairments (Wehmeier, Schacht, & Barkley, 2010). Emotional regulation may comprise the ability to appropriately identify emotions and the ability to appropriately modify or mask emotional expression during social situations (Saarni, 2000). Studies examining emotion regulation in children with ADHD have focused on their ability to identify emotions in naturalistic and experimental settings (Norvilitis, Casey, Brooklier, & Bonello, 2000), as well as the ability of children to control their feelings in these situations (e.g., Walcott & Landau, 2004). Further, it is likely that problems with emotional control may contribute to impaired peer relations of those with ADHD (e.g., Landau, Milich, & Diener, 1998).

One of the most consistent findings is that compared to typically developing children, those with ADHD have significantly more difficulties correctly identifying the six universal facial expressions of emotion [i.e., happiness, surprise, sadness, anger, disgust and fear (e.g., Corbett & Glidden, 2000)], and in particular are worse at identifying negative emotions (Singh et al., 1998). Children with ADHD also have trouble classifying emotional tone (i.e., happiness, sadness, anger, and neutral tone) in other's language (Corbett & Glidden, 2000). Furthermore, emotion identification difficulties are not specific to classification of emotions in others, but also occur when identifying emotions they are experiencing themselves (Norvilitis et al., 2000).

Compared to typically developing children, those with ADHD display more outward signs of sadness, anger, and guilt (Braaten & Rosen, 2000). Singh and colleagues (1998) suggested that the difficulties of children with ADHD in identifying negative emotions might reflect decreased attention to relevant emotional stimuli. Further, although the pattern of emotion identification accuracy is similar to that of healthy children, it is still reduced. Singh et al. speculated that children with ADHD might have problems identifying the correct and relevant stimuli necessary for identifying negative emotions.

Difficulties with emotion regulation in children with ADHD have also been identified through experimental frustration tasks. For instance, Scime and Norvilitis (2006) found that children with ADHD were more likely to feel frustrated on a puzzle task, although were less likely to report feelings of frustration when asked directly. Further, these children did not have the same ability to cope with their feelings of frustration. More severe and erratic emotional responses are also typical of children with ADHD (e.g., Wehmeier et al., 2010). These findings emphasize that although children with ADHD might be aware of coping strategies, they are unable to use them in emotionally charged situations. Others have reported that children with ADHD are less able to hide their disappointment in a range of similar tasks (e.g., Walcott and Landau, 2004), and that children's ability to maintain effective emotional control correlated negatively with displays of negative emotionality (Melnick & Hinshaw, 1998). Moreover, Walcott and Landau (2004) observed that boys with ADHD who were more impulsive were worse at regulating their emotions and inhibiting responses on a response inhibition task, indicating that behavioural inhibition problems might contribute to the emotional control problems observed in children with ADHD.

Neuroimaging in ADHD Research

Because of the increased interest in examining individual aspects of executive functions in ADHD, and the more selective knowledge we now have regarding how certain cognitive and behavioural functions may be affected in ADHD, it is worthwhile to examine how aspects of executive functions interact with brain structures. This knowledge will enable us to examine the morphological brain characteristics that correspond to behaviours in greater detail. While functional studies have already examined networks and circuits involved in performance of executive functions, there are many questions still left unanswered. It remains unclear how the underlying brain structure is related to cognitive and behavioural performance itself; more specifically, the neural substrates that form the basis of observed behavioural abnormalities are still vague (Baumeister & Hawkins, 2001). Furthermore, previous studies have examined the prefrontal cortex (PFC) as a region of interest (ROI) in ADHD with regards to executive functions. Converging evidence from MRI, *f*MRI, ERP, and PET studies has demonstrated that the ACC is also involved in tasks that are cognitively challenging and executive in nature. Taken together with the increasing evidence of abnormalities observed in this region in regards to ADHD, it is increasingly apparent that this is an important ROI. Up to this point, studies examining the morphological characteristics of neural networks involved in executive functions have mainly been broadly based, for instance, only examining the prefrontal region, frontal region, or total brain volume (Castellanos et al. 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002; Filipek et al., 1997).

Methods of Brain Volume Measurement used in ADHD Research

To conduct volumetric analysis, the following three methods are commonly used: a semi-automatic Talairach system analysis, voxel-based morphometry (VBM), and manual tracing. The volumetric Talairach system divides the brain into boxes based on the locations of the anterior and posterior commissures and outer brain limit. A grid of boxes is then placed over the brain and volume is measured based on the stereotactic grid of Talairach and Tournoux (1988). This system is based upon the following landmarks within the brain: the anterior and posterior commissures and an area above that horizontal line within the interhemispheric fissure. From these landmarks, sections of the brain are determined automatically, regardless of size and therefore age (Tisserand, Van Boxtel, Gronenschild, & Jolles, 2001). Advantages of the volumetric Talairach system are that it enables perfect reproducibility and extremely fast calculation of volume. A major disadvantage of this procedure is that measurements of small regions of interest (e.g., PFC subregions) are not completely accurate as small divisions of the brain are more difficult to demarcate making it more difficult to determine the borders between two regions. In addition, standard errors associated with the Talairach method tend to be larger than standard errors associated with manual tracing (Tisserand et al., 2002).

VBM is an automatic whole-brain analysis procedure in which grey and/or white matter maps are smoothed and spatially normalized, so that density of these areas can be examined on a voxel-by-voxel basis. One advantage of this process is that test-retest reliability is perfect; however, findings are not quantitative but qualitative (Tisserand et al., 2002). In manual tracing, total brain volumes and regions of interest are investigated using a variety of programs in which small areas can be traced. Manual tracing is time

consuming, but enables observations of individual variability and is most accurate in detecting volumetric differences (Tisserand et al., 2002), specifically when examining small samples. Comparisons of VBM to manual tracing have demonstrated that VBM can overestimate effects while manual tracing may be more sensitive to differences across small-scale regions (Kennedy et al., 2009).

Frontal Cortex

The first studies investigating frontal neural correlates of ADHD examined the frontal lobe as an entire region of interest (ROI). Researchers found that male children and adolescents had smaller frontal regions than those without ADHD (Filipek et al., 1997; Mostofsky et al., 2002; Castellanos et al., 2002). Brieber et al. (2007) found that there were decreases in middle frontal grey matter in those with ADHD, whereas Mostofsky et al. (2002) found that boys with ADHD had smaller total cerebral volume and premotor grey matter volume. These results suggested that decreased regional volumes in ADHD are not restricted to the PFC, and that other areas may also contribute to the deficits observed in ADHD. Further analyses indicated that the decrease in total cerebral volume was mostly accounted for by the smaller frontal lobes. However, Mostofsky and colleagues suggested that their results indicated that decreased volumes in ADHD were not specific to the PFC, but that these findings may be due to use of the Talairach tracing method.

Anterior Cingulate Cortex

In addition, studies have examined the morphological characteristics of the cingulate cortex in individuals with ADHD. This is not unexpected as the ACC has many reciprocal connections to the prefrontal and parietal regions, and is thought to play a

larger role in modulating complex cognitive, autonomic, and emotional states (Vogt, 2009). Further, specific regions are thought to be associated with specific cognitive functions. For instance, the dorsal ACC, or dorsal anterior midcingulate region, has been found to be involved in moment-to-moment adjustments in behaviour through feedback signals it receives from other neural nodes (Bush, 2009), whereas the rostral ACC, or perigenual ACC (i.e., Vogt, 2009) has been found to be more involved with emotional stimuli or tasks (e.g., Vogt, 2009). A new theory of ACC functioning has been proposed by Holroyd and Yeung (submitted), which describes the ACC [i.e., Vogt's (2009) dorsal anterior midcingulate cortex] as playing a role in selecting and maintaining options. That is, the ACC supports the selection and maintenance of related behaviours that work together to produce a goal. Furthermore, each option contains all sets of actions from each possible initiation state for a particular goal. Holroyd and Yeung explain that the midbrain dopamine system supports the ACC with regards to options. Once options are already learned and are being selected for use with a particular goal, the midbrain dopamine system reinforces use of the most appropriate option through tonic signalling to the ACC. More specifically, in this context, dopamine signals will select options with highly-valued goals against other actions which carry immediate payoff, but hinder progress to initial goal completion. Therefore, the ACC, with feedback from the dopamine system monitors and evaluates goal-directed action. It is important to emphasize that the ACC is not involved in the specific behaviours that occur in order to produce goals; these details are within the domain of the dorsolateral PFC.

Posner and Rothbart (2007) further explained that there are three attention systems within the brain: the orienting, alerting, and executive attention systems.

