Subcortical Volume and Executive Functions in Children with Attention-Deficit/Hyperactivity Disorder (ADHD)

by

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A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in

School and Clinical Child Psychology

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Abstract

Background. The subcortical regions, including the caudate and putamen, have been historically implicated in pediatric Attention-Deficit/Hyperactivity Disorder (ADHD). Along with differences in subcortical regions, children with ADHD generally show weaker executive function (EF). However, previous studies have not investigated the relationship between the caudate and putamen volume with EF. The current study investigated the clinical relevance of the caudate and putamen with respect to EF as measured through cognitive performance-based tasks and parent ratings of EF.

Method. Twenty-four children with ADHD (*M* =11.64; males =12) and 25 typically developing children (TDC; *M* = 11.09 years; males =14) underwent a high-resolution Magnetic Resonance Imaging (MRI) T1-weighted sequence. FreeSurfer 6.0 was used for subcortical volume reconstruction. Children with ADHD completed EF tasks related to working memory and inhibition. Parents completed behaviour rating scales measuring executive function (BRIEF-2). Data were analyzed using Multivariate Analysis of Variance, Multivariate Analysis of Covariance, Pearson correlations and linear regressions.

Results. Parents of children with ADHD reported significantly more EF challenges on the BRIEF-2 compared to the TDC group, F (5,43) = 20.89, p <.001, partial eta square =.71). No significant group difference was observed on the Working Memory (F (2, 46) = 1.38, p =.26, partial eta squared = .06) or on the Response Inhibition task (F (4, 39) = 2.48, p =.06, partial eta squared = .20) performance between the ADHD and TDC groups. Similarly, the results showed no significant group differences in the volumes of the right and left caudate and putamen, F (4,41) = .79, p >.05, partial eta square =.07). However, negative correlations were observed between right caudate volume and parent ratings of emotion regulation (r = -.51, p =.010) in the ADHD group. Linear Regression model suggested that 26.3% of the variance in emotion regulation in the ADHD group was accounted for by the right caudate volume.

Discussion. Our study showed significant EF difficulties based on parent ratings but not on performance-based tasks. No volumetric difference was observed in the caudate or the putamen between children with ADHD and the TDC group. Right caudate was related to parent ratings of EF in pediatric ADHD participants indicating the possibility of a brain-behaviour relation. These findings have implications for future treatment options in the identified subgroup of children with ADHD.

Preface

This thesis is original work by Tasmia M. Hai. However, some of the research conducted for this thesis forms part of a research collaboration, led by Dr. Frank P. MacMaster and Dr. Jean-Francois Lemay, University of Calgary, with Dr. Martin Mrazik, University of Alberta. The research project, of which this thesis is a part, received ethics approval from the University of Calgary Conjoint Health Research Ethics Board (CHREB), Project Name, "TAG-IT: Topographical Mapping of Attention Deficit Hyperactivity Disorder for Greater Intervention Targeting, CHREB 19-0499" and the University of Alberta Ethics Board, "TAGIT: Secondary Analysis: Pro00094923", September 27, 2019.

Acknowledgements

It truly takes a village to get here. This was a marathon expanding approximately 14 years of post-secondary education. It would not be possible to be here without the support of supervisors, mentors, friends, and family. First of all, I would like to thank my supervisors. Dr. Martin Mrazik, thank you for allowing me to pursue my research interest of studying neuroimaging and helping me finish my thesis. Dr. Frank MacMaster for his unwavering support, guidance, mentorship, and trust in my abilities throughout this process. Six years ago, at the beginning of my MSc, I took a course with Dr. MacMaster. Little did I know at that time that course would change the entire trajectory of my graduate career. I am forever grateful for believing in me and allowing me to go beyond my comfort zone and letting me pursue my research interests. A special thank you goes to Dr. Jean-François Lemay for his incredible support, mentorship, guidance, and encouragement. I am so lucky to have had his constant encouragement and support throughout these past 5+ years. I would also like to extend a big thank you to my examining committee members, professors at U of A and U of C, and my supervisors during my practicums and internship.

To all my mentors and supervisors at the University of Toronto, Baycrest Health Sciences and Sunnybrook, they carved the path for me to be in graduate school. They made it possible for the undergrad who thought grad school was never possible to make it a reality. A special thank you to Dr. Morris Moscovitch and Dr. Raluca Petrican, who were the first to believe in me when I was a naïve 2nd-year undergraduate student.

To all my friends in Toronto, thank you for making time for me and letting me recharge. My grad school besties, Laura and Ayelet, thank you for always listening to my "judging" and complains and supporting me through this journey.

My family, thank you for never questioning my decision to pursue this academic journey, supporting me every step of the way. Special thanks to my dad for teaching me what perseverance looks like and my sister, who reviewed so many drafts starting with my undergraduate statement of intent to reviewing internship and job applications. I am forever grateful for their help, pushing me to strive to be the best. A big shout-out also goes to my niece, who has not only taught me so much about child development but also made me smile during times when it felt like nothing was going right.

I would be remiss if I didn't thank my childhood hero, Michael Schumacher. To him and his family, I might just be one of his millions of fans, but Michael, with his relentless pursuit of greatness, showed me how to never give up and believe in myself even when things go awry.

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Chapter One: Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder. According to the Diagnostic and Statistical Manual of Mental Health Disorders-Fifth Edition (DSM-5), ADHD is characterized by excessive levels of inattention or impulsivity and hyperactivity. Recent estimates suggest that the prevalence of ADHD ranges between 5-9% in Canadian school-aged children (Brault & Lacourse, 2012; Polanczyk, Willcutt, Salum, Kieling, & Rohde, 2014). In addition to the core symptoms, children with ADHD often face challenges with their academic, motor, and social functioning (Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Biederman et al., 2004; Wolraich et al., 2019). They also frequently have lower educational attainment, increased risk of injury and other mental health disorders, thus increasing the use of societal resources such as increased annual medical costs compared to peers and reduced efficiency at work by parents and impediments due to behaviour problems of their child (Hakkaart-van Roijen et al., 2007; Matza, Paramore, & Prasad, 2005). Furthermore, a recent estimate of the financial and socio-economic burden from the United States suggested that the direct economic cost of raising a child with ADHD is about five times higher than raising a child without ADHD (Zhao et al., 2019).

Executive functions (EF), an umbrella term, is often used to describe higher-order goal-oriented processing skills such as planning, inhibition, and working memory (Diamond, 2013). These higher-order skills help with concentrating, paying attention, and controlling automatic behaviours and are often associated with academic success (Borella, Carretti, & Pelegrina, 2010; Cortés Pascual, Moyano Muñoz, & Quílez Robres, 2019; Doebel, 2020), job success (Bailey, 2007; Chan, Wang, & Ybarra, 2021) and overall improved quality of life (Schwörer, Reinelt, Petermann, & Petermann, 2020; Stern, Pollak, Bonne, Malik, & Maeir, 2013). It is widely accepted that children with ADHD often exhibit EF deficits (Bünger, Urfer-Maurer, & Grob, 2021; Kofler et al., 2019; Toplak, Bucciarelli, Jain, & Tannock, 2009; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Substantial research has demonstrated that children with ADHD have EF deficits across a number of domains, including working memory, response inhibition, set-shifting and planning tasks (Bünger et al., 2021; Kofler et al., 2019, 2011; Rapport et al., 2008; Willcutt et al., 2005). Estimates predict that between 21% to 60% of individuals with ADHD show impairment on EF tasks (Kofler et al., 2011). While numerous studies have demonstrated EF challenges in children with ADHD, the findings are inconsistent with studies showing variable EF performance across the different domains (Huang-Pollock, Karalunas, Tam, & Moore, 2012; Kofler et al., 2019; Willcutt et al., 2005). Furthermore, comorbidities and intellectual functioning can impact EF performance (Bental & Tirosh, 2007; Kofler et al., 2019).

In addition to EF challenges, studies have shown that children with ADHD have neuroanatomical and neurochemical differences, particularly in brain regions that are related to EF skills (Altabella, Zoratto, Adriani, & Canese, 2014; Cortese & Coghill, 2018; Cortese et al., 2014; Hai et al., 2020; Hoogman et al., 2019; MacMaster, Carrey, Sparkes, & Kusumakar, 2003; Rubia, 2018). Shaw et al. (2007) showed that the rate of prefrontal cortical thinning is significantly different between those with the ADHD diagnosis and those without. Other cross-sectional studies have shown similar results, with thinner cortex in the superior frontal gyrus in the ADHD group compared to control participants (Overmeyer et al., 2001; Yang, Carrey, Bernier, & MacMaster, 2015). A recent large scale meta-analysis with over 2200 ADHD participants (mean age = 19.22 years, range = 4 – 62 years) found lower surface area in the frontal, cingulate, and temporal regions and lower cortical thickness in the fusiform gyrus and temporal pole (Hoogman et al., 2019). The same group investigated subcortical areas with over

1700 ADHD participants and concluded that individuals with ADHD also had reduced volumes in caudate, putamen, and the hippocampus (Hoogman et al., 2017). Moreover, some studies have found differences in the total cerebellum volume in children with ADHD compared to their typically developing peers (Bledsoe, Semrud-Clikeman, & Pliszka, 2011). Similarly, differences in neurochemicals such as glutamate, N-acetyl choline and Gamma-aminobutyric acid (GABA) have been reported in children with ADHD compared to their age-matched peers (Edden, Crocetti, Zhu, Gilbert, & Mostofsky, 2012; Hai et al., 2020; MacMaster et al., 2003; Tafazoli et al., 2013). Thus overall, the current literature supports neurochemical and neuroanatomical differences in ADHD.

While numerous studies have shown neuroanatomical differences, only a handful of studies to date have combined neuroimaging and EF task performance to better understand the neuroanatomy associated with EF skills (Almeida et al., 2010; Gau, Tseng, Tseng, Wu, & Lo, 2015; Shang, Wu, Gau, & Tseng, 2013). It is important to understand the relevance of structural differences with commonly used EF measures as it will enable us to better understand the clinical relevance of these brain regions. This approach will allow us to determine whether structural neuroimaging findings can be considered potential biomarkers of ADHD. Biomarkers have the ability to improve diagnosis and subsequent treatment options as, currently, diagnosis of ADHD is based on behavioural symptoms with limited emphasis on biological relevance (Pallanti & Salerno, 2020). However, most of the multimodal studies published to date were conducted using functional neuroimaging or diffusion tensor imaging (DTI) technologies. The proposed study will correlate structural neuroimaging results with EF performance, linking the fields of neuroscience and psychology to better understand the biological basis of ADHD.

Current clinical guidelines, including the Canadian ADHD Resource Alliance (CADDRA), recommend multimodal treatment involving pharmacological and psychosocial intervention for managing ADHD symptomology (CADDRA, 2018; Fabiano et al., 2009; Wolraich et al., 2019). Pharmacological treatments for ADHD comprise stimulant and non-stimulant medications. Stimulants, including methylphenidate and amphetamine, are typically the first-line pharmacotherapies for patients with ADHD (National Institute for Health and Care Excellence, 2018). The stimulant medication generally inhibits dopamine and norepinephrine transporter, acts as an agonist at the serotonin receptors, and redistributes vesicular monoamine transporter. Non-stimulant medication typically includes Atomoxetine, clonidine and guanfacine. These medications increase synaptic noradrenaline production by binding to the norepinephrine transporter. In the prefrontal cortex, norepinephrine transporters are also responsible for the regulation of dopamine reuptake, as dopamine transporters are scarce in this region. However, medications often have undesirable side effects, including changes in appetite, weight, and sleep (Hansen & Hansen, 2006), and only 70% overall efficacy (Mechler, Banaschewski, Hohmann, & Häge, 2021; Van der Oord, Prins, Oosterlaan, & Emmelkamp, 2008). The long-term outcome associated with medication use and its efficacy are not well known to date. Age- and gender-specific differences regarding pharmacological treatment are still underrepresented in ADHD research. Furthermore, medication compliance in children and adolescents with ADHD is often an issue and requires extensive parental support. Thus, there is an increasing need for novel treatment approaches that specifically target the underlying pathology of ADHD versus a systemic medication effect.

The National Institute of Mental Health (NIMH) in the United States created a framework, the Research Domain Criteria Project (RDoC), for better understanding and treatment of mental health disorders (National Institute of Mental Health, 2020). This framework aims to integrate multimodal information, including genetics, imaging, behaviour, and self-reports, to understand fundamental processes involved in the development of mental health disorders, with the hope of designing screening tools, diagnostic systems, and treatment options. The RDoC framework focuses on precision medicine, where objective biomedical tests can be used to monitor human neurodevelopment and the progression of different disorders (Hawgood, Hook-Barnard, O'Brien, & Yamamoto, 2015). Following the RDoC recommendations, the current study proposes to better understand the etiology of ADHD using neuroimaging biomarkers such as volume of subcortical regions, reports of behaviour from parental perspectives and performance on neuropsychological measures. The findings from this study seek to offer new targets for intervention and indicators of treatment outcomes for ADHD.

Research Purpose

The primary purpose of this study is to investigate EF differences in children with ADHD compared to typically developing controls (TDC) using performance-based tasks (working memory and inhibition tasks) and behaviour ratings completed by parents. The secondary purpose of this study is to examine differences in the volume of the subcortical regions (caudate and putamen) of children with ADHD compared to TDC. Importantly, this study will investigate relationships between neuroanatomy and EF to form links between the fields of neuroscience and psychology. This study will take on a multimodal approach to understand processes impacted in children with ADHD.

Research Questions

1. Do children with ADHD demonstrate EF deficits on performance-based measures assessing inhibition and working memory when compared to the TDC group?
2. Do children with ADHD demonstrate EF deficits on behaviour rating scales as observed by parents when compared to TDC?
3. What are the differences in subcortical volume in children with ADHD and TDC in the caudate and the putamen?
4. Are there relations between the subcortical volume and EF performance on measures such as inhibition and working memory?
5. Are there relations between subcortical volume and EF performance based on parent ratings of EF challenges?

Organization of Dissertation

The following dissertation contains five chapters, including an introduction, literature review, methods, results, and discussion. Chapter One, the introduction, includes the research problem, purpose, questions, and objectives. Chapter two includes a literature review on topics related to ADHD, neuroanatomical findings of ADHD, and EF. Chapter three outlines the research methods used in this study. Specifically, chapter three describes the design employed, selected outcome measures, data collection process, participants included, data analysis procedures, and attainment of research ethics approval. Chapter four reports the results of the study, including a description of study participants and the findings from each of the five research questions. Finally, chapter five includes a discussion of the results, strengths and limitations of the study, clinical implications of the findings, as well as future directions for research.

Chapter Two: Literature Review

Overview

This chapter provides a description of the current literature regarding ADHD, EF, and neuroanatomy of ADHD. Following the review of the literature, relevant theories of ADHD and EF are discussed, and the overlap between the different ADHD and EF theories is also explained. The end of the chapter discusses the research questions and expected findings from the study. The overarching goal of this project was to gain a better understanding of the etiological factors of ADHD. First, different EF skills are discussed as measured through objective tools such as performance-based cognitive tasks and subjective measures reported by parents. Secondly, common neuroanatomical markers impacted by ADHD, such as the subcortical regions of ADHD, are explained. Lastly, the relationship between EF and subcortical volumes of the caudate and putamen is presented. Given that areas of the subcortical brain regions are commonly implicated in ADHD, this study wishes to provide a better understanding of how these subcortical regions are related to commonly used EF measures. Specifically, the study hopes to understand whether deficits in EF in ADHD are related to structural abnormalities in the subcortical regions of the brain.

What is Attention-deficit/hyperactivity-disorder (ADHD)?

ADHD is characterized by developmentally inappropriate levels of inattention or hyperactivity and impulsivity (American Psychiatric Association, 2013). It is a common neurodevelopmental disorder with an estimated prevalence of 5-9% in Canadian school-aged children (Brault & Lacourse, 2012; Polanczyk et al., 2014). Although individuals with ADHD are often diagnosed in their childhood, many individuals obtain a diagnosis as an adult (Faraone & Biederman, 2005; Piñeiro-Dieguez et al., 2016). Furthermore, between 50% to 78% of children with ADHD continue to exhibit core symptoms of ADHD into adolescence and adulthood (Biederman, Petty, Evans, Small, & Faraone, 2010; Wilens & Spencer, 2010).

In addition to the core features, children with ADHD frequently struggle with EF challenges (Bünger et al., 2021; Huang-Pollock et al., 2012; Kofler et al., 2019; Willcutt et al., 2005), academic difficulties (Berchiatti, Ferrer, Badenes-Ribera, & Longobardi, 2021; Wolraich, 2005), and motor difficulties (Hyde et al., 2021; Kaiser, Schoemaker, Albaret, & Geuze, 2015). The core symptoms of ADHD changes throughout development with differential patterns of behaviours observed in young children, compared to adolescents and adult (Franke et al., 2018). Moreover, symptoms of ADHD when left untreated or not addressed, can lead to the development of other mental health disorders (Biederman et al., 2006; Furczyk & Thome, 2014), including increased mortality rate in people diagnosed with ADHD (Catalá-López et al., 2022; Dalsgaard, Østergaard, Leckman, Mortensen, & Pedersen, 2015). Estimates from a recent study conducted in the United States stated that the economic burden on families raising children with ADHD is five times higher than families raising children without the diagnosis of ADHD (Zhao et al., 2019). Early diagnosis and subsequent interventions are key to reducing some of the functional and economic challenges, thus altering the developmental trajectory of the disorder.

Clinically, ADHD is quite heterogeneous and more complex than described by the symptom criteria listed in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; Steinhausen, 2009). The DSM-5 currently distinguishes three different presentations of ADHD, ADHD predominantly inattentive presentation, ADHD predominantly hyperactive-impulsive presentation and ADHD combined presentation (APA, 2013). Even though there are three subtype presentations, substantial individual differences exist within the different subtype presentations (Gaub & Carlson, 1997; Heidbreder, 2015; Murray, Ribeaud, Eisner, Murray, & McKenzie, 2019). Additionally, ADHD profile changes throughout development, with young children showing more motoric hyperactivity, while inattentive symptoms of ADHD are more prominent in adolescents and adults (Franke et al., 2018). Moreover, between 67-80% of children and over 80% of adults with ADHD have at least one other mental health disorder, and about 40% have at least two other disorders, further increasing variability in clinical presentations. (Barkley, Murphy, & Fischer, 2008; Bishop, Mulraney, Rinehart, & Sciberras, 2019).

While the current literature supports EF challenges in individuals with ADHD, there are inconsistencies regarding the findings, with some research showing impaired performance on all neuropsychological performance-based measures (Semrud-Clikeman, Walkowiak, Wilkinson, & Butcher, 2010; Toplak et al., 2009), while other studies showed variable performance on neuropsychological EF measures (Fair, Bathula, Nikolas, & Nigg, 2012; Willcutt et al., 2005). Specifically, in their meta-analysis, Willcutt et al. (2005) reported how some domains of EF had weaker effect sizes than others. These inconsistencies are likely due to different conceptualization of EF (no consensus regarding definitions), different instruments used to measure EF, sample size, and sample characteristics (Kofler et al., 2019). Given the heterogeneity in EF findings, it would be beneficial to understand the subgroups of children with ADHD who have specific EF deficits on the different neuropsychological measures and use that information to provide more targeted treatments and interventions. Additionally, potential biomarkers of ADHD (i.e., neuroanatomical differences) can be looked at in relation to individual variations on specific EF tasks to better understand the functional impact of these neuroanatomical markers.

How common is ADHD? ADHD is a commonly diagnosed neurodevelopmental disorder with an estimated prevalence rate of 5-9% in school-aged children (APA, 2013). Most of the reported prevalence rates are based on research studies conducted in the United States. However, current prevalence rates in Canada are similar to those in the United States, with about 5% of school-aged children diagnosed with ADHD (Brault & Lacourse, 2012). Furthermore, the prevalence rate varies internationally (Faraone, Sergeant, Gillberg & Biederman, 2003) and across the different methodologies used to make these estimates (Barkley, 2014). Overall, the worldwide pooled prevalence of ADHD is estimated to be about 5.3% (Polanczyk, De Lima, Horta, Biederman, & Rohde, 2007).

How is ADHD diagnosed? ADHD is diagnosed based on the current DSM-5 standards (American Psychiatric Association, 2013). The DSM-5 divides ADHD symptoms into two domains: inattention and hyperactivity/ impulsivity. In order to meet the diagnostic criteria for ADHD, individuals need to display at least six of the nine symptoms related to the specific symptom cluster, and these symptoms need to be present for at least six months (APA, 2013). The DSM-5 does not include subtypes of ADHD; instead, it describes different subtype presentations based on clusters of symptoms: ADHD predominantly inattentive presentation (ADHD-I), ADHD predominantly hyperactive/impulsive presentation (ADHD-HI), and ADHD combined presentation (ADHD-C). Additionally, there needs to be functional impairment due to the presentation of the symptoms, and these impairments must occur across two or more settings (i.e., home, school).

What are some Theoretical Models of ADHD?

The heterogeneous symptom presentations, different comorbidities and divergent developmental trajectories have led to numerous frameworks and models to describe ADHD and its associated outcomes (Luo, Weibman, Halperin, & Li, 2019; see Figure 1). Some theorists have taken on a cognitive perspective; others have used behavioural and motivational models to explain ADHD (Barkley, 1997; Nigg, 2001).

Barkley's behavioural inhibition model (Barkley, 1997) is one of the most often-cited theories of ADHD. According to this theory, the challenges exhibited by children with ADHD are due to deficits in behavioural inhibition. In his theory, Barkley argues that symptoms associated with hyperactivity and impulsivity are related to deficits in inhibition and that symptoms of inattention are the result of deficits in the speed of information processing and selective attention. However, a significant criticism of Barkley's behavioural inhibition theory is that it is unable to explain the challenges experienced by individuals who only present with inattention alone.

Another theoretical model explaining the etiology of ADHD is the Motivational Dysfunction theory (Nigg, 2006; 2001; Volkow et al., 2009). This is a bottom-up theory of ADHD that proposes that challenges exhibited by individuals with ADHD are due to dysfunctional responses to reward and/or punishment contingencies (Nigg, 2006). Researchers argue that, due to changes in neural circuits arising from the prefrontal cortex regions, individuals with ADHD are unable to learn from mistakes and monitor reward and punishment (Sagvolden, Johansen, Aase, & Russell, 2005). While there is neuroimaging support for this theory, there are inconsistencies in the results. For example, some studies have found that task performance in individuals with ADHD improved and/or normalized with response contingencies (e.g., Carlson & Tamm, 2000; Slusarek, Velling, Bunk, & Eggers, 2001), while other studies reported that reinforcement or response task performance improved for all children evaluated, regardless of the ADHD diagnosis (e.g., Scheres, Oosterlaan, & Sergeant, 2001; Shanahan, Pennington, & Willcutt, 2008).

Recently, ADHD has been conceptualized through an Endophenotype Model to better explain the heterogeneity of the symptom (Nigg, Blaskey, Stawicki, & Sachek, 2004). The term ‘endophenotype” is commonly used to refer to the measurable components of behaviour correlating with etiological factors that can help predict the development of the disease/disorder. While the current literature has reported numerous endophenotypes for ADHD (e.g., cognitive functioning, genetic factors, delayed gratification), the neuropsychological profile is one of the most well-researched endophenotype candidates. Furthermore, it is important to evaluate the clinical relevance of the candidate endophenotype using neuroimaging measurements to better understand the neurobiological implication of different disorders (Castellanos & Tannock, 2002; Doyle et al., 2005). For example, studies have shown motoric hyperactivity to be related to cerebral blood flow in the basal ganglia and performance on delay aversion tasks was related to nucleus accumbens and the anterior cerebellar vermis. However, it has been argued that neuropsychological profiles may not be a consistent phenotype of ADHD, given that some individuals with ADHD have age-expected or above age-expected performance(Arnett, McGrath, Flaherty, Pennington, & Willcutt, 2022). So, future research is required to better understand neuropsychological profiles as endophenotypes.

Although the Behavioural Inhibition Model and Motivational Dysfunction Model models provide unique perspectives to understand the etiology of ADHD, they do not fully explain all the challenges observed in individuals with ADHD. Researchers are now moving towards new and more comprehensive models to explain the etiology of ADHD using the endophenotype theorical approach (Doyle et al., 2005; Mash & Barkley, 2014). The biopsychosocial model can take on a holistic view of ADHD by integrating the biological, psychological and social aspects of ADHD and explaining the different associated challenges (Engel, 1981).

Application of the Biopsychosocial Model to understand ADHD

The biopsychosocial model integrates perspectives from three different viewpoints to understand the challenges faced by individuals. The model incorporates biological factors, psychological factors, and sociological factors to understand behaviour (Engel, 1981). This model also explains that development is dynamic and multifactorial (Black & Hoeft, 2015). It is not dependent on one factor; instead, changes can occur across multiple domains and influence overall development. Molina (1983) further discusses that the model can be applied to understand different diseases and disorders (Molina, 1983). Thus, the biopsychosocial model can be used to examine the impact of risk and protective factors to understand the different developmental trajectories of ADHD.

In this current study, the biological and psychological components of the biopsychosocial model are being applied to understand ADHD. Specifically, the biological components of ADHD, such as differences in neuroanatomical regions and the psychological component of EF, are being further explored to better understand the interplay between these factors in the diagnosis, development, and treatment of ADHD.

Psychological Component of ADHD

The current study investigated the attentional capacities and EF skills in children with ADHD.

ADHD and Attentional Capacities. One of the core symptoms of ADHD is the inability to sustain attention for a period, which can lead to making careless errors or being unable to focus on tasks (American Psychiatric Association, 2013). These attentional challenges can impact learning and progress in school-related tasks. The exact mechanisms underlying the attentional system and how they impact children with ADHD are currently speculative. In the 1940s, attentional problems were observed in individuals with damage to the frontal lobe. However, this observation was not supported by studies conducted in the late 1980s, where it was found that attentional problems were related to damage to both subcortical and cortical regions (Zillmer, Spiers, & Culbertson, 2008).

The attentional system is multifactorial and complex, with various functions interlinked with each other, including alerting, orienting, and executive control (Petersen & Posner, 2012). Executive control is an umbrella term used to describe processes related to the ability to control one's behaviour, and is further subdivided into functions such as execute, sustain, stabilize, shift and encode (Mirsky, Pascualvaca, Duncan, & French, 1999). These functions can be measured using various neuropsychological-based tasks and are dependent on a network of different cortical and subcortical areas (Petersen & Posner, 2012). Generally, the attentional mechanism is considered to be of limited capacity, with some theories suggesting shared attentional resources between different sensory modalities (Wahn & König, 2017). In contrast, other researchers suggest that the attentional system flexibly uses attentional resources based on need or task demand (Wahn & König, 2015). Additionally, recent studies have indicated that different cortical regions are responsible for processing different features of the auditory and visual stimuli (Chaplin, Rosa, & Lui, 2018).

Generally, children with ADHD are impaired in at least three of these attentional functions compared to children without ADHD (Mirsky et al., 1999). Previously, studies have reported deficits in alerting, orienting, and executive control (Casagrande et al., 2012; Huang-Pollock & Nigg, 2003). However, findings reported in the current literature related to attentional impairments are inconclusive. It is also possible that some children with ADHD have a variety of deficits in these attentional challenges, while others do not show challenges to the same extent (Lin et al., 2017). As clinical practitioners, it is crucial to tease out the different attention components that might be affecting a child with ADHD, so that appropriate strategies and interventions can be provided.

What are Executive Functions?

EF is an umbrella term used to refer to a complex range of cognitive abilities, including goal-directed planning, impulse control, cognitive flexibility, and self-monitoring (Barkley, 2014; Diamond, 2013; Miller & Cohen, 2001). There is presently no real or official consensus in the literature regarding the exact definition, as indicated by a meta-analysis that concluded that there are around 18 different definitions of EF (Wasserman & Wasserman, 2013). However, it is generally accepted that EFs represent a family of top-down cognitive processes needed to make judgments and decisions and initiate purposeful behaviour (Duff & Sulla, 2015). The frontal lobe, specifically the prefrontal cortex (PFC), is primarily involved in these higher-level processes (Stuss, Donald & Knight, Robert, 2002). However, recent neuroimaging research shows other regions, such as the anterior cingulate cortex and basal ganglia are involved as well (Cortese & Castellanos, 2012; Rubia, 2018; Salehinejad, Ghanavati, Rashid, & Nitsche, 2021). While some researchers argue that EF is a single construct (Jurado & Rosselli, 2007), others define EFs as a group of related but distinct processes, hot and cool EF (Friedman & Miyake, 2017; Miyake et al., 2000). Some of the prominent theoretical models of EF are the "unity and diversity of EF theory by Miyake et al. (2000), Barkley's Behavioural Inhibition Theory (Barkley, 1997), and Baddeley and Hitch's Central Executive Theory (Baddeley & Hitch, 1974).

What are some theoretical models of EF?

As mentioned in the previous section, numerous theories have originated to explain the construct of EF (see Figure 1). The following section describes some of these prominent theories of EF in greater detail.

Automatic and Controlled Processes. Traditionally, EF processes were considered higher-order cognitive processes that required controlled processing of information. These views of EF stem from Donald Broadbent's (1958) model of automatic and controlled processes. According to Broadbent's model, a filter serves as a buffer that selects information for conscious awareness (Broadbent, 1958, 1982). The filter determines which information is considered relevant or irrelevant for further processing. Select information will pass through the filter (as relevant), while the remaining information is ignored (irrelevant; Broadbent, 1958). Subsequently, Shiffrin & Schneider (1977) proposed the dual processing model. They suggested that given the limited ability to pay attention to information, certain information is preferred over others. In this dual processing theory, automatic processing stimulates a series of nodes that get activated in response to a stimulus without needing the individual to exert control or attention. In contrast, controlled processing entails a temporary sequence of activation that is effortful, slow and requires attention from the subject (Schiffrin & Schneider, 1977). These authors introduce the concept of Selective Attention, where a separate component exists that control what information is paid attention to and what information is left unattended. Based on this model, EF was conceptualized as skills that are primarily associated with attentional skills.

Supervisory Attentional System (SAS). Norman and Shallice (1986) proposed an EF model called the supervisory attentional system (SAS) model. This model suggests that a system exists that acts as a mediator for novel situations in which inhibition may be necessary to make a decision (Shallice, 1988; 2002). Shallice proposes that EF challenges seen in many psychopathologies occur due to deficits in the SAS system (Shallice, 2002).