Moreover, findings from imaging studies support the presence of these systems and have indicated that the ACC is one of the important neural structures within the executive attention system. Posner and colleagues have also stated that the executive attention network, via pathways in the ACC, is involved in regulation of behaviour as well as cognitive and emotional systems. This finding has been supported by various imaging studies and analyses (e.g., Bush et al., 1999; Botvinick, Cohen, & Carter, 2004),

Although morphometric studies of the ACC have been conducted, there have been no consistent findings regarding ACC volume differences in those with ADHD relative to controls. Results from varying studies have found smaller volumes of the ACC in the left hemisphere (e.g., Carmona et al., 2005), decreased ACC volume in the right hemisphere in treatment-naive but not in chronically treated children (i.e., Pliszka, Lancaster, Liotti, & Semrud-Clikeman, 2006b), or even lack of volumetric differences between an ADHD and control group (Mostofsky et al., 2005). Some studies have found that children with ADHD have thinner cingulate cortices than healthy controls and that progressive thinning of this region was associated with poor clinical outcome as rated by the Children's Global Assessment Scale and persistence of DSM-IV designated ADHD (Shaw et al., 2006). Functional MRI (*f*MRI) studies comparing neural activity in those with ADHD relative to controls have found decreased activation (e.g., Tamm, Menon, Ringel, & Reiss, 2004), or lack of activation during unsuccessful inhibition (Pliszka et al., 2006a) in those with ADHD. As the ACC has been implicated in error detection, attention monitoring, and goal-directed feedback, Bush (2010) postulated that abnormalities in the ACC could underlie the three main symptoms (i.e., hyperactivity, impulsivity, and inattention) of ADHD. Thus, continued examination of the ACC is

considerably important as this region is an important node in the attention networks relevant to performance of executive functions.

Objectives and Hypotheses

Although there have been an extensive number of studies that examined neural correlates of ADHD, there are many inconsistent findings in the volumetric analysis of regional areas in the brains of children with ADHD. Further, due to the high degree of labour involved in manual tracing, few studies have employed in-depth, manual volumetric imaging studies of the ACC. Thus, this study will examine whether four subregions of the ACC (namely, subgenual, subcallosal, rostral, and dorsal) differ between children with ADHD and healthy matched controls, as well as whether specific ACC regions are atypically sized within children with ADHD. The ACC, in particular its dorsal region, has been found to be different in many studies that examined its activity or structure in those with ADHD relative to healthy individuals. Furthermore, as explained by Crosbie, Pérusse, Barr, and Schachar (2008), genes, along with environmental factors, combine to influence structural and cellular aspects of the brain, which further interact to influence physiology and cognition. Together, these factors combine to produce observed behaviour such as the inattention, impulsivity, and hyperactivity of ADHD. Therefore, it is important to further examine the ACC in greater detail to better understand the extent to which volumetric abnormalities may contribute to the symptomatology of ADHD. Based on the extent volumetric research, it is hypothesized that ACC volumes will be significantly reduced in those with ADHD relative to matched controls.

To further examine the relationship between cognitive and behavioural symptoms prevalent in children with ADHD and brain structure, analyses of the associations between ADHD symptomatology and ACC subregions will be conducted. This study will investigate the relationship between subregional ACC volumes and performance on executive functioning tasks as well as behavioural ratings (e.g., hyperactivity and attention). Because prior studies have found that the dorsal ACC, via other neural structures, is involved in response selection (e.g., Bush, 2011) and monitoring of current behaviour towards completion of a goal (e.g., Holroyd & Yeung, submitted; Posner & Rothbart, 2007), it is hypothesized that this region, along with the rostral ACC will be associated with performance on incongruent trials of the Stroop task. As the ACC is an important node within the executive attention network (e.g., Posner & Rothbart, 2007), it is also hypothesized that dorsal and rostral ACC volumes will be associated with divided-attention tasks. Less is known about the role that other subregions of the ACC play in executive function task performance as well as school behaviour.

Method

Participants

Magnetic resonance (MR) images of ten Spanish children with ADHD and ten matched-normal controls, ages 7-10 years old, were used in this study. Of those with ADHD, five were diagnosed with ADHD-PI and five with ADHD-C. The sample included thirteen males and seven females. All children were identified as right-handed. One participant with ADHD-C and one with ADHD-PI were receiving stimulant drug therapy (i.e., Concerta). The groups were matched by age, gender, and school grade. Children with comorbid medical conditions or neurological disorders such as oppositional defiant disorder, conduct disorder, and Tourette syndrome were excluded from participation. While groups with different ADHD subtypes are sometimes separated for analysis (e.g., Batty et al., 2010), they are often examined together (e.g., Carmona et al., 2009; Luders et al., 2009). The latter approach was taken in this study. Members of the control group were recruited from the classrooms of participants with ADHD.

MR scans and recruitment of participants occurred at the Complutense University and the Ruber International Hospital in Madrid, Spain. Images were collected under the supervision of J. Alvarez-Linera Prado, MD. Children were assessed by a licensed clinical neuropsychologist (Elena Perez-Hernandez, PhD) and were eligible for study participation if they met the diagnostic criteria from the *DSM-IV-TR* (APA, 2000). ADHD diagnosis was further supported with ratings from the Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1992), which has been adapted and standardized for the Spanish population (Reynolds & Kamphaus, 2004).

Procedure

Full assessment and neuroimaging data collection occurred in three stages. First teachers completed questionnaires examining participants' classroom behaviour (stage 1). Following this stage, the neuropsychological tasks were administered to the children at the Complutense University (stage 2). For children who were taking medication, administration of neuropsychological tasks occurred prior to their first medication dosage of the day. Participants then underwent magnetic resonance imaging at the Ruber International Hospital (stage 3). Stage 1 to Stage 3 took approximately 1.5 months.

Materials

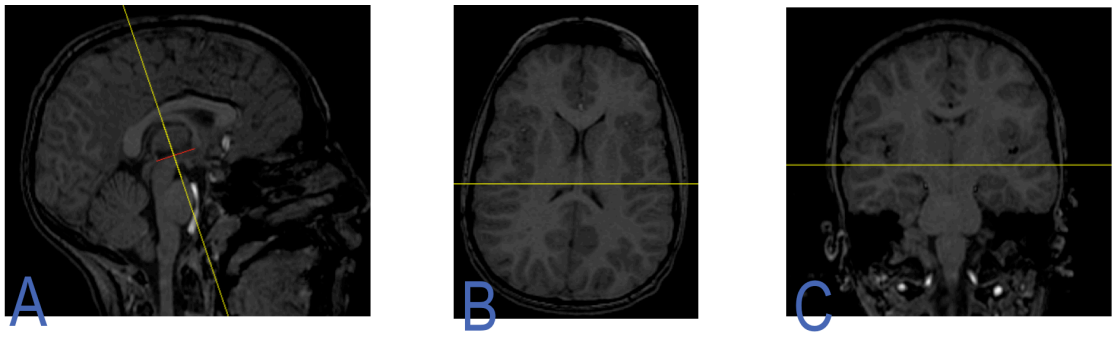
MRI data sets (.8999 mm thickness) were acquired across the whole brain on a GE Signa HDxt 3.0T scanner at the Ruber International Hospital in Madrid, Spain. T1-weighted images with contiguous 1.8mm axial slices were obtained over an acquisition matrix of 256 X 192. In a previously conducted study using the same data set, Analyze 9.0 software (Mayo Clinic, 2009) was used for post-acquisition processing, including alignment, total brain volume, parcellation, and compartmental volumetric extraction of total brain volume (Caulfield, 2010), on an Apple iMac workstation connected to a Wacom tablet.

Alignment

An alignment procedure was conducted on the MRI scans to standardize their position within Cartesian coordinates and orientation in the yz, xz, and xy planes (Figure 1). To align the yz plane, the mid-sagittal slice was identified using the anterior and posterior commissures (AC-PC) and cerebral aqueduct as markers. A line was then

drawn from the PC to the AC. A perpendicular line was pitched 90º to the plane of the AC-PC line. These steps created a horizontally aligned plane with the AC-PC line. To align the xz plane, the image was rolled left or right until the longitudinal fissure appeared vertical at a 90º angle while in the transverse view. To align the xy plane, a horizontal line was tilted left or right until it appeared perpendicular to the longitudinal fissure in the coronal view. After alignment, a visual inspection in the transverse and coronal view ensured the left and right ocular sockets were equal in diameter. If the ocular sockets appeared uneven, then the alignment in the transverse and coronal views was reexamined.

Figure 1. (A) Alignment in the XY plane. (B) Alignment in the XZ plane. (C) Alignment in the YZ plane.



Parcellation of the ACC

Based on a parcellation protocol by Howard et al. (2003), a horizontal line was drawn through the AC-PC to mark the dorsal/orbital parcellation on the midsagittal slice. To delineate the ACC from the rest of the brain, a parcellation procedure based on McCormick et al. (2006) was used. To mark the posterior boundary of the dorsal ACC

(plane C), a vertical line was drawn in the middle of the gyrus anterior to where the ascending marginal sulcus (i.e., ascending ramus) joined the cingulate sulcus horizontally in the sagittal orientation (see Figure 2). To delineate the dorsal ACC from the rostral ACC, a parcellation boundary (plane A) was drawn on the second slice anterior to where the tips of the genu were no longer connected in the coronal orientation. To delineate the subcallosal and subgenual ACC, parcellation lines (plane B) were drawn on the slice anterior to the slice where the putamen first appeared in the coronal orientation. For each brain, the location of plane B could differ in the left and right hemisphere. The subcallosal region was located between plane A and plane B. The subgenual region began on the slice where the putamen first appeared and continued until the cingulate cortex was no longer present posteriorly. The longitudinal fissure divided each subregion into the left and right hemisphere. Thus, each brain tracing was composed of eight ROIs (see Figure 3).

Figure 2. Sequential demarcation of plane C, plane B, and plane A.

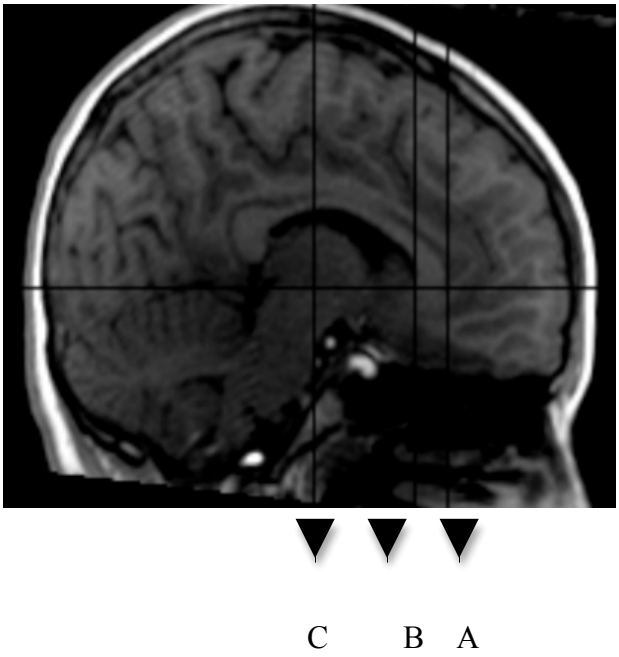
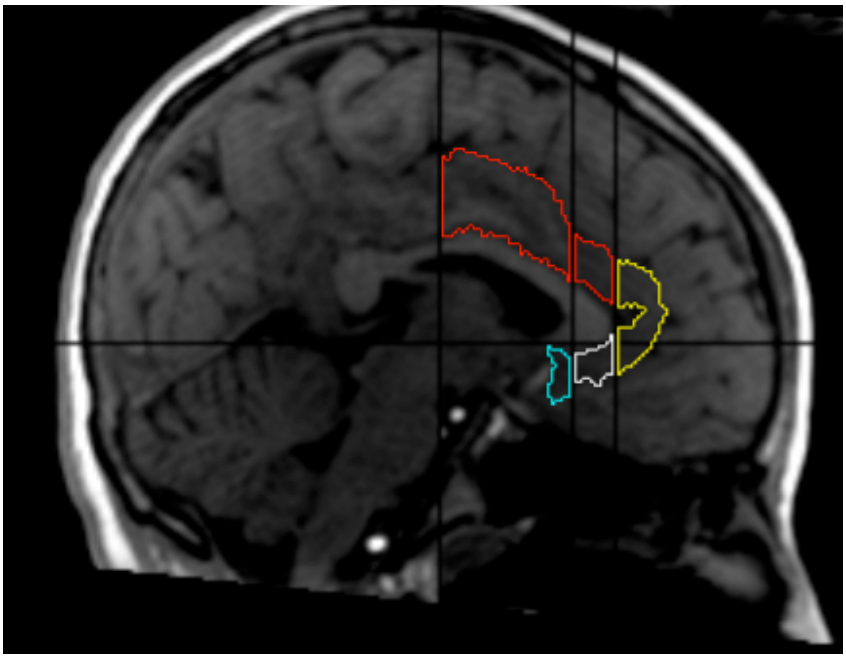


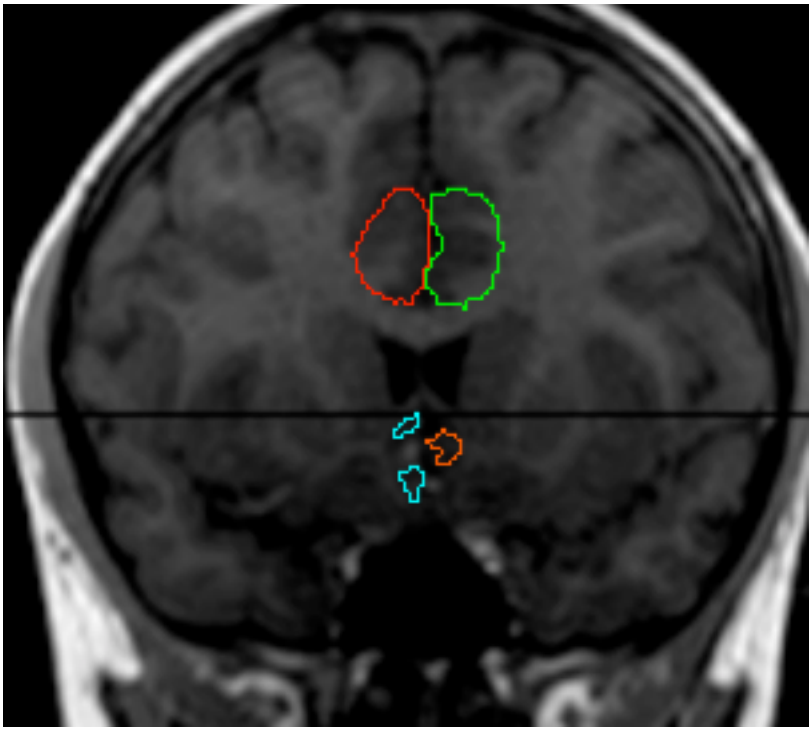
Figure 3. View of the dorsal (red), rostral (yellow), subcallosal (white), and subgenual (blue) left hemisphere ROIs in the sagittal orientation.



Tracing Protocol

All ROIs were traced in the coronal orientation and edited in both the coronal and sagittal orientations. Each ROI was traced separately in the left and right hemispheres using the longitudinal fissure as a guideline and the interior boundary (see Figure 4).

Figure 4. Coronal orientation of the dorsal and subgenual ACC.



Dorsal ACC

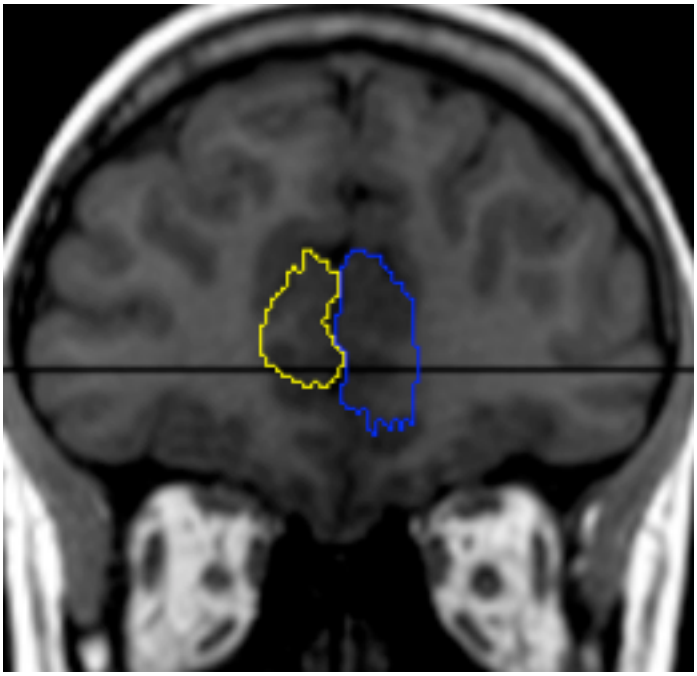
The dorsal ACC (dACC) was traced on continuous slices beginning on the slice anterior to plane C and ending at plane A. Akin to the protocol from McCormick et al. (2006), a circle was drawn for this subregion with the callosal sulcus as the ventral boundary and the cingulate sulcus (CS) as the dorsal boundary (see Figure 4). If a paracingulate sulcus was present, then it was taken to be the dorsal boundary (Fornito et al., 2006). The lateral boundary of each tracing was the outer edge of the cingulum.

Rostral ACC

The rostral ACC (rACC) was traced on continuous slices beginning at the slice anterior to plane A and ending when the cingulate, and if present, the paracingulate cortex, disappeared in the coronal orientation. As it was often difficult to determine

where the rACC ended in the coronal orientation, the sagittal orientation was used to guide tracing in the most anterior regions, as well as to determine its anterior ventral boundary. For this ROI, the dorsal cingulate sulcus, or when present, the paracingulate sulcus, was the superior boundary for each tracing. If the ventral cingulate sulcus was continuous with the superior rostral sulcus, the ventral cingulate sulcus was the inferior boundary. If they were separate, the superior rostral sulcus was traced as the inferior boundary in order to include paracingulate sulcus in the tracing (i.e., Fornito et al., 2006; Leonard, Towler, Welcome, & Chiarello, 2009). Similar to the dACC, circles were traced from the longitudinal fissure, following the guideline of the cingulate sulcus in the dorsal region, around the cingulum bundle, medial to the corpus callosum, and ventral around the cingulum bundle to the ventral boundary (see Figure 5).