Central Executive. Baddeley and Hitch's Central Executive Theory (Baddeley & Hitch, 1974) is another example of an EF model. The Central Executive Model describes a model for working memory. According to Baddeley et al. (1974), there are three components of working memory, the phonological loop, the visuospatial sketchpad, and the central executive. The phonological loop is involved in the temporary storage of verbal information; the visuospatial sketch pad temporarily stores visuospatial information, and the central executive coordinates the phonological loop and visuospatial sketch pad and simultaneously controls the working memory system. While some researchers consider working memory as a core component of EF deficits observed in ADHD (Kofler, Rapport, Bolden, & Altro, 2008; Kofler et al., 2018; Rapport et al., 2008), others argue that working memory deficits are one of several EF weaknesses observed in children with ADHD (Barkley, 2014; Willcutt et al., 2005).

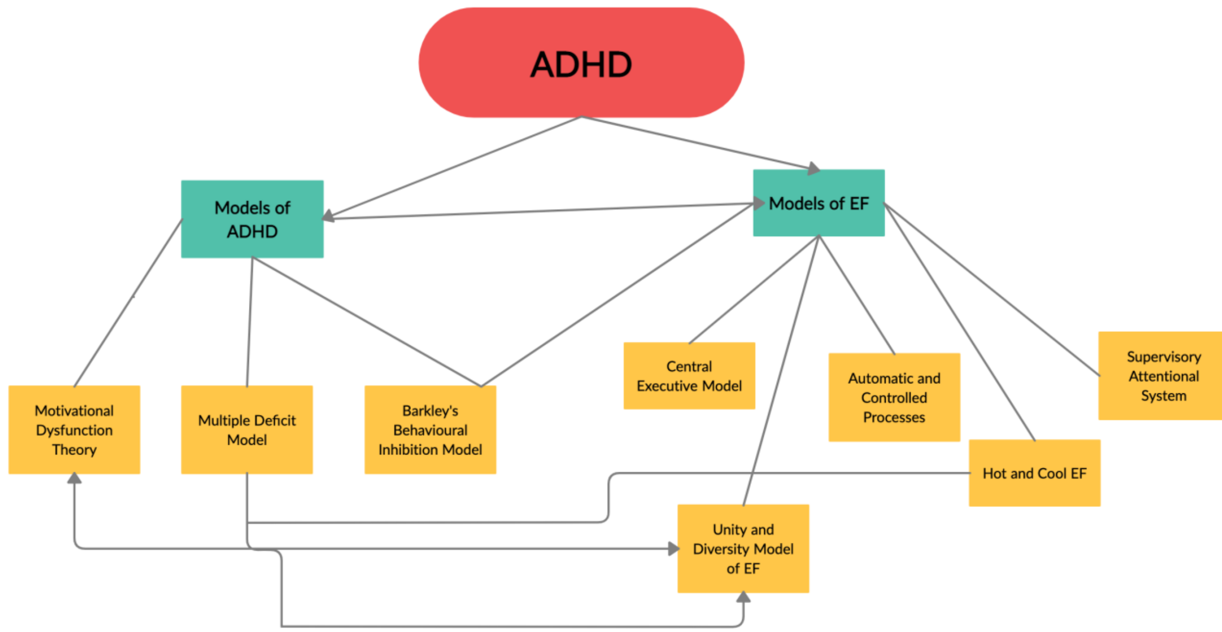
The Unity and Diversity of Executive Functions Theory. This model proposes that there are three aspects of EF, updating, inhibition, and shifting. In their study, Miyake et al. (2000) used confirmatory factor analysis (CFA) to test whether different EF tasks can be grouped together. The CFA analysis extracted three correlated variables from nine different EF tasks that were related to EF domains of shifting, working memory and inhibition. The results from the study indicated that these three different domains were different from one another but had moderate correlations with each other (Miyake et al., 2000). The authors concluded that EF skills are not a single entity but instead composed of multiple domains (Miyake et al., 2000). The authors further revised their model to suggest that EF skills such as inhibition, updating, and shifting can all be necessary for complex tasks such as planning and goal maintenance. Still, these core EF skills can be broken down into different components, thereby supporting their multiple domain theory of EF (Friedman & Miyake, 2017).

Hot and Cool executive function circuits. Zelazo and Muller (2011) proposed a new model for EF based on the relation with emotions. According to this model, a distinction can be made between primarily cognitive (i.e., "cool") and affective (i.e., "hot") aspects of EF. Based on this model, cool EF is elicited by relatively abstract and decontextualized problems, such as inhibiting automatic responses or retaining information in working memory, whereas hot EF is required for problems involving high affective components (e.g., delay aversion; Zelazo & Müller, 2011). Given the association between ADHD and impairment on cognitive or cool EF tasks, Zelazo and Muller propose that ADHD should be considered a disorder of cool EF (e.g., deficits in cognitive tasks such as inhibition and working memory). One of the benefits of the proposed model is that it includes both cognition and emotion in understanding EF. This model is analogous to the dual pathway model of ADHD, where the cool and hot EF functions are suggested to be modulated by different cortico-striatal circuits and different branches of the dopaminergic system (Sonuga-Barke, 2003).

Overlap between EF and ADHD models.

Figure 1 illustrates the overlap between some of the EF models and theoretical models of ADHD. Barkley's Behavioural Inhibition model is often used to describe ADHD and its symptoms (Barkley, 1997). It is important to note that while EF deficits are common in individuals with ADHD, these are not the only area of concern. Furthermore, Willcutt et al. (2005) stated that "EF weaknesses are neither necessary nor sufficient to cause all cases of ADHD. Difficulties with EF appear to be one important component of the complex neuropsychology of ADHD.”

Figure 1 Schematic showing the different models of ADHD and Executive Functions.



Executive Functions in Children with ADHD

EF deficits are commonly reported in pediatric ADHD, as reported by numerous studies (Kofler et al., 2019; Ramos, Hamdan, & Machado, 2020; Willcutt et al., 2005). However, the existing EF literature in pediatric ADHD is inconclusive. Some cross-sectional studies, including meta-analysis have found impaired performance on all neuropsychological performance-based measures (Ramos et al., 2020; Semrud-Clikeman et al., 2010; Toplak et al., 2009), while other studies showed variable performance on different neuropsychological EF measures (Fair et al., 2012; Willcutt et al., 2005). Current estimates predict that approximately 33%–50% of children with ADHD exhibit EF difficulties (Biederman et al., 2004; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Willcutt et al. (2005) also indicated that these inconsistent results might be due to differences in sampling procedures and the diagnostic criteria used to define the ADHD groups. Also, challenges with controlling for other factors such as intelligence, reading ability, and comorbidities could make it difficult to interpret some of the available findings (Kofler et al., 2019; Willcutt et al., 2005). Some studies have also reported biological sex differences associated with the cognitive deficits observed in ADHD (Loyer Carbonneau, Demers, Bigras, & Guay, 2020).

As School and Clinical psychologists, we are more likely to observe the impact of ADHD on cognitive functions measured through our psychological instruments. It is also essential to understand the application of these deficits measured on lab-based tests in real-world settings, as studies suggest that they are not sufficient in capturing more complex, day-to-day executive problem-solving situations (Goldberg & Podell, 2000; Shallice & Burgess, 1991). Some of the reasons being, many neuropsychological EF tasks involve multiple EF skills as well as non-EF skills. Such traditional but non-specific tasks may be helpful for screening individuals for severe

EF deficits; however, they may be too broad to identify specific aspects of EF challenges observed in children with ADHD. Many traditional neuropsychological tasks may also lack sensitivity to detect more subtle EF deficits as they were initially developed to measure EF deficits in individuals with severe brain damage (Snyder, Miyake, & Hankin, 2015; Zillmer et al., 2008). As a result, effect sizes reported in meta-analysis for different EF tasks may be smaller not due to true differences in the magnitude of impairments but due to the ceiling effects of the task.

It is also possible that some children with ADHD show performance that are in the average range in these neuropsychological tests, while parents and teachers report continued difficulties. As practitioners, we need to understand the contexts where these challenges are being observed and be mindful of the limitations of our psychological instruments. Thus, it is crucial to measure EF through multiple perspectives when assessing EF difficulties of children with ADHD and its impact on their everyday functioning. It is also essential to not only look at areas of weakness during case conceptualization but also focus on areas of strengths that can be used to provide strategies to parents and educators (Climie & Henley, 2016).

How is EF measured?

Traditionally, EF skills were measured through performance-based cognitive tasks (Zillmer et al., 2008). However, critics have raised concerns regarding the psychometric properties of EF tasks utilized to measure specific cognitive processes, including low internal and test-retest reliability, as well as weak construct and ecological validity. In response to the critics of EF performance-based tasks, behaviour rating scales were designed to evaluate everyday demands of EF in the natural setting by parent/caregiver and teacher reports.

Performance-based measures of EF. Performance-based measures of EF skills are designed to assess specific EF skills, such as working memory or inhibition. These tasks typically involve evaluating an individual's accuracy, response time, and/or response speed under a time constraint. Additionally, these tests require trained individuals to administer the tests in a standardized format where stimulus presentation is carefully controlled to ensure that each examinee experiences the task in the same manner (Toplak, West, & Stanovich, 2013). Furthermore, these tests are completed in controlled lab-based settings with minimal distractions. Some common examples of EF tasks are the Halstead-Reitan Battery (Mazur-Mosiewicz & Dean, 2011), Developmental Neuropsychological Assessment (NEPSY-II; Korkman, Kirk, & Kemp, 2007), Continuous Performance Tests (CPT; Conners, 2014), Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993), and Delis-Kaplan Executive Function System ([D-KEFS]; Delis, Kaplan, & Kramer, 2001).

Behaviour rating scales of EF. Behaviour rating scales are another way to measure EF skills, specifically in the pediatric population (Toplak et al., 2013). They are cost-effective and considered to be an efficient way to gather information about children. Given that neuropsychological tests measure performance at a one-time point, an alternative option to obtain EF deficits in everyday life was through behaviour rating scales (Strauss, Sherman, & Spreen, 2006). Behaviour rating scales assess EF skills applied to daily problem-solving situations through parent or teacher reports (Roth, Isquith, & Gioia, 2014). Additionally, these behaviour questionnaires can address whether EF challenges are present in multiple settings (e.g., home, school) and are not limited to situation-specific impairments (Strauss et al., 2006).

The most commonly used rating scale of EF are the Behavior Rating Inventory of Executive Function (BRIEF); Gioia, Isquith, Guy, Kenworthy, & Baron, 2000) and the Comprehensive Executive Function Inventory (CEFI; Naglieri & Goldstein, 2014). These rating scales require the responders to make global judgments about an individual's perceived traits, including the frequency, severity, or intensity of symptoms (Dirks, Treat, & Weersing, 2007). However, there are limitations as these scales are subjective and often have inconsistencies across informants (Schneider, Ryan, & Mahone, 2020).

Biological Components of ADHD

The current study is specifically interested in studying brain level changes measured through neuroimaging techniques.

ADHD and Biological Brain Development. Since the categorization of ADHD as a neurodevelopmental disorder, numerous studies have demonstrated brain-level changes in children with ADHD compared to typically developing peers (Cortese & Coghill, 2018; Hoogman et al., 2017, 2019; Rubia, 2018). These changes in the brain have been shown using different magnetic resonance imaging (MRI) techniques such as structural and functional MRI, white matter tractography using DTI and magnetic resonance spectroscopy (MRS). A variety of MRI techniques have been used in order to capture the structural, functional, and chemical differences in different brain regions to better understand the underlying mechanisms.

Structural MRI studies have shown differences in thickness and volume in the cortex of children with ADHD compared to their typically developing peers. Shaw et al. (2007) presented findings that showed that the rate of prefrontal cortical thinning is significantly different between those with the ADHD diagnosis and those without, reaffirming the evidence for a neurobiological basis. Other cross-sectional studies with children and adolescents with ADHD have shown similar results, with the thinner cortex in the superior frontal gyrus in the ADHD group compared to control participants (Hai et al., 2022; Overmeyer et al., 2001; Yang et al., 2015). A large scale meta-analysis conducted by the Enigma Consortium with over 2200 ADHD participants (mean age = 19.22 years, range = 4 – 62 years) found a lower surface area in the frontal, cingulate, and temporal regions and lower cortical thickness in the fusiform gyrus and temporal pole (Hoogman et al., 2019). The same group investigated subcortical areas with over 1700 ADHD participants and concluded that individuals with ADHD also had reduced volumes in caudate and putamen (Hoogman et al., 2017).

Functional neuroimaging studies have identified both hypoactivated and hyperactivated areas in children with ADHD, suggesting a differential impact of ADHD on the brain (Cortese & Coghill, 2018). Additionally, altered activation patterns during attention and inhibition tasks were observed in the right prefrontal cortex regions, basal ganglia, cerebellum, anterior cingulate cortex, and supplementary motor area (Cortese et al., 2014; Rubia, 2018). Furthermore, reduced functional connectivity during motor response inhibition tasks between the Inferior Frontal Cortex (IFC) and basal ganglia has been reported in children with ADHD (Rubia, 2018). A recent meta-analysis using resting-state fMRI to investigate connectivity between different brain regions found altered connectivity within the Default Mode Network (DMN) (Sutcubasi et al., 2020). Overall, fMRI studies have shown that ADHD is not due to just underperformance on one task; instead, there are complex interactions between different brain regions that are likely causing the observed deficits in performance on tasks (Cortese, Aoki, Itahashi, Castellanos, & Eickhoff, 2021).

Altogether, these different neuroimaging techniques have allowed researchers and clinicians to be aware of the widespread and significant brain level changes that occur in children with ADHD. For researchers and scientists, the neuroimaging data allows them to understand the mechanisms that might be causing some of the ADHD symptoms. Subsequently, these mechanisms can then be targeted in the future for designing treatment options. For clinicians, these neuroimaging data provide further information to consider when deliberating case conceptualization and recommending treatments. Clinicians can also help parents and educators understand the multifaceted impact of ADHD by discussing some of the brain complexities involved.

Subcortical Volume Differences. The impact of the cortical regions, specifically the Prefrontal cortex (PFC), in ADHD is well-documented (Rubia, 2018; Shaw et al., 2007). However, the PFC, along with being involved in numerous EF skills, also makes extensive connections with the sensory, motor and subcortical regions (Cubillo, Halari, Smith, Taylor, & Rubia, 2012). The basal ganglia, which includes the caudate, putamen and globus pallidus, are the core subcortical regions involved in the frontostriatal pathway implicated in ADHD (Cubillo et al., 2012). The dorsal striatum (i.e., the caudate and putamen), pallidum, hippocampus and amygdala are also associated with the abnormal reward processing found in ADHD (Carmona et al., 2009; Sonuga-Barke, Auerbach, Campbell, Daley, & Thompson, 2005). Some theorists have suggested alternative neurodevelopmental models of ADHD (Carmona et al., 2009; Halperin & Schulz, 2006). For example, Halperin & Schulz (2006) suggested that developmental deviations in the subcortical regions may contribute to the etiology of ADHD, given the typical onset of ADHD symptoms during the preschool years. Others have proposed two different types of endophenotypes, one primarily associated with the inattentive subtype and the other related to more hyperactive/impulsive symptoms (Carmona et al., 2009). Regardless of the fairly consistent evidence of frontal lobe anomalies in individuals with ADHD, it is not clear whether these differences in frontal regions are primary deficits causing ADHD symptoms or they are secondary to developmental deviations in the subcortical areas. Furthermore, without longitudinal studies, it is challenging to understand the impact of development, and the impact of different risk and protective factors on changes in neuroanatomical regions.