Figure 5. Coronal orientation of the rostral ACC



Subcallosal ACC

The subcallosal ACC (sACC) was traced on continuous slices in the coronal orientation beginning at the slice posterior to plane A and ending at plane B. As the ACC can be asymmetrical, the posterior boundary of the sACC could be different for both the left and right hemispheres. For this ROI, the inferior boundary of the genu of the corpus callosum was the dorsal tracing boundary and the continuation of the cingulate sulcus or superior rostral sulcus from the rACC was the ventral boundary. The midline boundary was the longitudinal fissure. The ROI was traced in a circle from the longitudinal fissure at the corpus callosum in a circle on continuous slices.

Subgenual ACC

The subgenual ACC (sgACC) was traced on continuous slices in the coronal orientation beginning on the slice posterior to plane B and continuing until the cingulate gyrus was no longer present (see Figure 4).

Classifying paracingulate sulcus

As there is intra-individual sulcal variability in the cingulate region (e.g., Leonard et al., 2009), it was often difficult to determine whether a true paracingulate cortex was present. Therefore, a procedure by Fornito et al. (2006) was followed to evaluate the appropriateness of including paracingulate cortex with the tracings of the ACC. Briefly, presence of the paracingulate sulcus was evaluated separately for each hemisphere. A paracingulate sulcus was classified as present if it was visualized in at least three slices from the most midsagittal slice of each hemisphere. Further, the sulcus needed to be at least 20 mm long in each of those three slices.

Asymmetry analysis

The coefficient (R-L)/[(R+L)(0.5)] was used to determine interhemispheric asymmetry, with negative scores indicating leftward asymmetry and positive scores indicating rightward asymmetry (e.g., Filipek et al., 1997).

Assessment Instruments

Demographic information was collected during the intake interview and SES was measured using the Barratt Simplified Measure of Social Status (Barratt, 2006). The following valid and reliable instruments have been standardized for a Spanish-speaking population and were administered by the Neuropsychologist Elena Perez-Hernandez, PhD.

Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1992)

A comprehensive measure in which children's behaviours in a wide variety of areas (e.g., internalizing and externalizing psychopathology, executive functioning, adaptive skills) are rated by teacher-, parent-, and self-report. Scores are reported as T-scores, which have a mean of 50 and a standard deviation of 10. Scores greater than 69 indicate clinically significant impairment, and scores greater than 59 are indicative of one being "at risk" for the measured construct. The BASC has been adapted and standardized for use with Spanish populations (Reynolds & Kamphaus, 2004). Only teacher ratings were examined for these analyses.

Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2004)

Digit span forwards/backwards, letter-number sequencing, and arithmetic subtests were used to assess working memory. Similarities, vocabulary, information, and word

reasoning subtests were used to derive a composite verbal comprehension index score. Block design, picture concepts, matrix reasoning, and picture completion subtests were used to derive a perceptual reasoning index score. All composite scores were combined to derive a full scale IQ score.

Attention

The battery to assess attention was designed by Elena Perez-Hernandez, PhD (http://eprints.ucm.es/8447/1/T30734.pdf). It includes tasks to examine sustained, selective, alternating, and divided attention in two modalities, auditory and visual, based on the model of attention proposed by Sohlberg and Mateer (1989). One task serves to examine sustained visual attention and is labeled, "hand hunter". It is a traditional cancellation task with 374 items and duration of 5 minutes. The second task ("in the zoo") evaluates auditory sustained attention and uses 300 animal sounds. The child is trained to raise a hand every time s/he hears the horse sound. The visual selective attention task is a cancellation task using a target stimulus (specifically a EURO coin) and look-alike distracters. The child is given a pen to cross each target stimulus in a matrix during three minutes. The pen colour is changed every minute. In the auditory selective attention task ("in the woods") the child is trained to raise her/his hand every time s/he hears a bird sound while similar background noises are presented. There are 180 stimuli and only 15 are target bird sounds. Duration of each task is three minutes. Reported scores are raw scores (i.e., number correct).

Stroop Task

This test consists of two parts. Participants read a printed sheet with colour names such as blue and red printed in incongruous colours such as black and green. In the first, congruent trial, participants read the words as printed, regardless of the colour it is printed in. In the second, or incongruent trial, participants name the colours the words are printed in, while ignoring the colour name that is printed. Time scores from the two conditions are manipulated to derive the interference score. Scores greater than zero are indicative of greater resistance to interference.

Statistical Procedures

Multiple independent-samples *t* tests were conducted to determine whether there were between group differences in age, IQ, and total brain volume (TBV). Chi-square analyses were conducted to examine whether the proportion of males and females in the two groups were the same. Multiple ANCOVAs were conducted with TBV as a covariate to examine volume differences within and between the ADHD group and controls. Independent-sample *t* tests were conducted to examine differences in cognitive and behavioural functioning between the two groups. The critical value for all comparison was $p < .05$. Bonferroni corrections were applied to control for multiple comparisons.

Single measure intra-class correlation coefficients were calculated and used for reliability analyses, including intra- and inter-rater reliability. For intra-rater reliability, two brains were selected at random and retraced by the primary researcher following completion of all other tracing. For inter-rater reliability, one brain scan was selected at random and traced by a second expert tracer. Intra-class correlation analyses were conducted. Inter- and intra-rater reliability coefficients should be greater than .90.

Analyses of the relationships between performance on neuropsychological tasks and ROI volumes, using Pearson's *r,* were conducted with the effects of TBV partialed out. Regression analyses were conducted to examine whether ACC subregions predicted performance on cognitive and behavioural measures.

Results

Participant Characteristics

Due to the small sample size, the ADHD-PI and ADHD-C groups were combined for all analyses. All participants were right-handed. The proportion of females and males in each group did not differ significantly, $\chi 2$ (1, N =20) = .22, p = .639. SES did not differ significantly between groups, t(18) = .08, p = .935. Participants did not significantly differ in age, t(18) = -.12, p = .908, but an independent samples t test revealed that the FSIQ for the ADHD group was significantly lower than the control group, t(18) = 3.55, p= .002 (see Table 1).

Table 1. Summary of participant characteristics.

	ADHD	Controls
Characteristic		
n	10	10
Age, mean (SD)	8.84 (1.06)	8.79 (0.84)
Sex, number	4 females	3 females
IQ, mean (SD)	95 (16.80)	120 (14.46)
IQ Range	76-126	104-135

Note. SD = standard deviation. Age is reported in years and IQ scores are standard scores.

Behavioural Ratings

Significantly higher teacher ratings of attention problems were observed for the ADHD group relative to the control group, $t(18) = -7.58$, $p < .001$. No significant differences were observed for teacher ratings of hyperactivity between the two groups, $t(18) = -1.95$, $p = .067$. (see Table 2). No significant differences in behaviour were observed for amount of conduct problems, $t(18) = -2.28$, $p = .035$, or aggression problems, $t(18) = -1.54$, $p > .05$.

Cognitive Tasks

Accuracy on an auditory divided attention task was significantly worse for the ADHD group relative to the control group, $t(8.44) = -2.50$, $p = .035$ (see Table 3). Significance was not sustained after the Bonferroni correction was applied. No other significant between-group differences were observed for the other attention tasks, all ps $> .05$. Resistance to interference, as measured by the Stroop task, was not different for the two groups, $t(18) = -0.53$, $p = .603$.

Table 2. Teacher ratings for comparison groups from the BASC.

	ADHD			Controls		
BASC Scores	M	SD	Range	M	SD	Range
Hyperactivity	60.20	16.22	41-85	49.40	6.54	41-57
Attention Problems	69.30*	6.08	53-73	51.50	4.28	43-56
Conduct	57.50	10.48	41-82	49.30	4.42	43-56
Aggression	54.10	9.02	44-69	49.20	4.40	43-56

Note. BASC = Behavior Assessment System for Children.

*p <.0001.

Table 3. Resistance to interference on Stroop task and accuracy on attention tasks.

Cognitive Test			ADHD			Controls		
			M	SD	Range	M	SD	Range
Stroop			51.50	4.50	40-56	52.80	6.34	40-62
Attention	Sustained	V	123.60	70.76	0-217	143.60	68.65	82-222
		A	20.25	4.40	11-25	22.44	2.88	17-25
	Selective	V	59.57	7.79	48-68	70.33	21.21	44-100
		A	9.71	3.04	5-13	10.29	2.63	7-14
	Alternating	A	7.88	5.64	2-17	12.88	5.14	4-18
	Divided	V	170.00	47.40	109-230	202.67	37.58	160-275
		A	14.88*	7.55	2-24	21.89	2.57	17-24

Note. V = Visual; A = Auditory

* = $p < .05$.