Although many of the studies described above indicate significant reductions in brain regions in ADHD, there are inconsistencies across studies. One meta-analysis found that individuals with ADHD showed decreased gray matter volume relative to controls in the right basal ganglia, specifically a decrease in the right putamen and right caudate volume (Norman et al., 2016). The ENIGMA working group carried out a large meta-analysis to understand the structural alterations of subcortical regions in 1700 participants with ADHD and 1500 healthy controls (ages 4-63 years old). The results from the ENIGMA working group found smaller caudate, putamen, hippocampus, amygdala, accumbens and intracranial volumes in individuals with ADHD compared to controls (Hoogman et al., 2017). Hoogman et al. (2017) findings showed small effect sizes, meaning that approximately 95% of the groups (ADHD and control) overlap. This means that the differences observed between the ADHD and typically developing groups can be interpreted as negligible or as very small differences. Moreover, a recent study of over 900 ADHD participants between the ages of 9-10 years old did not find any significant group differences in the subcortical regions (Bernanke et al., 2022). The inconsistencies reported across studies in subcortical volume could be due to differences in diagnosis, methodologies used, the impact of long-term medication use and age range of the participants. As a result, it is still essential to continue to understand and better characterize subcortical volume differences in children with ADHD.

Summary

Overall, ADHD is a complex and heterogeneous neurodevelopmental disorder, with numerous biological, social, and psychological differences observed when compared to typically developing peers. While it is difficult for a single study to compare all aspects of ADHD, the current project aims to better understand the brain-behaviour relation of ADHD. Specifically, the study aims to focus on the EF challenges reported in children with ADHD using commonly used neuropsychological performance-based measures and parent behaviour rating scales. The study also seeks to address the subcortical volume differences in children with ADHD. Lastly, the study aims to understand the relation between the neuroanatomical regions and the EF performance.

Hypotheses

Based on the current literature available regarding EF and subcortical volume differences in children with ADHD compared to TDC, the following hypotheses are proposed for each research question.

1. Do children with ADHD demonstrate EF deficits on performance-based measures assessing inhibition and working memory when compared to typically developing controls?
    a. Hypothesis: Based on the current literature, weaker overall performance on the EF-related tasks in the ADHD samples compared to the healthy control participants, are expected. However, children with ADHD are expected to

demonstrate variable performance across the different EF performance-based measures. That is, not all children with ADHD would demonstrate weak performance across the selected EF measures used in the study. Specifically, the current study hypothesizes that children with ADHD would demonstrate weaker performance on tasks assessing inhibition and non-verbal working memory as these EF deficits had a large effect size according to previous meta-analysis (Willcutt et al., 2005). The more variable performance with some children with ADHD showing similar performance compared to the TDC group is expected for the verbal working memory tasks, given findings from previous meta-analyses (Sowerby, Seal, & Tripp, 2010; Willcutt et al., 2005).

2. Do children with ADHD demonstrate EF deficits on behaviour rating scales as observed by parents when compared to TDC?
    a. Hypothesis: Based on the current literature, significantly lower EF skills are expected from parent reports of children with ADHD compared to the TDC group (Toplak et al., 2009, 2013).
3. What are the differences in subcortical volume in children with ADHD and TDC in the caudate and putamen?
    a. Hypothesis: Based on a previous meta-analysis, this study expects to observe smaller volumes in the caudate and putamen in children with ADHD compared to our TDC group (Hoogman et al., 2017). Due to the sample size of the current study and to minimize multiple comparisons, the present study did not expect to find reduced volumes in other subcortical regions.

4. Are there relations between the subcortical volume and EF performance measures such as inhibition and working memory?
    a. Hypothesis: The current literature is limited regarding the relations between EF skills and subcortical volumes. However, given the role of the basal ganglia in different EF skills, we expect that subcortical volume will have associations with EF performance. Specifically, smaller volumes of the caudate and putamen will correlate to weaker performance on the neuropsychological tasks measuring inhibition and working memory.
5. Are there relations between subcortical volume and EF performance based on parent ratings of EF challenges?
    a. Hypothesis: To the best of the author's knowledge, no study to date has investigated the relations between parent reports of EF skills and subcortical volumes in children with ADHD. However, based on our knowledge of the subcortical region in EF and a previous study with typically developing children (Mahone, Martin, Kates, Hay, & Horská, 2009), we expect that volumes of the caudate and putamen will negatively correlate with EF deficits as reported by parent ratings.

Chapter Three: Methods

This chapter is organized into seven sections. First, the chapter provides a description of the study design and sampling procedures. Next, an overview of the data collection, selected measures used in study and reconstruction of the images obtained from MRI is described. Finally, the statistical analyses conducted, and the attainment of ethics are outlined.

This research project was part of a larger cross-sectional study investigating neuropsychological, neuroimaging, and neurophysiological differences observed in pediatric ADHD titled "Topographical Mapping of Attention-Deficit/Hyperactivity Disorder for Greater Intervention Targeting (TAGIT)." This study took place at the University of Calgary. Secondary analysis of the data collected by the author of this dissertation was completed at the University of Alberta.

Study Design

The current study used a cross-sectional observational design as participants did not undergo any treatment or interventions. This study was part of a larger study as, indicated above, that involved multimodal data collection related to neuropsychological, neuroimaging, and neurophysiological properties of children with ADHD and typically developing controls. Due to the cross-sectional nature of the study, the participants were selected based on inclusion and exclusion criteria (Mann, 2003). The author of this dissertation was involved in study design, completing ethics application, recruitment, data collection of all clinical measures and neuroimaging, data analyses and interpretation of the EF and subcortical volumes. As the data was collected at the University of Calgary, the Research Ethics Board at the University of Alberta considered this study to be a secondary data analysis conducted as part of the author's dissertation project.

Sampling and Participants

The goal of this study was to understand the EF and neuroanatomical differences (subcortical regions) in children with ADHD compared to TDC. The population of interest were children diagnosed with ADHD and children without the diagnosis of ADHD. The study data collection was completed in a total of 36 days, from June 2019 to November 2019.

Inclusion Criteria. Participants in the ADHD group had to have (1) a confirmed ADHD diagnosis from a healthcare professional, verified through discussion with an experienced Developmental Pediatrician, (2) a behaviour rating score greater than 65 (T-score) on the Conners-3 parent rating scale, (3) confirmation of ADHD diagnosis on the Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID; Sheehan et al., 2010), and (4) no intellectual disability (a cognitive screener standard score > 80). All participants in the ADHD group were requested to undergo a 48-hour washout period (no stimulant medications). Participants in the TDC group did not have a diagnosis of psychiatric disorder (including ADHD) and this was confirmed using the MINI-KID.

Exclusion Criteria. Participants were ineligible to take part in the study if they had (1) a diagnosis of Autism Spectrum Disorder (ASD), traumatic brain injury, seizure disorder, intellectual disability, or any other medical conditions that could impact their cognitive scores, (2) metal in their body that would prevent them from taking part in MRI, and (3) unwilling to complete a 48-hour medication washout period.

Measures

EF is an umbrella term with varying definitions. Researchers are often not in agreement regarding the exact definition of EF (Wasserman & Wasserman, 2013). As a result, it can be challenging to measure EF using tests that all researchers agree upon. The current study was also an extension of a previously conducted study (see Hai et al., 2020), so the decision was made to continue using similar EF measures with newer norms when available.

Neuropsychological Measures. This study measured two primary domains of EF in both children with ADHD and a typically developing control group. These two domains were working memory and response inhibition. Specifically, for measuring working memory, the Digit Span Backwards and Spatial Span Backwards subtests from the Wechsler Intelligence Scale for Children (WISC-V) and WISC-V Integrated were used (Wechsler, 2014). Commission, Omission and Perseverative errors on the Conners' Continuous Performance Test (CPT III; Conners, 2014) and Colour Word Interference test from the Delis Kaplan Executive Function System (D-KEFS; Delis, Kramer & Kaplan, 2001) were used to measure inhibition. Detailed descriptions of these performance-based EF measures are presented below.

Working Memory. For this study, the WISC-V, Digit Span Backwards and WISC-V Integrated Spatial Span Backwards tasks were used. The overall Digit Span Backward task's reliability coefficient is .81 for the normative sample, suggestive of good internal consistency (Watkins, Dombrowski, & Canivez, 2018). The overall Spatial Span Backward task's reliability coefficient for the normative sample was .81, suggesting good internal consistency (Raiford, 2017).

Inhibition. The current study used the Color-Word Interference from the D-KEFS and the CPT-III to measure inhibition. Test-retest reliability for this the D-KEFS Colour Word Interference task was found to be 0.75 for children between the ages of 8-12 years old (Delis et al., 2001). The split-half reliability estimates for the CPT-III task were .92 for the normative sample and .94 for clinical samples, indicating good internal consistency. Test-retest reliability for the CPT-III was .67, suggesting adequate consistency across administrations (Conners, 2014).

Behavioural Measures-Parent Rating Scale. Parents completed two behaviour rating scales for the current study, i) Conners-3 Parent Rating Scale (Conners, 2008) and ii) Behavior

Rating Inventory of Executive Function, Second Edition (BRIEF-2; Gioia, Isquith, & Guy, 2015).

Conners Parent Rating Scale, 3rd Edition (Conners-3). The Conners-3 Parent Rating Scale was used to measure ADHD symptoms in the sample. The Conners-3 is commonly used in children and adolescents between the ages of 6 to 18 years to detect ADHD-related challenges (Conners, 2008). The assessment features multiple content scales that assess ADHD-related concerns such as inattention and hyperactivity as well as related problems in executive functioning, learning, aggression, and peer/family relations. Conners-3 rating scales have high levels of internal consistency, with Cronbach's alpha ranging from 0.77 to 0.97 (mean Cronbach's alpha = 0.90), and test-retest correlations ranging from 0.71 to 0.98 (Conners, Pitkanen, & Rzepa, 2011).

Behaviour Rating Inventory of Executive Function, Second Edition (BRIEF-2). Parents completed the BRIEF-2, a measure typically used to assess parental perceptions of EF behaviours (Riccio & Gomes, 2013). The BRIEF-2 parent form consists of 63 items with nine theoretically and empirically derived clinical scales and three index scales that measure different aspects of EF. The Behavioral Regulation Index (BRI) composite includes the Inhibit and Self Monitor subscales. The Emotional Regulation Index (ERI) composite consists of the Shift and Emotional Control subscales. The Cognitive Regulation Index (CRI) is comprised of the Initiate, Working Memory, Plan/Organize, Organization of Materials, and Task-Monitor subscales. The BRIEF-2 provides T-scores (M = 50; SD = 10) for the clinical and composite scales, with higher scores representing greater degrees of executive dysfunction. For all scales, T-scores at or above 65 are considered abnormally elevated. The BRIEF-2 exhibited excellent internal consistency

(Cronbach's $\alpha = .97$). Cronbach's alpha scores for the different subscales ranged from .77 to .92 (Jacobson, Pritchard, Koriakin, Jones, & Mahone, 2016).

MRI Acquisition Protocol

All participants underwent a high-resolution MRI T1-weighted sequence using a 3 Tesla General Electric Discovery 750W MRI scanner with a 32-channel head coil. Structural MRI parameters were as follows: TR = 8.2ms, TE = 3.2ms, flip angle = 10°, field of view (FOV) = 256 mm^2, acquisition matrix size = 300x300, voxels = 0.8mm^3 isotropic.

Data Collection Procedures

Participants were recruited through flyers posted around the University of Calgary campus, referrals from health care professionals in the Calgary community and through social media such as Facebook and Twitter. The author of this dissertation was responsible for conducting all the assessment components under supervision. First, informed consent from parents and assent from participants was obtained. Then parents and the participants completed the MINI-KID, a semi-structured interview to evaluate eligibility for the study (Sheehan et al., 2010). Parents also completed Conners-3 rating scales to confirm their child's ADHD diagnosis.

Following receiving consent, the author completed the Intellectual Quotient (IQ) screener that included the three subtests from the WISC-V and WISC-V Integrated with the participants. If the child was found to be intellectually deficient on any of the WISC-V and WISC-V Integrated screener measures (e.g., a scaled score of four or less, $M = 10$, $SD = 3$), the participants were thanked for their participation, and no further testing took place.

All eligible participants then completed the additional neuropsychological measures, with parents completing the questionnaires in one assessment room and the child completing the assessments in a separate assessment room. The testing session lasted approximately 90 minutes. After completing the tasks, eligible participants underwent the neuroimaging portion. The neuroimaging portion of the study took about one hour and fifteen minutes to complete. All participants received a gift card valued at $150 for their participation in the research study.

MRI Reconstruction of Subcortical Regions

MRI-based brain volumetry is a widely used in vivo technique for identifying subcortical changes occurring in different neurodevelopmental disorders, including ADHD. While manual tracing completed by experts is considered the gold standard in terms of accuracy, it is time-consuming, difficult to learn, and accuracy is dependent on multiple factors (e.g., anatomical protocols, tracer experience, scan acquisition parameters, image quality, and the computer hardware/software employed in the tracing procedure). Numerous automated methods have been developed to reduce tracing time while ensuring excellent reliability. FreeSurfer software is an example of one such automated method (Fischl & Dale, 2000).

Neuroimaging preprocessing. FreeSurfer Software (Fischl & Dale, 2000) was used to obtain the subcortical volumes. FreeSurfer is a set of tools that construct models of the boundary between white matter (WM) and cortical gray matter (GM). The pipeline consists of several stages and includes motion correction, removal of non-brain matter such as skull and dura matter, an algorithm for finding and correcting the topological defects in the initial WM/GM surface, a method to deform the mesh for reconstructing the inner and pial surfaces, automated Talairach transformation, subcortical white and gray matter structures, and surface deformation for optimal differentiation of white and gray matter and gray and cerebrospinal fluid intensity boundaries. A detailed description of the FreeSurfer processing is described online (https://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurferMethodsCitation;

Dale, Fischl, & Sereno, 1999; Fischl & Dale, 2000; Fischl et al., 2002, 2004). This measurement technique has been validated in both adult and pediatric populations (Biffen et al., 2020; Dewey et al., 2010). See Figure 2 and 3 for examples of images obtained from FreeSurfer.