Volumetric Differences

Because total brain volume (TBV) differences can contribute to overall volume in certain ROIs, TBV was used as a covariate to examine volumetric differences between the two groups. The right dorsal ACC tended to be larger in the ADHD group relative to the control group, $F(1.17) = 4.04$, $p = .061$, $\eta_p^2 = .19$ (see Table 4), despite a smaller TBV. No other ROIs approached significance.

Table 4. Mean volumes of TBV and ACC Subregions.

Region	ADHD		Controls			
	M	*SE*	*M*	*SE*	*p*	η_p^2
TBV	1 488 356 .40	76 657.39	1 499 754.10	97 271.89	.774	.00
ACC	31 006.18	1 494.17	28 277.82	1 494.17	.214	.09
L dACC	9 366.19	615.37	8 127.81	615.37	.173	.11
R dACC	8 971. 08	571.77	7 344. 82	571.77	.061	.19
L rACC	5 033.05	331.45	4 648.05	331.45	.423	.04
R rACC	5 590.09	507.56	5 590.61	507.56	.999	.00
L sACC	614.58	86.34	810.92	86.34	.127	.13
R sACC	783.08	81.37	921.42	81.37	.246	.08
L sgACC	367.04	68.13	412.66	68.13	.642	.01
R sgACC	281.07	64.80	421.53	64.80	.144	.12

Note. *M* = mean; *SE* = standard error of the mean; L = left, R = right.

Reliability

Intra-Rater Reliability

For the entire ACC, intraclass correlations (ICC) = .96 for both brains. Reliability for ACC subregions ranged from .53-1.0. ICCs were low for left and right rACC and sACC.

Inter-Rater Reliability

For the entire ACC, ICC = .95 for both brains. Reliability for ACC subregions ranged from .81-.97. ICCs were lower than .90 for the right dACC and left rACC.

Asymmetry Index

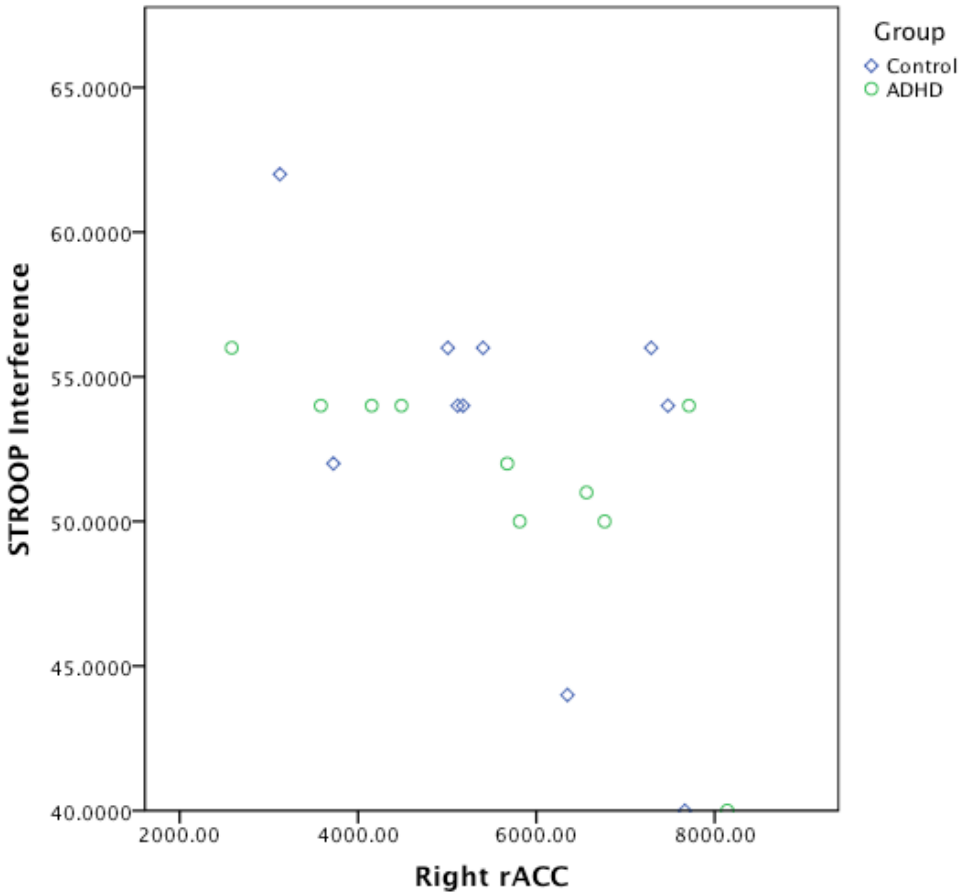
Significant differences in asymmetry between the groups were not observed, $t(18) = -.16$, $p = .875$. However, the ADHD group showed a rightward asymmetry, ($M = .004$, $SD = .129$) and the control group demonstrated a leftward asymmetry ($M = -0.01$, $SD = .255$). However, these results indicate a tendency to ACC symmetry.

Brain-Behaviour Relationships

Stroop Interference

Larger right rACC was associated with being more susceptible to interference for both the ADHD group, $r = -.71$, $p = .031$, $r^2 = .50$, and for the control group, $r = -.73$, $p = .026$, $r^2 = .53$ (see Figure 6).

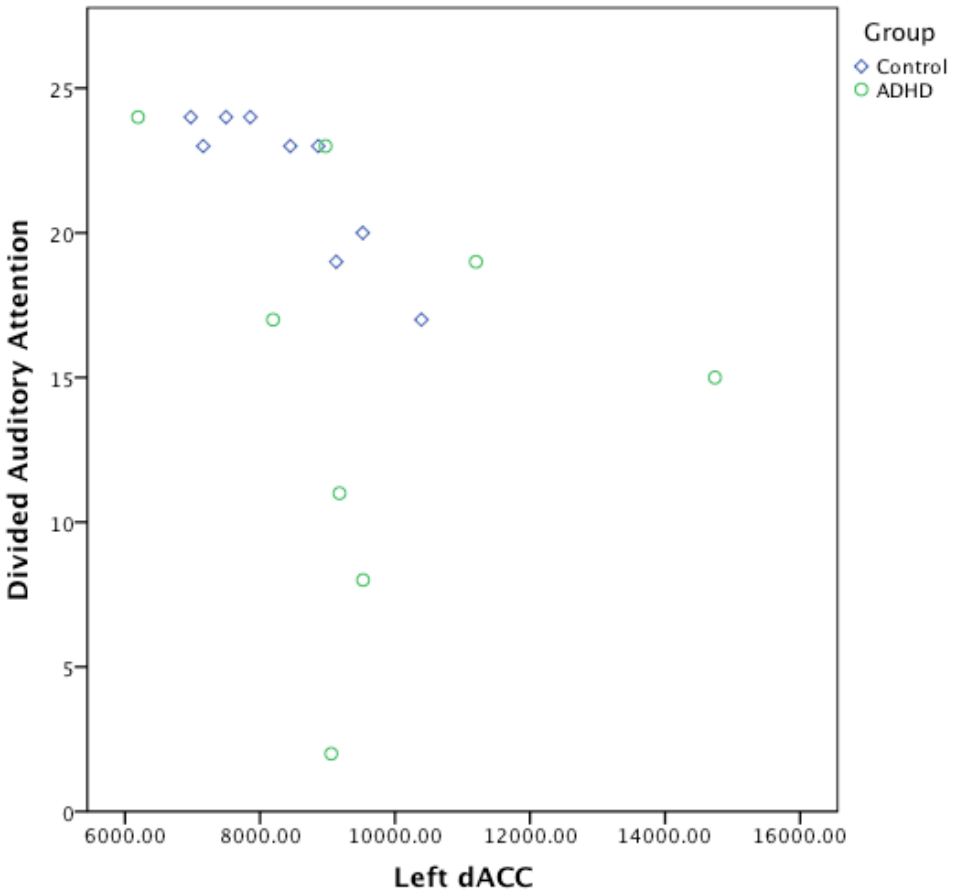
Figure 6. Relationship between Stroop Interference scores and right rACC.



Divided Attention

Greater accuracy on an auditory divided attention task was associated with a smaller left dACC for the control group, $r = -.91$, $p = .002$, $r^2 = .83$. No significant relationships were observed for the ADHD group on this task (see Figure 7).

Figure 7. Relationship between accuracy on a divided auditory attention task and left dACC.



Hyperactivity

Teacher ratings of hyperactivity were negatively associated with the left sgACC, $r = -.69$, $p = .041$, $r^2 = .48$ (see Figure 8), and right sgACC, $r = -.72$, $p = .029$, $r^2 = .52$ (see Figure 9), for the control group. No significant correlations were observed for the ADHD group .