Figure 2 Coronal, Axial and Sagittal view of the FreeSurfer Subcortical Region Segmentation

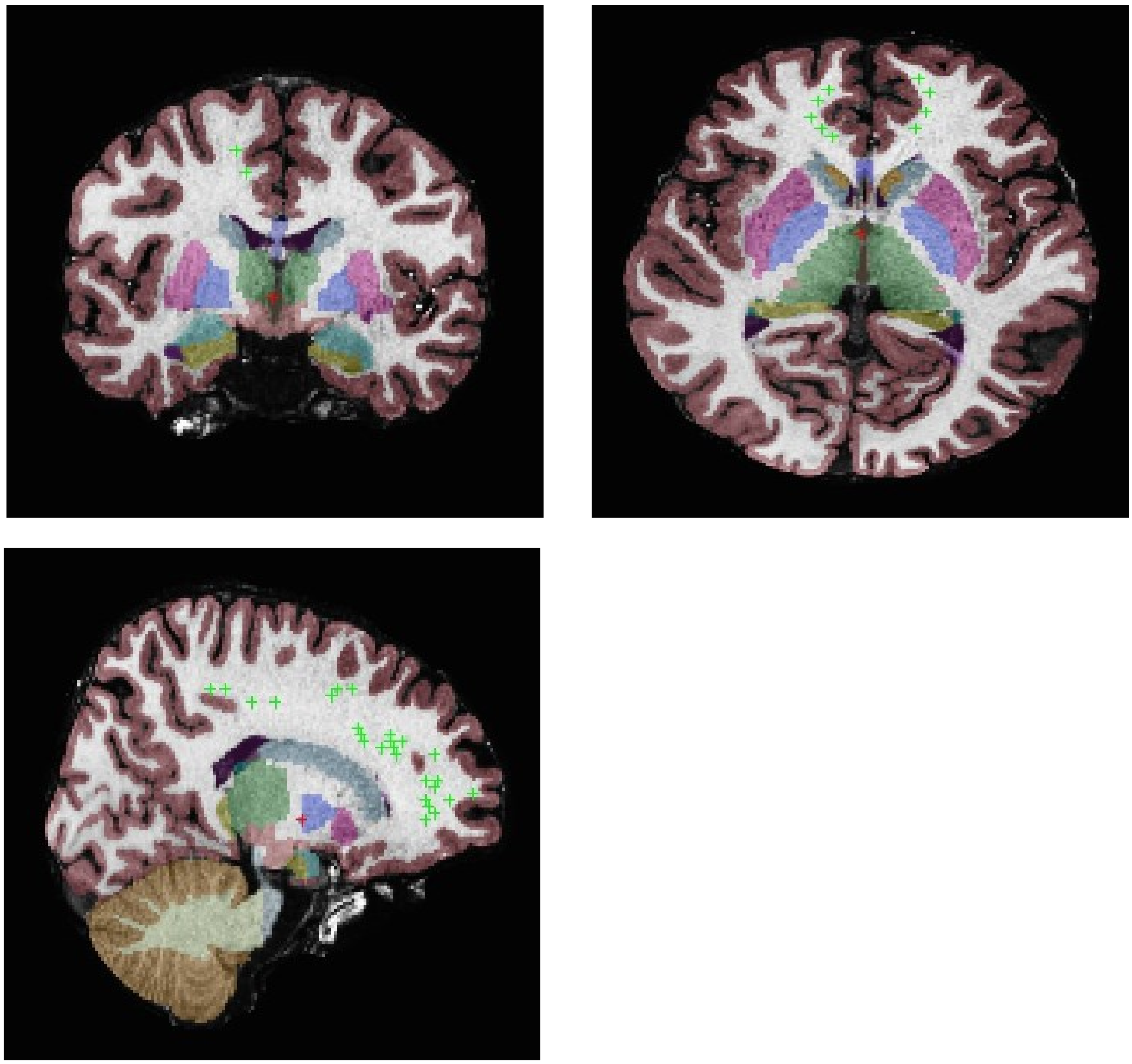
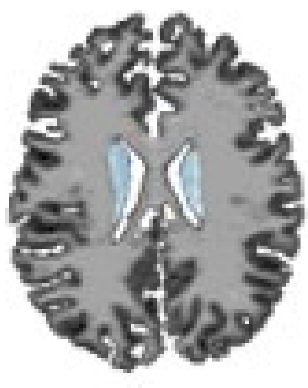
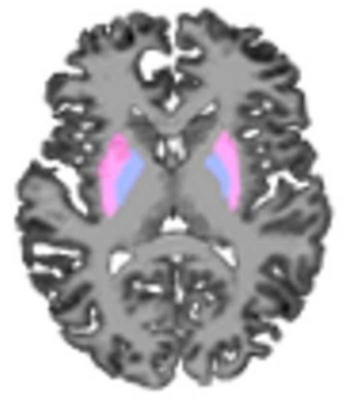


Figure 3 Subcortical Regions of Interest a) Caudate and b) Putamen

A) Axial view of the Caudate in light blue



B) Axial view of the putamen in pink.



Quality Control. As previously indicated, FreeSurfer is a widely utilized tool and the reconstruction procedure outlined is generally considered accurate. However, sometimes the voxels are inaccurately labelled. As a result, quality control procedures as delineated by the ENIGMA consortium were used (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Furthermore, inadequately reconstructed scans typically due to head motion and artifacts were removed.

Data Analyses

The Statistical Package for the Social Sciences (SPSS) version 26.0 was used to conduct all the planned data analyses.

Data Management. Following completion of the assessments, raw scores were converted into T-scores, or standard scores based on age-based norms. Only the T-scores and standard scores of the test measures were included in the data analysis. The data were inspected for missing values and outliers prior to running any statistical analyses. The data were also evaluated for normality, linearity, homogeneity of variance, and homoscedasticity to meet the assumptions of the parametric analysis. Neuroimaging data obtained from FreeSurfer software was evaluated through quality control measures listed on the ENIGMA consortium website to ensure suitability for analysis.

Descriptive statistics. The mean, standard deviation, and percentages were calculated to describe the participants. Variables such as age, biological sex, WISC-V Vocabulary Multiple Choice subtest scores, WISC-V Arithmetic, WISC-V Block Design Multiple Choice subtest and Conners-3 Inattention and Hyperactive scores are the basic descriptive statistics.

Research Question One (Do children with ADHD demonstrate EF deficits on performance-based tasks assessing inhibition and working memory when compared to typically developing controls?) Multivariate analysis of variance (MANOVA) was conducted to investigate the differences in performance between children with ADHD and the TDC group. Specifically, the two domains of EF - working memory and inhibition - were included in the MANOVA, and the group served as the between-subject factor. Univariate analyses for each EF measure were corrected for multiple comparisons using Benjamini-Hochbergs Principle (Benjamini & Hochberg, 1995).

Research Question Two (Do children with ADHD demonstrate EF deficits on behaviour rating scales as observed by parents when compared to TDC?) MANOVA was conducted to measure group differences on the BRIEF-2. Univariate analyses for each EF subscale were corrected for multiple comparisons with Benjamini-Hochbergs Principle (Benjamini & Hochberg, 1995). This provided information about the parental perception of their children's EF challenges.

Research Question Three (What are the differences in subcortical volume in children with ADHD and TDC in the caudate and putamen?) Multivariate Analysis of Covariance (MANCOVA) was carried out to investigate the differences in volumes of the caudate and putamen in children with ADHD compared to the TDC group, with total intracranial volume (ICV), age and dummy coded biological sex as covariance. Benjamini-Hochberg's principle was used to correct for multiple comparisons (Benjamini & Hochberg, 1995). Post-hoc analyses were also conducted to evaluate differences in other subcortical regions.

Research Question Four (Are there relations between the subcortical volume and EF performance measures such as inhibition and working memory?) To examine the associations between subcortical volumes and EF performance on neuropsychological tests measuring inhibition and working memory skills, both Pearson and Spearman correlations were conducted for the ADHD and TDC groups. Typically, Pearson correlations are used for normally distributed data. However, Spearman correlations generally have lower variability when working with variables that feature heavy-tailed distributions and/or have outliers (de Winter, Gosling, & Potter, 2016).

Research Question Five (Are there relations between subcortical volume and EF performance based on parent ratings of EF challenges?) Both Pearson and Spearman correlations were conducted to investigate the relations between subcortical volumes with EF skills reported by parents on the BRIEF-2. Linear regressions were conducted using variables with significant correlations to investigate the relationships between subcortical volume and parent ratings of EF.

Ethics and Data Storage

Data collection for this study took place at the Alberta Children's Hospital, University of Calgary. The original study was approved by the Research Ethics Board at the University of Calgary (CHREB-19 0499). Secondary analysis of the data was approved by the University of Alberta (Study ID Pro00094923) for the completion of the author's dissertation. The University of Calgary considered the study to be of low risk. Risk factors identified were uneasy feelings resulting from answering questions related to their mental health and feeling uncomfortable being inside the MRI. However, the findings from the study may allow us to better understand subcortical volume differences in pediatric ADHD. It will help further extend our conceptualization of ADHD as a neurodevelopmental disorder with an underlying biological basis (American Psychiatric Association, 2013). The ethics board viewed the benefits of the study to outweigh the potential risks. While neuroimaging research with the pediatric population can be challenging due to the relatively long acquisition time compared to CT scan, MRI imaging provides high anatomical resolution and multiplanar imaging capability that can extend our knowledge of the brain and its associated disorders (Downie & Marshall, 2007). Furthermore, MRI is considered relatively safe due to its non-ionizing radiation properties (Downie & Marshall, 2007). All the data collected for this study is electronically stored on an online server at the University of Calgary, which is password protected and monitored by a Research Associate in charge of the Child and Adolescent Imaging Research Centre (CAIR) at the University of Calgary.

Chapter Four: Results

Data Management

The data were inspected for missing values and outliers prior to running any statistical analyses. The data were also evaluated for normality, linearity, homogeneity of variance, and homoscedasticity to meet the assumptions of parametric analysis.

Missing data and outliers. Data analyses began with the examination of missing values and outliers. The data were scanned and analyzed using box plots, scatter plots, and histograms. Missing cases from the neuropsychological measures were analyzed using Little's Missing Completely at Random (MCAR) test and were found to be less than 5%; thus listwise deletion was conducted (Tabachnick & Fidell, 2013).

Normality, Linearity, Homogeneity of Variance and Homoscedasticity. Normality was examined using the skewness and kurtosis values obtained from the dataset. All the measures met the acceptable range of -2 to +2 skewness values (Field, 2009) and -7 to +7 kurtosis values (Hair, Black, Babin, & Anderson, 2010). Additionally, visual inspection of the distribution using histograms was conducted to ensure that the dataset was normally distributed. Linearity was assessed between the dependent variables through visual inspection of bivariate correlations and was deemed to have met this assumption. Box's test was used to evaluate homoscedasticity, and Levene’s test was used to evaluate homogeneity of variance.

Sample and Sampling Procedures

The current study recruited a total of 55 participants. Two participants were excluded because they did not meet the study eligibility criteria: one participant had a diagnosis of ASD, and one participant failed to observe the 48-hour medication washout period. Also, one participant withdrew within one hour of joining due to extreme shyness and anxiety. Lastly, three additional participants were excluded due to their subcortical volumes data being outliers, as indicated through quality control measures completed on subcortical thickness outcomes according to Enigma Consortium protocols (available freely for download from http://enigma.ini.usc.edu/protocols/imaging-protocols/). There were some additional missing data due to participants being unable to complete the EF performance tasks. A final sample of 24 children with ADHD (age range 7.53-16.4 years old) and 25 TDC (age range 7.26-16.87 years) between the ages of 7–16 years old were included in the present analyses. All participants completed EF assessments comprising of inhibition and working memory. All participants also underwent T1-weighted structural MRI.

Group Differences in Screening Measures

There were no age or biological sex differences between the two groups. As expected, there were significant group differences in ADHD symptoms, as reported by parents on the Conners-3 rating scale. Specifically, parents of children with ADHD endorsed higher levels of Inattentive (t (47) = 7.08, p < .001, Cohen's d = 2.02) and Hyperactive/Impulsivity (t (47) = 8.83, p < .001, Cohen's d = 2.51) symptoms compared to the TDC group. There was no significant group difference in the three intellectual functioning screener that were completed: WISC-V Arithmetic subtest (t (47) = 1.57, p = .12, Cohen's d = 0.45), WISC-V Integrated Vocabulary subtest (t (47) = .90, p = .37, Cohen's d = 0.26) and WISC-V Integrated Block Design subtest (t (47) = 0.32, p = .75, Cohen's d = 0.09). Lastly, there were no other significant differences in demographic information between the two groups (see Table 1 for demographic information).

Research Question One. (Do children with ADHD demonstrate EF deficits on performance-based tasks assessing inhibition and working memory when compared to typically developing controls?) MANOVA did not show any group differences on the Working Memory task performance between the ADHD and TDC groups (F (2, 46) = 1.38, p =.26, partial eta squared = .06). Similarly, MANOVA conducted did not show any group differences on the Response Inhibition task performance between the ADHD and TDC groups (F (4, 39) = 2.48, p =.06, partial eta squared = .20). However, univariate analysis of variance showed that children with ADHD made more perseverative errors than the TDC group on the CPT-3 task (F (1, 42) = 8.18, p = .007, partial eta squared = .16). No other significant differences in performance were observed (see Table 2).

Research Question Two. (Do children with ADHD demonstrate EF deficits on behaviour rating scales as observed by parents when compared to TDC?) The results are summarized in Table 3. The results from the MANOVA indicated significant difference in parent ratings between children with ADHD and the TDC group (F (5,43) = 20.89, p <.001, partial eta squared =.71). Specifically, across all the index scores, parents of children with ADHD reported significantly higher EF challenges compared to the TDC. These increased EF challenges were reported on all three subscales, Behaviour Regulation Index (F (1,47) = 53.44, p <.001, partial eta square =.53), Emotion Regulation Index F (1,47) = 31.26, p <.001, partial eta square =.40, and Cognitive Regulation Index F (1,47) = 64.86, p <.001, partial eta square =.58. Furthermore, significant challenges were also reported by parents on scales specifically related to Inhibition, F (1,47) = 46.48, p <.001, partial eta square =.50 and Working Memory F (1,47) = 106.88, p <.001, partial eta square =.70.

Research Question Three. What are the differences in subcortical volume in children with ADHD and TDC in the caudate and putamen? Table 4 summarizes the subcortical findings. MANCOVA was completed after controlling for age, ICV and dummy coding biological sex. The results showed no significant group differences in the volumes of the right and left caudate and putamen, F (4,41) = .79, p >.05, partial eta square =.07).

Research Question Four. (Are there relations between the subcortical volume and EF performance measures such as inhibition and working memory?)

No significant correlations were observed between caudate and putamen volumes with any of the performance-based EF measures. See Table 5 for more details.

Research Question Five. (Are there relations between subcortical volume and EF performance based on parent ratings of EF challenges?) Both Spearman and Pearson correlations were conducted. There was no difference between Spearman and Pearson correlations, and so only the Pearson correlations are presented. Significant relations were observed with right caudate volume and parent ratings on the BRIEF-2 ERI subscale (r = -.32, p = .02). No other significant correlations were found with any of the other BRIEF-2 subscales with the right caudate. Similarly, no other significant correlations were observed with the BRIEF-2 subscales with left caudate, right putamen and left putamen volumes (see Table 6).

When correlations were conducted separately for the ADHD and TDC group, significant correlations were observed for the ADHD group for right caudate volume with BRIEF-2 ERI subscale (r = -.51, p = .01). No such correlation was observed in the TDC group on the BRIEF-2 ERI subscale (r = -.06, p = .77; see Table 7 and 8 for more details).

Linear Regression was completed with BRIEF-2 ERI subscale and right caudate volume for the ADHD group. Results showed that a significant amount of the variance in the BRIEF-2 ERI subscale was explained by the right caudate volume, (F (1, 22) = 7.85, p = 0.01, R^2 = 0.263). This suggests that 26.3% of the variance in emotion regulation in the ADHD group was accounted for by the right caudate volume (See Figure 4).

Table 1

Participant characteristic information, including demographic information, intellectual functioning test results, and ADHD symptoms

	ADHD group (n = 24)		TDC (n = 25)				
Variable	*M*	*SD*	*M*	*SD*	*t*	Cohen's *d*	*p*
Age (years)	11.64	2.64	11.09	2.76	0.71	0.20	.48
Conners-3 Inattention (T-score)	75.67	11.51	55.04	8.72	7.08	2.02	< .001**
Conners-3 Hyperactivity/Impulsivity (T-score)	77.87	11.67	53.12	7.60	8.83	2.51	< .001**
WISC-V Integrated Vocabulary (standard score)	103.54	13.14	106.80	12.15	.90	0.26	.37
WISC-V Integrated Block Design (standard score)	106.67	12.13	107.80	12.51	.32	0.09	.75
WISC-V Arithmetic (standard score)	97.08	13.59	102.40	9.91	1.57	0.45	.12
Biological Sex	n	%	n	%	χ^2	p	
Male	12	50	14	56	0.18	.67	
Female	12	50	11	44			
Handedness							
Right	19	79.2	23	90.0	1.65	.20	

Left	5	20.8	2	8.0		
Medication						
Yes	21	87.5	1	4.0		
Methylphenidate	7	33.3				
Amphetamine	4	19.0				
Alpha-2 adrenergic agonist	1	4.8				
Antidepressant	2	9.5				
Combination of stimulant and non-stimulants	7	33.3				
Other (non-psychiatric)			1	4.0		
No	3	12.5	24	96.0		
Parent income						
Below Alberta Median Family Income (under $99,000)	8	33.3	3	12.0	3.20	.07
Above Alberta Median Family Income (Above $99,000)	16	66.7	22	88.0		
Ethnicity						
Caucasians	22	91.7	16	64.0		
Asians	1	4.15	4	16.0	6.73	.08
Other	1	4.15	5	20.0		

* indicates p value < .05, ** indicates p value < .01

Note: Alberta median income data were obtained from (Statistics Canada, 2018), Wechsler Intelligence Scale for Children-Fifth Edition

Table 2

Executive Function Performance Scores of the ADHD and Typically Developing Control (TDC) Groups

	ADHD (n = 24)		TDC (n = 25)		MANOVA		
Variable	*M*	*SD*	*M*	*SD*	*F*	*p*	Partial Eta squared
Working Memory							
Digit Span Backwards (standard score)	96.88	12.49	102.40	11.28	2.64	.11	.05
Spatial Span Backwards (standard score)	101.46	15.98	101.40	13.11	.00	.99	.00
Response Inhibition							
CPT-3 Omission Errors T-score (n=22)	62.41	16.72	54.61	13.99	2.67	.11	.06
CPT-3 Commission Errors T-score (n=22)	56.86	7.58	55.18	7.81	.53	.47	.01
CPT-3 Perseverative Errors T-score (n=22)	68.77	17.00	54.95	14.97	8.18	.007	.16**
DKEFS Inhibition (standard score)	98.41	14.09	103.18	11.81	1.48	.23	.03

** Indicates *p* value < .01

Table 3

Parent Ratings of Executive Function (BRIEF-2) in the ADHD and Typically Developing Control (TDC) Groups

	ADHD (n = 24)		TDC (n = 25)		MANOVA		
Variable (T-Score)	*M*	*SD*	*M*	*SD*	*F*	*p*	Partial Eta squared
Behaviour Regulation Index	67.83	11.29	49.2	5.80	53.44	<.001	0.53**
Inhibition	68.00	11.97	48.32	7.90	46.48	<.001	0.50**
Emotional Regulation Index	64.88	12.30	49.44	6.14	31.26	<.001	0.40**
Cognitive Regulation Index	70.33	9.54	50.56	7.58	64.86	<.001	0.58**
Working Memory	71.33	7.85	49.60	6.85	106.88	<.001	0.70**

** Indicates *p* value < .01

Table 4

Subcortical Volume Measurements of the ADHD and Typically Developing Control (TDC) Groups

	ADHD (n = 24)		TDC (n = 25)				Partial Eta Square
	M	*SD*	*M*	*SD*	*F*	*p*	
Right Hemisphere							
Caudate	4343.46	463.27	4430.92	467.51	1.36	.25	.03
Putamen	5753.32	589.00	5718.40	638.66	0.10	.76	.002
Left Hemisphere							
Caudate	4183.68	421.96	4242.08	461.46	0.78	.38	.02
Putamen	5820.22	581.75	5703.36	684.81	0.01	.91	.00

These results are after correcting for age, biological sex (dummy coded) and intracranial volume (ICV)

Table 5

Correlations between Subcortical Volumes and Performance on the EF Task

	Variables	1	2	3	4	5	6	7	8	9	10
1	Right Caudate	-	*r*=.904**	*r*=.458**	*r*=.498**	*r*=-.100	*r*=.119	*r*=.118	*r*=.107	*r*=.100	*r*=.115
			p=.000	*p*=.001	*p*=.000	*p*=.493	*p*=.416	*p*=.446	*p*=.466	*p*=.492	*p*=.430
2	Left Caudate		-	*r*=.379**	*r*=.474**	*r*=-.053	*r*=.077	*r*=.122	*r*=.096	*r*=.044	*r*=.123
				p=.007	*p*=.001	*p*=.719	*p*=.600	*p*=.432	*p*=.510	*p*=.762	*p*=.399
3	Right Putamen			-	*r*=.948**	*r*=.071	*r*=.162	*r*=.133	*r*=-.042	*r*=-.026	*r*=.028
					p=.000	*p*=.626	*p*=.265	*p*=.391	*p*=.773	*p*=.859	*p*=.850
4	Left Putamen				-	*r*=.061	*r*=.216	*r*=.111	*r*=-.024	*r*=-.023	*r*=.053
						p=.675	*p*=.136	*p*=.471	*p*=.870	*p*=.877	*p*=.719
5	WISC_V Spatial Span					-	*r*=.235	*r*=.162	*r*=-.402**	*r*=-.399**	*r*=-.234
							p=.104	*p*=.294	*p*=.004	*p*=.005	*p*=.106
6	WISC-V Digit Span						-	*r*=.263	*r*=-.303*	*r*=-.470**	*r*=-.318*
								p=.084	*p*=.034	*p*=.001	*p*=.026

7	DKEFS Inhibition	-	*r*=-.155	*r*=-.127	*r*=-.060
			p=.316	*p*=.412	*p*=.698
8	CPT-3 Omission Errors		-	*r*=.196	*r*=.654**
				p=.176	*p*=.000
9	CPT-3 Commission Errors			-	*r*=.462**
					p=.001
10	CPT-3 Perseverative errors				-

** indicates correlation significant at the 0.01 level (2-tailed).

* Indicates correlation is significant at the 0.05 level (2-tailed).

Table 6

Correlations between Subcortical Volumes and Parent Ratings of EF

Variables		1	2	3	4	5	6	7	8	9
1	Right Caudate	-	*r*=.904**	*r*=.458**	*r*=.498**	*r*=-.244	*r*=-.321*	*r*=-.088	*r*=-.229	*r*=-.148
			p=.000	*p*=.001	*p*=.000	*p*=.091	*p*=.024	*p*=.546	*p*=.113	*p*=.311
2	Left Caudate		-	*r*=.379**	*r*=.474**	*r*=-.134	*r*=-.254	*r*=.000	*r*=-.134	*r*=-.083
				p=.007	*p*=.001	*p*=.357	*p*=.078	*p*=.999	*p*=.360	*p*=.572
3	Right Putamen			-	*r*=.948**	*r*=-.106	*r*=-.161	*r*=.039	*r*=-.164	*r*=.024
					p=.000	*p*=.467	*p*=.270	*p*=.788	*p*=.262	*p*=.871
4	Left Putamen				-	*r*=-.077	*r*=-.151	*r*=.097	*r*=-.122	*r*=.060
						p=.600	*p*=.302	*p*=.508	*p*=.405	*p*=.684
5	BRIEF-2 Behaviour Regulation Index					-	*r*=.763**	*r*=.826**	*r*=.969**	*r*=.820**
							p=.000	*p*=.000	*p*=.000	*p*=.000
6	BRIEF-2 Emotional Regulation Index						-	*r*=.687**	*r*=.737**	*r*=.711**
								p=.000	*p*=.000	*p*=.000
7	BRIEF-2 Cognitive Regulation Index							-	*r*=.802**	*r*=.937**
									p=.000	*p*=.000
8	BRIEF-2 Inhibition								-	*r*=.791**
										p=.000
9	BRIEF-2 Working Memory									-

** indicates correlation significant at the 0.01 level (2-tailed).

* Indicates correlation is significant at the 0.05 level (2-tailed).

Table 7

Correlations between Right Caudate Volume and Parent Ratings of EF Skills (BRIEF-2) in the ADHD group

	Variables	1	2	3	4	5	6
1	Right Caudate	-	*r*=-.251 *p*=.237	*r*=-.513* *p*=.010	*r*=-.067 *p*=.757	*r*=-.286 *p*=.175	*r*=-.105 *p*=.625
2	BRIEF-2 Behaviour Regulation Index		-	*r*=.599** *p*=.002	*r*=.653** *p*=.001	*r*=.953** *p*=.000	*r*=.601** *p*=.002
3	BRIEF-2 Emotional Regulation Index			-	*r*=.507* *p*=.011	*r*=.596** *p*=.002	*r*=.525** *p*=.009
4	BRIEF-2 Cognitive Regulation Index				-	*r*=.617** *p*=.001	*r*=.881** *p*=.000
5	BRIEF-2 Inhibition					-	*r*=.588** *p*=.003
6	BRIEF-2 Working Memory						-

** indicates correlation significant at the 0.01 level (2-tailed).

* Indicates correlation is significant at the 0.05 level (2-tailed).

Table 8

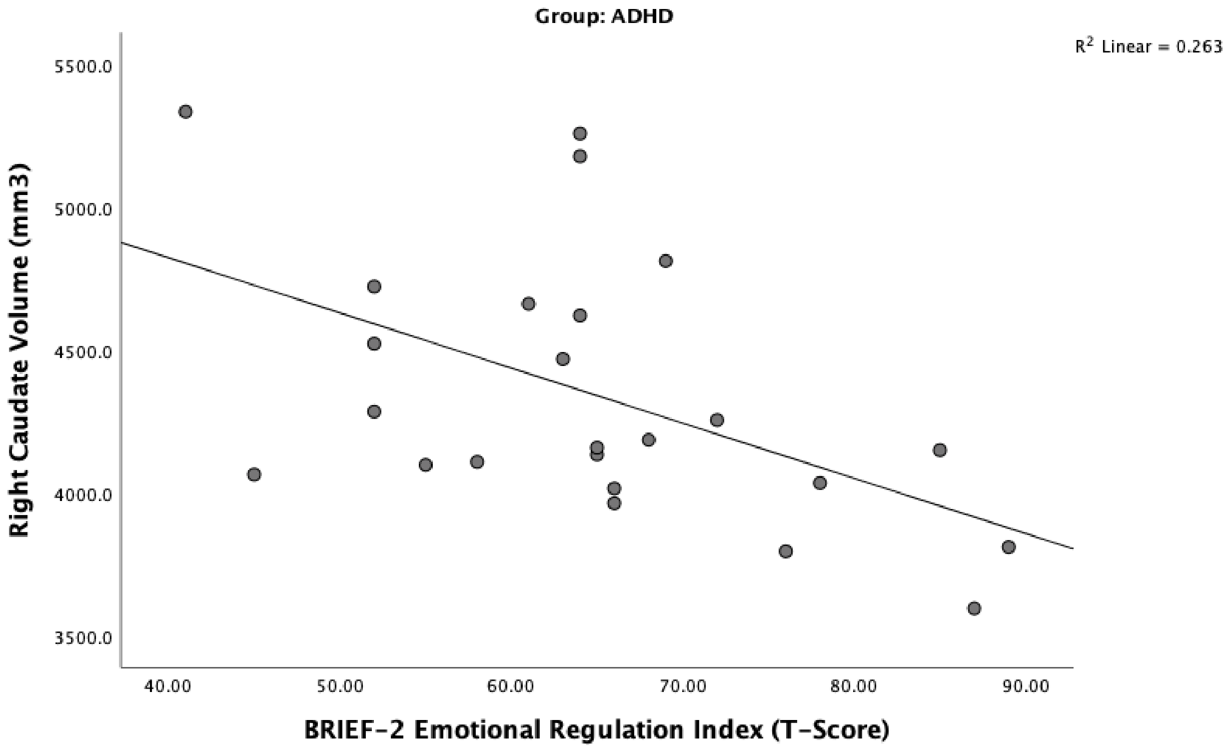
Correlations between Right Caudate Volume and Parent Ratings of EF Skills (BRIEF-2) in the TDC group

	Variables	1	2	3	4	5	6
1	Right Caudate	-	*r*=-.305 *p*=.139	*r*=-.062 *p*=.767	*r*=.026 *p*=.902	*r*=-.160 *p*=.446	*r*=-.146 *p*=.488
2	BRIEF-2 Behaviour Regulation Index		-	*r*=.464* *p*=.020	*r*=.548** *p*=.005	*r*=.913** p=.000	*r*=.528** *p*=.007
3	BRIEF-2 Emotional Regulation Index			-	*r*=.207 *p*=.322	*r*=.353 *p*=.083	*r*=.269 *p*=.194
4	BRIEF-2 Cognitive Regulation Index				-	*r*=.511** *p*=.009	*r*=.797** *p*=.000
5	BRIEF-2 Inhibition					-	*r*=.416* *p*=.039
6	BRIEF-2 Working Memory						-

** indicates correlation significant at the 0.01 level (2-tailed).

* Indicates correlation is significant at the 0.05 level (2-tailed).

Figure 4 Correlation of BRIEF-2 Emotional Regulation Index score with Subcortical volume of the Right Caudate across the ADHD group



Chapter Five: Discussion

The primary goal of this study was to investigate the differences in EF and neuroanatomical regions (subcortical regions) in children with ADHD compared to typically developing peers. Specifically, the current study used a multimodal approach to examine EF and understand whether the EF skills are related to subcortical volumes in pediatric ADHD. These findings hoped to link the fields of neuroscience and psychology to better understand the biological basis of ADHD. The present study intended to answer the following five research questions:

1) Do children with ADHD demonstrate EF deficits on performance-based measures assessing inhibition and working memory compared to the TDC group?

2) Do children with ADHD demonstrate EF deficits on behaviour rating scales as observed by parents compared to the TDC group?

3) What are the differences in subcortical volume in children with ADHD and TDC in the caudate and the putamen?

4) Are there correlations between the subcortical volume and EF based on performance on tasks measuring inhibition and working memory?

5) Are there correlations between subcortical volume and EF ratings reported by parents on behaviour rating scales (BRIEF-2)?

Overall, this study was able to show that there are EF challenges observed in children with ADHD compared to their typically developing peers. These differences were reported by parents on the behaviour rating scale. On objective cognitive measures of EF, the difference in

EF was less pronounced and only seen in one of the response inhibition tasks. Regarding subcortical volumes, no significant group differences were observed in either the caudate or putamen of children with ADHD compared to TDC. However, the current study demonstrated the clinical relevance of the right caudate volume in relation to EF challenges reported by parents. Thus, indicating the importance of caudate volume as a possible biomarker of ADHD. The following sections will delve further into the results and implications of the findings.

Research Question One: EF deficits in performance-based measures

EF difficulties are often reported in children with ADHD based on objective measures (Kofler et al., 2019; Willcutt et al., 2005). The purpose of the first research question was to replicate previous findings and observe whether EF challenges were present on tasks measuring working memory and response inhibition. The expected results were based on numerous studies, including meta-analysis, that reported medium to large group level EF challenges in children with ADHD (Barkley et al., 2001; Hai et al., 2020; Kofler et al., 2011; Tenenbaum et al., 2019; Toplak et al., 2009; Willcutt et al., 2005). Specifically, it is estimated that between 21% to 60% of pediatric ADHD cases have exhibited some form of executive dysfunction using different EF tasks and criteria (Coghill, Seth, & Matthews, 2014; Fair et al., 2012; Kofler et al., 2019).

In contrast to our hypotheses, the results from the current study did not show any overall significant group differences in EF based on performance on objective cognitive tasks. The only significant difference was observed on a response inhibition task, where children with ADHD made more perseverative errors than their peers. No other significant group difference was observed on any of the other measures of response inhibition. Similarly, no significant group difference was seen on the tasks measuring spatial and auditory working memory.