Figure 8. Relationship between teacher ratings of hyperactivity and left sgACC.

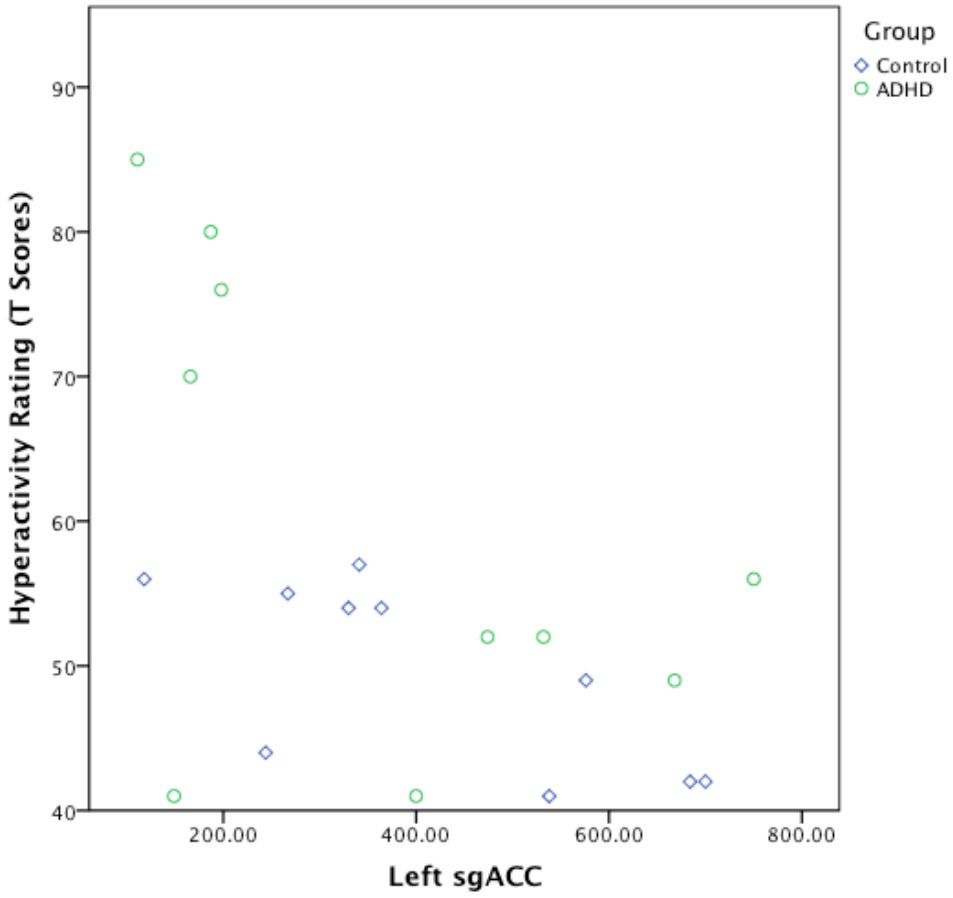
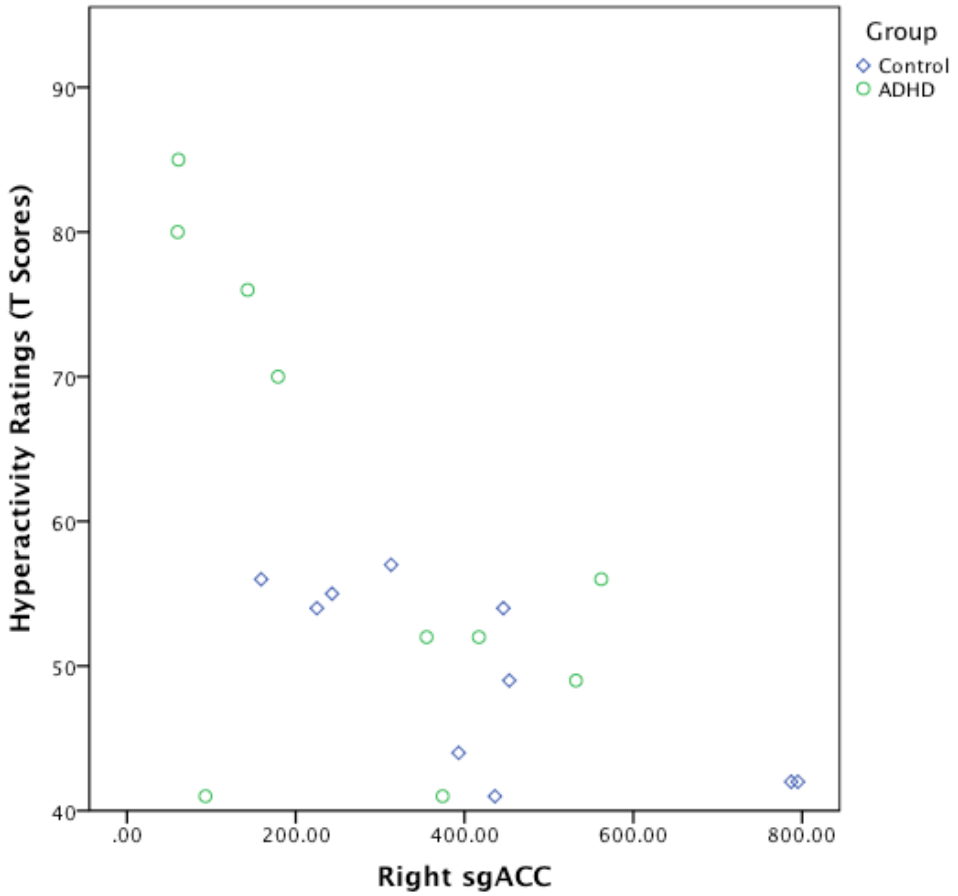


Figure 9. Relationship between teacher ratings of hyperactivity and right sgACC.



Attention Problems

No significant correlations were observed between either group for either the subgenual or subcallosal regions, $p > .05$.

Discussion

One of the goals of the current study was to examine whether volumetric differences of the ACC were observed between children with ADHD and matched healthy controls. In contrast to our hypothesis, the right dACC was marginally significantly larger for the ADHD group compared to the control group. In general, ACC regions tended to be larger in the ADHD group relative to healthy controls, whereas total brain volume was generally larger for the control group compared to the ADHD group.

What do Observed Volumetric Differences Tell Us About the Structural Morphology of those with ADHD Relative to Healthy Children?

Although the volumetric findings of this study are inconsistent with our hypotheses, the results are in line with previous findings from this research group, which found larger volumes of lateral and right orbitolateral PFC in a Spanish ADHD group (Caulfield, 2010). Significant volume differences were also observed between the two ADHD subtypes. While this study did not examine differences among the two subtypes of ADHD and controls, it would be informative to examine these differences in future studies as the two subtypes are increasingly becoming considered two separate developmental disorders (e.g., Diamond, 2010).

It was not unexpected that morphological differences were observed in the right dACC. Right frontal-striatal and frontal-parietal networks are thought to be atypical in individuals with ADHD (McAlonan et al., 2007; Mostofsky et al., 2002; Rubia et al., 1999). Mostofsky et al. (2002) divided the brain into functionally relevant subregions and found bilateral frontal grey matter decreases in boys with ADHD, with more significant

decreases in the right hemisphere. Mostofsky and colleagues stated that these differences were indicative of abnormalities in neuronal structures in those with ADHD, which was not surprising given that the right frontal region is involved in sensory-attentional processes as well as response inhibition. Furthermore, the dorsal region of the ACC is one of the brain regions considered most abnormal in ADHD, and is thought to be involved in cognitive activities that are particularly impaired in this disorder as well (Bush, 2009). It was noted that McCormick et al.'s (2006) ACC parcellation protocol might differ from other structural divisions of the cingulate cortex. For instance, Vogt's division would have included part of our posterior dACC as part of the posterior cingulate cortex (PCC; Vogt, 2009). Rubia et al. (1999) found that underactivations of the right cingulate cortex during an inhibition task included sections of Brodmann Area 31 (i.e., PCC). These authors concluded that in addition to anterior parts of the frontal lobes being implicated in the abnormalities of the midline attention system in ADHD, so too were its posterior aspects. Therefore, a significant finding for this ROI is consistent with past findings that have implicated right frontal pathophysiology in ADHD.

As mentioned previously, these results differ from previous studies in that the right dACC was larger, rather than smaller, for the ADHD group compared to controls; all other ROIs, with the exception of the subcallosal regions, followed the same trend. While other studies have examined morphological differences (volume, shape, density) in pediatric samples over a wide range of childhood ages (e.g., Castellanos et al., 2002; Durston et al., 2004), the distribution of ages in the current study was much narrower, ranging in age from 7-10 years, enabling the examination of specific brain processes at a more specific developmental stage.