It is important to note that while the current literature states that children with ADHD often have difficulties with EF, the results have been inconsistent across studies. Specifically, some studies have reported neurocognitive heterogeneity in children with ADHD as a common phenomenon (Harmon et al., 2018; Kofler et al., 2019; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). This heterogeneity in presentation could be for numerous reasons. For example, Kofler et al. (2019) reported that only 35% of children with ADHD were impaired when EF was considered a unitary construct. However, this prevalence rate changed to 89% when EF impairment was considered multi-dimensional and observed in at least one of the three primary EF domains (working memory, inhibition or set-shifting). If the result of the current study is considered within this multi-dimensional theoretical model of EF, then the present study did show children with ADHD making more perseverative errors on a task that requires them to sustain attention and inhibit responses. EF challenges were observed on one task but not consistently observed across all EF tasks used in the present study. These results also support the need to assess EF utilizing a variety of standardized measures. Measuring EF using multiple standardized tools and tapping into different EF constructs will allow researchers and clinicians to better understand the holistic impact of ADHD and provide interventions accordingly. Thus, it is recommended for best clinical practice that a variety of EF tasks tapping into different EF domains are used when assessing for a diagnosis of ADHD to obtain the complete picture of the disorder.

Another explanation for the current results could be external factors such as reading skills, intelligence and comorbid disorders impacting EF. Some studies have shown that performance-based measures of EF may be correlated with IQ, where EF impairments on certain tasks are correlated with IQ scores (Ardila, Pineda, & Rosselli, 2000; Friedman et al., 2006;

Mahone et al., 2002). Given that there were correlations observed between some of the IQ measures with EF tasks in this study, it is possible that the lack of EF difficulties was due to the current sample having age-expected IQ scores. Other studies have also shown that EF skills are impacted by comorbidities such as learning disability and internalizing behaviours (Faedda et al., 2019; Menghini et al., 2018). The current study did not exclude participants who had a diagnosis of learning disability or any internalizing disorders and, therefore, could have impacted the overall findings.

Moreover, it is possible that the children in the ADHD group were resilient and have learned skills that are necessary to perform well on EF tests and thus showing no overall group differences (Chan et al., 2021). Koffler et al. (2019) estimated that approximately 10% of children with ADHD were classified as unimpaired on all three EF tasks in their study. So, there may be a subgroup of children with ADHD with intact EF. It is also possible that the EF measures chosen in the current study were less sensitive in detecting EF difficulties. Future research with alternate EF measures such as the NEPSY-II or CANTAB is needed to study the EF difficulties in ADHD. Future studies may also consider using innovative methods of measuring EF through virtual reality tasks where it is possible to obtain more ecologically valid measure of EF (Seesjärvi et al., 2021) .

From the perspective of the biopsychosocial model, social factors such as family socioeconomic status (SES), reduced environmental stress, parenting styles, and living in urban cities with better access to treatment and diagnosis could have also played a role in the development of EF skills. For example, previously, a meta-analysis found that parental education level and higher SES can have an impact on children's EF performance, albeit a small effect size suggesting some relationship between SES and EF (Lawson, Hook, & Farah, 2018).

Furthermore, other studies have shown that children with ADHD can have lower EF when parents report higher levels of stress and use a more authoritarian parenting style (Hutchison, Feder, Abar, & Winsler, 2016; McLuckie et al., 2018). While the current study was unable to assess the impact of these social factors on EF due to its limited sample size and low statistical power, it will be important for future research to continue to understand the varying EF profiles in children with ADHD and understand the impact of social determinants of health. It will also be essential to study EF changes throughout developmental periods using longitudinal study designs to understand the impact of different risk and protective factors. More longitudinal studies like the adolescent brain developmental study (ABCD) study are required to understand the long-term effect of different disorders over time.

In summary, the results from the current study support the need to measure EF through a multi-construct theoretical framework that allows for the detection of specific EF skills. This could lead to the detection of neuropsychologically impaired subtypes of ADHD and potentially inform etiological models of ADHD, identify novel intervention targets, and tailor interventions according to their specific difficulties to maximize treatment efficacy.

Research Question Two: EF deficits based on behaviour rating scales

The purpose of the second research question was to investigate EF challenges as reported by parents using behaviour rating scales. The findings showed significant EF challenges based on parent reports on all three subscales of the BRIEF-2, Behavioural Regulation Index (BRI), Emotional Regulation Index (ERI) and Cognitive Regulation Index (CRI), in children with ADHD compared to their typically developing peers. These findings are consistent with the existing literature where parents of children with ADHD frequently report struggles on the behaviour rating scales (Schneider et al., 2020; Toplak et al., 2009).

These EF difficulties stated by parents represent more global perspective and require parents to estimate EF challenges over the past six months. Furthermore, these findings suggest that children with ADHD not only struggle with common EF domains such as working memory and inhibition but in other areas as well. For example, parents reported difficulties in skills such as planning, task monitoring, and initiating.

One of the interesting findings from the current study is the challenges reported by parents around emotional regulation. Emotional regulation challenges are quite prevalent in children with ADHD and were included as a diagnostic criterion (Faraone et al., 2019; Shaw, Stringaris, Nigg, & Leibenluft, 2014). This conceptualization was seen in the earlier diagnostic criteria for ADHD but was changed in the DSM-III (APA, 2022). However, children with ADHD often show more negative affect, temper outbursts, and emotional lability when presented with negative and challenging situations (Rohr, Bray, & Dewey, 2021; Shaw et al., 2014). While emotional dysregulation is not uncommon in other disorders, children diagnosed with ADHD frequently show emotional dysregulation in the form of reduced patience, unwillingness to wait for their turn, high frustration, anger, and irritability (Barkley & Fischer, 2010; Faraone et al., 2019). It has also been suggested that children with ADHD often struggle with downregulating these high-intensity emotions as they lack the ability to use their EF skills to regulate their emotions and behaviour.

In the current literature, some studies have reported emotional dysregulation in children with ADHD (Faraone et al., 2019; Graziano & Garcia, 2016; Sobanski et al., 2010). Specifically, studies have estimated that between 34-70% of adolescents and adults diagnosed with ADHD experience difficulty in emotional regulation (Faraone et al., 2019; Graziano & Garcia, 2016; Sobanski et al., 2010). Although it is not a formal diagnostic criterion, there is an increased need to support children with ADHD in managing these symptoms. There are also studies in infants that showed that early temperamental characteristics in infants who are colicky and fussy could later develop ADHD in childhood (Frick, Bohlin, Hedqvist, & Brocki, 2019; Olson, Bates, Sandy, & Schilling, 2002). As a result, it is crucial to better understand how to support children with ADHD, specifically with emotional regulation, to prevent long-term adverse outcomes. The current study's results further support the need to refine diagnostic criteria for emotion dysregulation in individuals with ADHD (Shaw et al., 2014).

According to the dual-pathway model, EF is divided into cool EF (attention, working memory, planning, and inhibition) and hot EF, which are related to neuropsychological processes involving emotion and motivation (Sonuga-Barke, 2003). It is possible that the subgroup of children that took part in this study had more challenges with hot EF. The current study did not measure emotion regulation through objective measures and is unable to rule out whether similar difficulties would have been observed. The present study did use the BRIEF-2 to measure emotional dysregulation. The BRIEF-2 emotional-regulation index score is based on an individual’s ability to effectively respond to emotional stimuli and modulate emotional reactivity in a flexible manner that facilitates adaptive functioning. These domains of EF are typically challenging to measure using performance-based tasks that are normed-based, given that most tasks would use all of these skills, response inhibition, response execution, and emotion regulation. Thus it is hard to measure emotional regulation as a single EF construct using objective tasks (Tenenbaum et al., 2019).

Overall, the parent ratings obtained from the current study support the need to measure EF from a parent perspective along with using standardized assessment tools commonly used by clinical psychologists when completing psychological assessments. The comprehensive approach to an assessment allows for a better understanding of the impact of ADHD both in clinical settings as well as in their everyday environment. These findings also further suggest the need to better understand different phenotypes of ADHD to provide effective treatment (medications, behaviour therapy or combination) for individuals diagnosed with ADHD.

The difference in EF based on Performance-Based Tasks and Caregiver rating scales

Generally, both performance-based measures and informant rating scales have been used to study EF in children with ADHD. However, the extent to which these measures reflect the same underlying EF construct is often debated. In the current study, the results from the performance-based tasks showed some challenges in EF specifically related to making more perseverative errors on a response inhibition task compared to their peers. On the contrary, parents reported substantial EF challenges on the behaviour rating scales across all domains of EF measured on the BRIEF-2. Overall, the results from the current study show somewhat divergent EF findings when measured through performance-based tasks compared to parent ratings of EF. It is important to understand why such differences in findings were observed.

Firstly, it has been argued that performance-based measures and rating scales tap into different elements of EF (Gross, Deling, Wozniak, & Boys, 2015; Schneider et al., 2020; Toplak et al., 2009, 2013). Performance-based measures may be more related to abilities, whereas rating scales are related to the application of these abilities on everyday tasks in the home or school setting. The discrepancy between abilities and applied skills can help clinicians and researchers inform interventions. For example, children in the current study have the ability to inhibit responses and hold information in their minds (working memory). However, they may struggle to apply these skills when asked to use them in everyday school or household tasks. Thus, this subgroup of children will likely require different types of interventions than children who lack the EF skills as measured on performance-based tasks.

Secondly, it is possible that the performance-based measures were less sensitive in detecting EF challenges in the current sample. It has been argued that performance-based measures lack ecological validity as they are typically administered in a controlled environment with clear and structured instructions. Performance-based tests are a snapshot at one-time point in an optimal setting. As a result, performance-based measures generally show limited correlations with "real-life" or "day-to-day" functioning (Gross et al., 2015; Schneider et al., 2020). It is possible that lab-based tasks might miss difficulties that are observed by parents and teachers in settings where external factors such as the presence of distraction and different expectations are set on individuals.

Using rating scales to study EF can be beneficial as multiple raters such as parents and teachers can provide perspectives on the child's everyday functioning in numerous settings. When required to formulate clinical case conceptualization, rating scales can be useful to identify EF challenges in the absence of impaired performance on objective tasks in the clinical/lab setting (Davidson, Cherry, & Corkum, 2016; Schneider et al., 2020). Rating scales are also easier to administer and cost-effective compared to completing standardized measures. Additionally, EF rating scales can measure more than core EF components such as Initiate, Organization of Materials, and Attention that do not map onto performance-based measures. Furthermore, behaviour rating scales can offer a global perspective on symptoms of behavioural dysregulation, working memory and inhibition (McAuley, Chen, Goos, Schachar, & Crosbie, 2010).

While the current study results show mostly null findings related to group differences observed on performance-based cognitive measures, it is important to highlight the benefit of using both cognitive measures and parent ratings to understand EF challenges in children with ADHD. When possible, corroborating rating scales and cognitive measures are recommended. Behaviour ratings are subjective measures. Indeed, informant ratings could be influenced by situational factors, such as levels of parental frustration and stress as well as teacher stress (Gross et al., 2015). Moreover, there is often low inter-rater reliability between parent and teacher ratings on the behaviour rating scales, impacting clinical formulation. As a result, it is not recommended to eliminate using performance-based measures completely in assessment process. Rather, the current study highlights the importance of using both types of information when making clinical diagnoses.

Overall, the results from the present study support the need to use both performance-based measures and informant rating scales to obtain valuable information about the individual. As alluded to in the previous section, there are advantages and disadvantages associated with both types of EF measures, and an integrated approach can be considered best practice when formulating case conceptualization and targeting interventions for individuals with ADHD.

Research Question Three: Subcortical volume in children with ADHD

The third research question of the current study was to investigate anatomical differences in subcortical regions in children with ADHD compared to their peers. To answer this question, differences in volumes of the caudate and putamen were compared between the two groups. The results found no significant volumetric differences between children with ADHD and their peers in either the caudate or the putamen after controlling for age, biological sex and ICV. These findings are in contrast to the expected hypotheses, as previous studies, including a large-scale meta-analysis, showed altered volumes in these subcortical regions (Hoogman et al., 2017).

Despite these previous subcortical findings, the results of the current study are not surprising, given the lack of consistency in the existing literature regarding the neuroanatomical differences observed in children with ADHD, including a recent large sample of children with ADHD showing no significant subcortical difference (Bernanke et al., 2022; Cortese & Coghill, 2018; Rubia, 2018; Samea et al., 2019). One reason for the differences could be the use of medication (duration and type of medications) and its impact on different brain regions. The children that took part in the current study were not medication naïve. While they had undergone 48 hours wash-out period, it is difficult to rule out the impact of medication use long-term. In addition, medication compliance can also impact the efficacy of medication use and the overall long-term impact on different brain regions. Furthermore, some children with ADHD often take "holiday" breaks from their medication which also makes it challenging to statistically control for the impact of long-term medication use and its effects on different brain regions.

Age is another factor that could have had an impact on the current findings. Previously researchers have suggested that the anatomical changes in the subcortical region occur earlier in children with ADHD when compared to cortical changes (Halperin & Schulz, 2006; Rosch et al., 2018). The discrepancies in dorsal striatum morphology in ADHD tend to progressively reduce through the adolescent years. This was similarly reported in the ENIGMA meta-analysis, where the effect size of the subcortical volume differences was larger when the sample was reduced to children only (Hoogman et al., 2017). As the caudate reaches its maximum volume around ten years, there is a decline in the potential relationship between caudate volume and ratings of hyperactivity/impulsivity in children with ADHD (Castellanos et al., 2002; Hoogman et al., 2017). Thus, it is possible that the current study did not observe any differences in the caudate and putamen volume due to including a participant group that spans between the ages of 7-16 years old. If a younger sample group was recruited, it is possible that the subcortical differences would emerge. Furthermore, our lab has previously shown that school-aged children with ADHD tend to show more cortical abnormalities, consistent with what was previously reported (Hai et al., 2022; Yang et al., 2015). As a result, it is possible that due to early diagnosis and interventions, some of these subcortical differences were not observed.

Another probable explanation for the results of the current study could be due to methodological differences. There is constant improvement in MRI technology and different innovative ways to study in vivo brain changes. Some of the results available in the current literature were conducted with different MRI protocols, image acquisition parameters, MRI magnet resolutions and scanners. Besides, the large-scale meta-analysis is based on data collected from multiple MRI scanners of different companies (GE versus Philips versus Siemens). These technological differences may impact findings across sites and thus making it challenging to generalize results across different studies. The current study also used the software FreeSurfer 6.0 to create parcellation of different brain regions (Dale et al., 1999; Fischl et al., 2002, 2004). While these methodologies are validated, it still follows an atlas that is designed for adult brains. Human brains are unique, and therefore subtle differences could be missed by these automated neuroimaging pipelines.

Overall, the present study did not show any significant volumetric differences in the caudate or putamen. The existence of comorbidities, the impact of medications, sample heterogeneity and technological differences could have impacted the current findings. Given the heterogeneous presentation of ADHD and comorbidities associated with many individuals with ADHD, it can be challenging to identify common biomarkers of ADHD. There is a need to conduct further research to study the impact of comorbidities, long-term medication use and early intervention on neuroanatomical differences using the same study protocol across large multi-site centres to better understand the etiological factors of ADHD.

Research Question Four: Relations between the subcortical volume and EF performance

The fourth research question of the current study was to take on a brain-behaviour approach to investigate the relation between subcortical volume and EF performance in children with ADHD and the TDC group. Given the lack of research in this area, the present study hypothesized positive correlations between EF performance and subcortical volumes in the two participant groups.