In typical development, frontal cortex reaches peak neuronal density at approximately 12 years of age, with a subsequent proliferation in synaptic elimination. Concurrently, white matter tracts undergo a substantial increase in myelination (Giedd et al., 1999). It is important to emphasize that: 1) the anterior cingulate region encompasses areas other than the superior frontal regions, 2) caudal regions typically develop prior to rostral regions, and 3) regions more involved in basic processes develop prior to those involved in higher-order ones (Huttenlocher & Dabholkar, 1997; Kelly et al., 2009). Further, because our dACC region encompasses aspects of the PCC (as per Vogt, 2009), it would be reasonable to assume that the volume disparities are partly due to maturational differences between the two groups in the captured PCC area.

Moreover, decreases in cortical grey matter typically begin by approximately 8 years (Reiss, Abrams, Singer, Ross, & Denckla, 1996). Therefore, a lag in neuronal pruning in the ADHD group is a reasonable explanation given that the current sample has a mean age of 8.82 years and that part of the dACC encompasses what others would term PCC. In a study examining cortical thickness, Shaw et al. (2007) found that certain regions were thinner in those with ADHD. Healthy controls reached peak cortical thickness in 50% of areas measured by age 7.5, whereas those with ADHD reached the same stage in cortical maturity approximately three years later. Shaw et al. explained that the findings were indicative of a substantial delay in neuronal maturation of both grey and white matter in individuals with ADHD. Similarly, Castellanos et al. (2002) observed that while cortical volumes of those with ADHD were generally smaller than typically observed, cortical development simply occurred along a smaller scale and did not deviate substantially from normal development. One outcome of a delay in

maturation of the dACC is that the lag in development likely impacts the region's involvement in the midline attention system in ADHD (e.g., Carmona et al., 2005). Developmental delays in an area involved in this system therefore may be one of the reasons that attention problems are so prevalent and observed in ADHD (e.g., Bush, 2010; Carmona et al., 2005).

While cortical differences between the two groups were observed in the dACC, the other ACC ROIs did not differ significantly between groups. Likely, the reason that differences were not observed in other ACC subregions is because pruning should begin later in the more rostral regions and thus, there were no apparent differences at this developmental stage. Additionally, as the left hemisphere develops later than the right hemisphere (e.g., Olesen, Nagy, Westerberg and Klingberg, 2003), and given the associations of right hemisphere involvement in ADHD, volumetric differences would be less expected in the left hemisphere.

In contrast to the current study, Batty et al. (2010) examined cortical grey and white matter differences in boys with ADHD and found smaller volumes in all four lobes of the brain in children with ADHD (mean age = 12.65) relative to controls. While they observed that the pars opercularis, which is an area important for inhibiting behavioural responses, was significantly thinner in the ADHD group, cortical thickness of the caudal and rostral ACC was significantly larger. These results are consistent with our findings of larger ACC volumes. Further, while they found smaller TBV and grey matter in all four lobes, no concurrent decreases in white matter were observed. Although some of Batty and colleagues' findings were inconsistent with ours, overall their findings lend greater support to the conclusion that delays in maturation of grey matter are particularly

responsible for the volumetric differences observed in this study. However, to be fully comfortable with this conclusion, further experiments need to be conducted in which white and grey matter are examined separately.

The discrepant findings of this study relative to previous studies are also likely not attributable to the use of a Spanish sample in this study. McAlonan et al. (2007) found that children in China with ADHD also had smaller cortical regions and less white matter than typically developing children. Interestingly, studies in British samples reported inconsistent findings. Overmeyer et al. (2001) found that their ADHD sample had smaller brain volumes, whereas Batty et al. (2010) found a thicker ACC in their sample.

Additionally, the ACC was symmetrical in both groups. While laterality has often been observed in the ACC of adults (e.g., Kelly, 2009), reduced laterality has been observed in children during attention tasks (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002). Moreover, Kelly et al. (2009) found bilateral connections between ACC subregions and other brain structures. They found that increased lateralization of the ACC occurred with increased age. Therefore, it is not unexpected that there was symmetry in the ACC of both groups. It appears that laterality of the ACC is a function that develops fully only by late adolescence and adulthood (Kelly et al., 2009).

Finally, it is likely that differences in methodology of ACC tracing may have contributed to our discrepant findings. It was uncertain whether to include the paracingulate cortex in volume calculations of the ACC as well as when to include it. While some studies have not included paracingulate cortex under all conditions in their tracings (i.e., McCormick et al., 2006; Mostofsky et al., 2002), numerous authors have

included it as the two regions are the most physiologically and anatomically similar regions in the brains (Vogt, 2009; Whittle et al., 2009). Therefore, inter-study differences in ACC parcellation may have contributed to some of the inconsistent findings. Forty percent of the ADHD group had paracingulate sulci in the left and right hemisphere, whereas the paracingulate sulcus was present in 10% of the control group in the left hemisphere and 20% in the right hemisphere.

What is the Behaviour and Cognitive Profile of the ADHD group?

Given the discrepancies between these results and the extent literature, it became relevant to examine the behavioural and cognitive profile of the ADHD group to determine whether differences existed in these domains as well. Results indicated that teacher ratings of attention problems, hyperactivity, conduct problems, and aggression on the BASC were worse for the ADHD group relative to the control group. Lower accuracy on an auditory divided attention task was also observed. These results are consistent with the prevalent attention and impulsivity problems those with ADHD typically experience (APA, 2000; Berger & Posner, 2000); attention problems and hyperactivity were also within the high end of the "at risk" range and clinically significant range for the BASC. Further, difficulties in these areas are expected given past findings which have demonstrated that children with ADHD have attention problems (Hill et al., 2003) and behaviour issues (APA, 2000; Castellanos et al., 2002). The ADHD group also tended to be more susceptible to interference. Numerous examples of interference issues on the Stroop task have also been observed (Lansbergen, Kenemans, & van Engeland, 2007). Lansbergen et al. (2007) further suggested that poor performance on the Stroop task is reflective of impaired behavioural inhibition.

What do the Relationships Between Volumetric and Behavioural Findings Mean?

Overall, an interesting profile is underlying this study's results: Larger ACC volumes were often associated with worse cognitive performance, whereas smaller volumes were often associated with worse behaviour ratings. To further examine these patterns, a brief summary of the brain-behaviour relationships is presented below:

Dorsal ACC

For the control group, inverse correlations were observed for this region and accuracy on an auditory divided attention task. A similar pattern of activity was not observed for the ADHD group.

Rostral ACC

Inverse correlations were observed for the Stroop interference for both the control and ADHD group.

Subgenual ACC

For the control group, smaller volumes were associated with greater hyperactivity.

Except for the positive correlation between susceptibility to interference on the Stroop and the right rACC, similar patterns of associations were not observed between the two groups. These correlations suggest that in this small sample of children with ADHD, the specific subregions of the ACC are contributing differently to functioning in those affected with ADHD. Furthermore, the hypothesized brain-behaviour relationships to performance on attention tasks or behaviours to ACC regions were observed in the

control group, which further emphasizes that something atypical is occurring in the brains of those with ADHD.

These results are consistent with previous findings of relationships between performance on inhibitory control tasks and ROIs in control participants, but not with those with ADHD (Batty et al., 2010; Durston, Mulder, Casey, Ziermans, & van Engeland, 2006; Rubia et al., 2010). A number of studies have also found differing patterns of functional activation in those with ADHD (Durston et al., 2003; Rubia et al., 2010; Rubia et al., 1999; Tamm et al., 2004). Durston et al. (2003) noted that compared to typical children, those with ADHD activated a more diffuse network of regions during an inhibition task than expected. In another study, decreased activation in both anterior and posterior cingulate cortices was observed during a visual-spatial switch task (Rubia et al., 2010). Both groups concluded that the findings were reflective of a delay or abnormality in frontal-striatal circuitry. Konrad and Eickhoff (2010) also suggested that abnormal connectivity in those with ADHD could be a reflection of structural variation observed in this disorder.

Further supporting these findings, Kelly et al. (2009) examined the typical development of functional connectivity in the ACC, and found that caudal, dorsal, and rostral subregions developed prior to more anterior cingulate regions. In addition, diffuse patterns of proximal connectivity were observed in childhood, but stronger distal connections among established functional networks developed as a function of age and region. They further explained that motor and attention connectivity networks associated with caudal and dorsal ACC developed earliest. As the dACC of the current study encompassed some aspects of PCC and has typically developed more of its functional

connections, it is not surprising that these structures are still large in those with ADHD. Based on the theory that there is a maturational lag in those with ADHD, one would expect that the ROI would not have fully developed in children with ADHD. Although it might be expected to therefore find smaller regions, this would not be the case as white and grey matter mature simultaneously (e.g., Reiss et al., 1996). In ADHD, white matter connections might be more diffuse and scanty, whereas grey matter in these regions likely have not undergone much of the synaptic elimination process, thereby leaving this widely dispersed and also larger. One would expect that the leading reason for larger volume would be grey matter differences because if grey matter maturation was occurring at its typical rate, similar relationships should have been observed between the ADHD and control groups; as it is early in the myelination process significant white matter differences would not be expected to appear as of yet in this developmental stage. Considering this, the results support the idea that delays in maturation, rather than different activation or true deviations in morphology, are responsible for brain-behaviour variations.

Typically, cognitive abilities such as IQ, inhibitory control, and working memory are associated with diffuse brain regions in younger children, while these functions are associated with more specialized areas in older children and adults (e.g., Bunge et al., 2002; Baltes et al., 2006; Tsujimoto et al., 2008). As fractionation of the ACC also occurs with age (e.g., Kelly et al., 2009) this lends further support to the notion that neuronal maturation in ADHD was delayed in this sample. Because of a delay in fractionation, it is increasingly evident that regions and networks responsible for attention and inhibitory control continue to be located diffusely throughout the brain in

those with ADHD. Supporting this argument, Casey et al. (1997) found that in typically developing children, response time decreased with age on an inhibitory response task. Interestingly, right ACC activation (BA 24' and 32') was correlated with age. Casey et al. argued that throughout childhood, increasingly efficient attentional resources are responsible for decreased reaction times. Konrad and Eickhoff (2010) similarly stated that connectivity patterns of individuals with ADHD were reflective of the connectivity patterns observed in younger children. Given the results of these studies, it would not be surprising that most cognitive tasks were not correlated with an ACC subregion in the ADHD group, given that more proximal diffuse connections are normative in less mature brains.

One more issue to consider in reflecting upon these findings involves the impact of medication in ADHD neural networks development. Rubia et al. (2010) found that when children and adolescents with ADHD were given methylphenidate, connectivity patterns during a sustained attention task were normalized. Palomero-Gallagher and Zilles (2009) noted that the ACC has the highest density of dopaminergic innervations in the brain. As methylphenidate works by inhibiting reuptake of dopamine, it is possible that in medication-naïve children, lack of dopamine is contributing to reduced performance on the cognitive tasks by impacting connectivity in neural networks.

Strengths and Limitations

As marginally significant differences were only observed in one region, it is possible that the limited age range of our sample enabled the observation of larger, rather than smaller volumes. In previous studies (e.g., Kates et al., 2002; Mostofsky et al., 2002; Shaw et al., 2006; Ranta et al., 2009), age range of the pediatric sample was much

broader (e.g., 7-13 years). Broader age ranges allow the opportunity to see the developmental differences observed in ADHD over a wide range of areas as peak grey matter generally occurs at approximately 12 years for boys and 11 years for girls (e.g., Giedd et al., 1999). As the current sample has a mean of 8.82 years, we received a clearer picture of what structural brain delays look like at this particular age. In future, it would be interesting to conduct the same study with an addition control group of children who were younger than the current sample. This would provide further support for the hypothesis that children with ADHD suffer from delayed maturational processes, rather than true neural differences.

Another important caution is that although this study gives us another piece of the puzzle that dACC is atypical and likely involved in the pathophysiology of ADHD, the structural abnormalities of the dACC are obviously not solely responsible for the symptoms of ADHD. Based on the extent literature, morphometric differences in PFC, cerebellum, striatum, as well as connecting white matter tracts among the areas also contribute to the symptomatology of ADHD. Future studies should examine these regions as well as their relationships with one another. In addition, it would be beneficial to examine only the white matter in areas such as the ACC and PFC to determine whether growth and elimination of cortical matter is affected differentially in those with ADHD.

In addition, while manual tracing is considered the gold standard, there is subjectivity inherent in this method as human thinking is involved rather than simply being a solely automated procedure (Leonard et al., 2009; Niogi, Mukherjee, Ghajar, & McCandliss, 2010). One of the main limitations of this study is the ambiguity inherent in

tracing a region such as the anterior cingulate and paracingulate cortices (e.g., Leonard et al., 2009). As there is much variability in the sulcal patterns of these regions, it was at times difficult to determine some of the boundaries of certain ROIs such as the rACC. While reliability was high overall, it may be necessary to modify the protocol for regions such as the rACC for future studies to obtain reliabilities that are as high as the rest of the structure. It is important to note that the variability is inherent to the region and would not be improved by using a different method of tracing such as voxel-based morphometry.

As well, the method we define regions can make it difficult to draw conclusions about the importance of the results in understanding the neural correlates of ADHD (e.g., Bush, 2010; Kelly et al., 2009; Mostofsky et al., 2002; Vogt, 2009). For instance, many research groups have different ways of defining subregions of the ACC and thus have found that certain cognitive tasks correlate with different subregions of interest (e.g., Bush et al., 2000; Kelly et al., 2009). It is therefore difficult to explain findings in a consistent manner and this may explain the lack of consistency among studies with similar aims.

Additionally, this study did not examine grey and white matter differences, but rather examined the ACC. As these regions were not investigated separately, it is difficult to make conclusions as to why differences were observed in the right dACC. Were observed differences due to a lag in maturational development? Or, were the findings a result of the sample's gender differences? Moreover, as the data collection was out of our control, images were primarily collected for use with *MEG*. Thus, the image contrast was not optimal. It is possible that if the technicians had collected the images

with a better contrast as needed in MRI research, certain aspects such as the ambiguity of the tracings may have been dealt with more easily.

Another limitation of this study is the small sample size. Although it would have been beneficial to conduct this study with a greater number of participants to increase the power of these findings, the scans were collected prior to beginning this study. Therefore, in future, this study should be replicated with greater number of participants to confirm the findings. However, it is important to emphasize that because of the combination of a reliable protocol (i.e., as measured by ICC) and well-calibrated measurements (i.e., manual tracing) that were based on repeated measurements (i.e., slice-by-slice tracing), this issue, while remaining relevant, is less problematic.

It is also unclear whether medication had an effect on the results of this study. Two participants in the ADHD group were taking Concerta. Past studies have found medication-related differences in brain volume in ADHD studies (Pliszka et al., 2006), such that there were differences in brain structure in medication naïve versus chronically treated patients. In this study, one of the participants taking Concerta had the largest total ACC volume. Therefore, it is possible that having 20% of the ADHD sample on medications could have affected the study's results in some way.

Although the groups were matched on age and grade, there were significant between-group differences in full scale IQ. This difference may have played a role in the findings. However, it is difficult to disentangle as it is often unclear whether IQ differences could have played a role in observed volumetric differences (e.g., Batty et al., 2010; Yang et al., 2011).

Moreover, the inconsistent results observed in our study could be due to the mixture of the two different subtypes of ADHD in our study. In community samples, 80% of children are typically diagnosed with ADHD-C whereas approximately 15% have ADHD-PI. In comparison, half of this ADHD sample was composed of children with ADHD-C and half of the children were diagnosed with ADHD-PI. It is probable that in studies with larger samples, the distribution of the ADHD group likely follows that of community samples. Furthermore, it is possible that having these two groups led to convergent results as there have been suggestions that these two subtypes are truly different disorders (e.g., Diamond, 2010). However, as the clinical groups were quite small, there would not have been enough power to examine differences among three groups.

Another significant consideration when interpreting the results of this study is that children in the ADHD group had no concomitant disorders. This issue is worth considering as more than half of children with ADHD typically have a comorbid disorder such as oppositional defiant disorder or conduct disorder. Mood, anxiety, and other neurological disorders (e.g., Tourette syndrome) also frequently co-occur with ADHD (APA, 2000). Therefore, while this study examines a "clean" sample of ADHD, future studies could consider the full spectrum of the disorder to attain results that might be considered as having greater ecological validity. On the other hand, controlling for comorbid conditions enables researchers to remove the variance associated with those disorders that may be shared with ADHD (e.g., Narr et al., 2009). This factor also contributed to difficulties with recruitment, thereby increasing duration of recruitment for the study's participants.

It is also important to be aware that there was an IQ difference of approximately one standard deviation between each group. Therefore, it is possible that differences in IQ could have contributed to some of the observed differences in the sample.

Conclusions

The results of this study indicated that children with ADHD had significantly larger dACC than controls. While this result is inconsistent with the extent literature's findings of generally smaller neural structures in children with ADHD, there are many possible reasons for this study's findings. Firstly, this finding supports the conclusion that regions which are important in attention and motor processes likely contribute to the symptomatology of ADHD. Secondly, it has previously been concluded that delays in cortical maturation in those with ADHD contribute to cognitive difficulties and likely account for morphometric differences that have been observed in ADHD. While seemingly contradicting these findings, larger dACC is supported by this theory. It is likely that delays in synaptic elimination in this region are contributing to the volumetric findings in this study. Furthermore, different patterns of relationships were found between ACC subregions and cognitive tasks as well as behavioural ratings for the two groups. These findings further support the notion that something atypical is occurring in the cortical development of ADHD, and that it is likely a delay in cortical maturation, both in terms of grey matter elimination as well as an overall delay in myelination. Future studies should aim to look at both grey and white matter differences in both areas and examine relationships among different brain regions as well as among subregions of the same region.

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