The results from the current study did not find any significant correlations between subcortical volume and EF performance on objective measures. These findings are in contrast to the expected results. It is possible that the subcortical volume of the caudate and the putamen may not be related to the EF tasks selected in this study. It is also possible that EF tasks are related to cortical regions and less impacted by subcortical regions in the preadolescent years. Another possible reason could be the sample size was not large enough to observe significant correlations. While the current study showed some EF challenges specifically related to perseverative errors in the response inhibition task, it is possible that other brain regions are functionally involved that were not investigated in this study. The brain-behaviour relationship has been a long-standing issue and one that requires further evaluation and replication by future studies. While null findings are observed in the current study, the conclusions should be taken with caution. Future research studies are needed to better understand the role of subcortical regions as a relevant biomarker of ADHD.

Research Question Five: Relations between subcortical volume and parent ratings of EF performance

The final research question of the current study was to investigate the relation between subcortical volumes and EF challenges as reported by parents in children with ADHD and TDC group. This research question combines the findings from Question 2 and Question 3 to identify whether parent ratings of EF skills are related to the volumes obtained from caudate and putamen to identify biomarkers of ADHD.

The current study found significant correlations between right caudate volume and EF parent rating scales related to emotional regulation. The relationship indicated a negative correlation where a higher volume of right caudate was generally associated with lower emotional regulation challenges in children with ADHD. The regression model further showed that right caudate volume predicted 26.3% of the variance in BRIEF-2 ERI scores in the ADHD group. Overall, it indicates a possible association between right caudate volume and EF challenges in children with ADHD.

To the best of the author's knowledge, this is one of the first studies to find such a relationship. These results could suggest a possible brain-behaviour link between subcortical volume and emotional regulation. While exploratory, these results are consistent with the hypotheses, as the caudate has been indicated to serve as the entry point to both the basal ganglia and the dopaminergic reward systems (Damiani et al., 2021). Studies have shown reduced volume and increased asymmetry in the caudate in ADHD (Castellanos et al., 2002; Damiani et al., 2021; Hoogman et al., 2017). The caudate also plays an essential role in ADHD symptomatology. For example, it regulates motor, emotional, cognitive, and perceptual functions. Furthermore, the cortico-striatal network is linked to behavioural features characterizing ADHD, such as the inability to tolerate delays and impulsivity.

Previously, studies have reported other subcortical regions such as the nucleus accumbens, hippocampus, and amygdala to be altered in ADHD (Hoogman et al., 2017). Given the relationship with emotional regulation observed in the current study, the caudate may play a role in altering the connection between different regions involved in the limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuits and overall impact behaviour. While not studied in the present study, it is also possible that the reduced caudate volume impacts the connection with the amygdala, affecting emotional regulation in children with ADHD. Previously, fMRI, including resting-state fMRI studies, have shown altered activation of subcortical regions in individuals with ADHD (Cortese et al., 2014; Damiani et al., 2021; Samea et al., 2019). Specifically, altered functional connectivity was seen between the caudate, anterior cingulate cortex and the insula in the ADHD group (Damiani et al., 2021). Furthermore, with respect to emotion processing, elevated positive amygdala functional connectivity was associated with difficulty regulating negative emotions in children with ADHD (Hulvershorn et al., 2014). In addition, one study with neurotypical subjects showed that activity in the caudate was related to fewer errors in a go/no go task, thus indicating its role in behavioural inhibition and impulsivity when reacting to emotional stimuli (Hare, Tottenham, Davidson, Glover, & Casey, 2005). Overall, these studies suggest a possible link between caudate, the amygdala and emotional regulation.

While the relations between emotional regulation and caudate abnormalities are not well studied, the present finding opens the door for future research to better understand this relationship. Emotion dysregulation in ADHD has re-emerged as one of the core contributors to ADHD and has gradually attracted widespread consideration. The correlations observed between caudate volume and EF challenges suggest that neuroanatomical regions are implicated in the pathophysiology of ADHD (He et al., 2015). The results emphasize the benefit of parent ratings in measuring brain-behaviour relationships in children and extend previous work linking parent ratings of ADHD symptoms with regional brain volumes. These exploratory findings require replication in other neurodevelopmental disorders that impact EF (Autism Spectrum Disorder, Fetal Alcohol Spectrum Disorder and Learning Disability). Overall, the present results suggest that when used together with performance-based tests, the BRIEF-2 (parent rating scale) may be a better predictor of the brain-behaviour relationship of the subcortical region development in pediatric ADHD.

Implications

The result of the current study offers the research community and clinical practitioners some insight into the potential brain-behaviour relationship in pediatric ADHD. Following the RDoC framework to better understand development and abnormalities in brain development, the current study integrated different levels of information to investigate the psychopathology of ADHD (Casey, Oliveri, & Insel, 2014). Specifically, the findings from the present study indicate that there are no volumetric differences in the subcortical regions of caudate and putamen occurring in the brains of children with ADHD when compared to their typically developing peers (healthy control group). The subcortical regions of caudate and putamen have historically been considered regions impacted in ADHD. While previous structural and functional MRI studies have found alterations in the caudate and putamen, there may be a subgroup of children with ADHD without alterations in the dorsal striatum. This helps explain the heterogeneity of the presentation of ADHD and that commonly thought neuroanatomical markers are not consistently observed in ADHD.

Regarding EF, the current study found some interesting results. When EF is measured through objective tasks of working memory and inhibition, minimal challenges were observed at the group level. However, behaviour rating scales completed by parents indicated significant EF challenges across all domains of EF measured using the BRIEF-2. This highlights the importance of measuring EF through both objective measures and behaviour rating scales. Studies have indicated that rating scales are more holistic and can show challenges that occur over a span of time rather than the snapshot obtained from performance-based tasks (Wallisch, Little, Dean, & Dunn, 2018). Furthermore, measures such as the BRIEF-2 or CEFI can provide valuable intervention opportunities for individuals with ADHD, such as initiation, task monitoring, planning and emotional regulation, which are generally hard to measure using performance-based tasks. As such, the results recommend school and clinical psychologists to use both performance-based tasks and behaviour rating scales to diagnose and measure treatment outcomes. Pediatricians and other medical practitioners are encouraged to consult with psychologists to better identify challenges observed in individuals with ADHD. This will allow interventions to be provided in a more tailored fashion for children with ADHD. For example, individuals with ADHD who struggle with emotional regulation may benefit from receiving behavioural interventions related to emotional regulation (i.e., Dialectical Behaviour Therapy or Acceptance and Commitment therapy) along with medications. Educational staff may also be able to include emotional regulation strategies when completing individualized education plans for individuals with ADHD who have emotional difficulties. Furthermore, novel techniques such as neurostimulation techniques (transcranial magnetic stimulation [TMS] and transcranial direct current stimulation [tDCS]) can work as a supplementary treatment on top of medications (Rubia, 2018).

The findings from the current study also highlight that some individuals with ADHD are resilient and have learned strategies to perform well in some EF tasks. While parental ratings of ADHD symptoms were significantly high in children with ADHD, they were able to learn strategies to work around their challenges. As such, it is possible that different EF-related strategies may be taught to children with ADHD to alleviate some of their behavioural difficulties. This suggests the need to take on a strengths-based approach to working with individuals with different clinical disorders. By highlighting their strengths, it can be easier to target interventions in areas of challenge. These results also encourage educators and school staff to consult with school and clinical psychologists to adapt education plans according to the individual client's strengths and areas of need to facilitate a tailored academic programming.

The most important finding from the current study is the relations between right caudate volume and emotional regulation (ERI) on the BRIEF-2. To the best of the author's knowledge, this is one of the first studies to report such findings. The results highlight that deficit in EF in ADHD can be related to structural neural alterations. Specifically, emotional dysfunction, a highly debated topic in ADHD, was found to be correlated to lower volumes in the right caudate. These findings have important implications as children with ADHD with emotional symptoms are described as less likeable by peers, inflexible, lacking behavioural control and likely to have higher levels of hyperactivity/impulsivity in adulthood (Faraone et al., 2019; Lee et al., 2018). Additionally, a recent study of adolescents with more severe ADHD symptoms with emotional dysregulation challenges showed increased use of mental health services in adulthood (Girela-Serrano et al., 2022). Furthermore, adults diagnosed with ADHD with emotional dysregulation were also reported to have a significantly lower quality of life and social adjustment (Faraone et al., 2019). As such, the findings from the current study highlight the need to target interventions to manage the emotional regulation challenges in the identified subgroup of children. Appropriate interventions such as mindfulness, DBT, CBT, or other therapeutic modalities combined with lifestyle factors can be discussed with the client's healthcare team to ensure a good fit with the client's needs.

While the relationship between structural abnormalities and EF performance is evolving, the findings from the present study have the potential to add to the existing literature. The fMRI literature on ADHD has identified dysfunction in multiple neuronal systems involved in higher-level EF, cognitive and sensorimotor functions (Cortese et al., 2014; He et al., 2015; Samea et al., 2019). Similarly, Rohr et al. (2021) showed an association between functional connectivity changes in prefrontal, limbic, striatal, and visual brain regions with behavioural regulation challenges in children with ADHD. Given that caudate may be one of the neural substrates of EF, it is necessary to continue to explore these associations between structural abnormalities in the brain and EF in children and adolescents with ADHD. These well-characterized cross-sectional studies will allow researchers to conduct future meta-analyses and identify common neural substrates of EF. Additionally, future research is needed to better understand the role of the caudate in emotional regulation and its link to other subcortical regions.

Applying the biopsychosocial model, the result from the current study has the potential to influence the practice of school and clinical psychologists. When case conceptualizing and understanding test scores obtained through our psychological instruments, it is essential to consider other psychosocial factors. For example, it is important to understand the influence of parental education, parental stress, trauma, and access to early intervention on performance.

Based on the results, it is recommended that psychologists take on a holistic perspective and integrate information using standardized test measures and behaviour ratings scales, along with a thorough clinical interview to diagnose ADHD and measure the impact of interventions. The current CADDRA practice guidelines does not include any specific recommendation related to measuring EF (CADDRA, 2018). The practice guidelines could be updated and made more comprehensive to include information related to administration of assessment tools to measure EF.

One of the primary goals of the RDoC framework is to create better diagnostic systems and treatment options. The results of the current study suggest a need for alternate interventions and support for children with ADHD who show significant EF challenges based on parent reports (Doom et al., 2021). Given that stimulant medications have 70% efficacy with considerable side effects, alternative forms of treatment are required (Cortese et al., 2018; Van der Oord et al., 2008). An alternate treatment could include neurostimulation, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). With the continued success of rTMS in treating mood and anxiety disorders (MacMaster et al., 2019; Parikh, Strawn, Walkup, & Croarkin, 2022), it is possible that rTMS could be a complementary treatment option to support children with ADHD who have emotional regulation challenges. Currently, only a handful of studies have investigated the efficacy of rTMS treatments in individuals with ADHD (Bloch et al., 2008; Rubia, 2018). Given the results from the current study, children with ADHD may need interventions directed towards improving emotional dysregulation along with other symptoms of ADHD.

Overall, the results from the current study have the possibility to direct intervention choices. By better understanding the subgroup of children with EF challenges, clinicians can target impairments such as emotional dysregulation when observed in children with ADHD using behaviour rating scales. Since EF deficits impact academic and social functioning, specific EF interventions can improve long-term academic success and general functioning in children with ADHD.

Limitations

While the current study adds valuable information to the existing literature on ADHD, the results should still be evaluated in the context of some study limitations. First, it is essential to note that the ADHD sample in the current study was based on self-referrals. It is possible that the children and families who were involved in the study included a unique subset of the population, including individuals who are motivated to participate in research studies. Given the time commitment required for the study participation (8+ hours), the study may include participants who are generally managing their ADHD symptoms well. Thus, it is possible that the sample may have confounded between-group effect estimates.

The current study also did not investigate the effect of comorbidities on the different EF performance outcomes. Given the prevalence of comorbidities present in the literature regarding ADHD, it is possible that some of the results obtained in the study could have been better explained by the presence of other neurodevelopmental disorders such as having specific learning disorders or externalizing disorders such as ODD. The results could have also been impacted by internalizing disorders like anxiety and depression. Co-occurring conditions are common in ADHD, and thus the inclusion of children with these comorbidities was essential to maximize the external validity and generalizability of our findings.

Regarding EF measures, the current study only used neuropsychological measures related to working memory and inhibition. There are discrepancies in the existing literature regarding the definition of EF and what domains constitute EF. As a result, it would be essential to measure other domains of EF skills. For example, EF tasks that measure emotional regulation or emotion processing would be beneficial to understand the link between parent ratings and objective EF tasks. It would have been beneficial to corroborate teacher ratings of EF with neuropsychological findings to gather a better understanding of EF challenges in children with ADHD.

Another limitation of the current study is the sample size. Due to the small sample size, it was not possible to study the differences between the different presentations of ADHD. As such, the varying presentation subtypes (i.e., inattentive and combined) were collapsed into one heterogeneous group. The current study was also not able to investigate biological sex or gender differences. Lastly, the present study only studied two subcortical regions, caudate and putamen, to reduce multiple comparisons. It is possible that other areas of the cortex and the cerebellum could have anomalies in children with ADHD. Future research with a larger sample size is needed to better understand the etiology of ADHD.

Future Research

The current study provides some initial evidence to support the relations between emotional regulation challenges and volume of right caudate. However, more work needs to be done before emotional regulation can be included as a diagnostic criterion for ADHD. Future research needs to continue incorporating a holistic approach to studying the etiology of ADHD, including forming collaborations between neuroscientists, pediatricians, psychologists, geneticists, parents, and teachers to investigate brain networks, cognitive functions, genetics, and academic performance in children with ADHD. Such collaborations will also enable a better understanding of the relevance of subcortical regions as a potential biomarker.

Given the challenge with the small sample size in neuroimaging studies, future research needs to investigate larger cohorts of ADHD individuals to investigate other potential subgroups of ADHD based on neuroanatomical differences and characterize such groups with clinical data. By characterizing such subgroups based on neuroanatomical findings, it is possible to provide more targeted interventions. Also, with the improvement in MR technology, it is essential to continue to study neuroanatomical changes in children with ADHD. Future studies need to be conducted using 7T MRI to understand neuroanatomical changes with better MRI resolution.

Examination of the brain–behaviour relationships using teacher, adolescent self-report, and preschool versions of the BRIEF-2 are also warranted. These rating scales at different time points will allow explorations of brain-behaviour associations that can highlight the trajectory of brain development in children. Furthermore, as mentioned in the limitation section, the current study only used EF tasks that can be categorized under the cool EF (e.g., working memory and inhibition). However, parent ratings of EF indicated significant challenges related to emotion regulation which is considered a hot EF task. It would be essential to use tasks that are dependent on emotional regulation in the future to better understand the relationship between parent ratings of emotion regulation and performance on tasks that measures emotion regulation. Future studies may also consider using newer technologies such as virtual reality to measure EF.

The current study was only able to look at parts of the biological and psychological aspects of ADHD. In the future, to better understand the etiology of ADHD, other components of the biopsychosocial model need to be incorporated into research. The impact of different factors such as parent-child relationship, environmental factors, school experience and peers on brain development needs to be conducted in the future (Doom et al., 2021). Other biological factors such as hormonal change, impact of puberty, sleep, diet, and physical activity need to be incorporated in future models. Finally, and possibly more critical than any of the other recommendations for future research, is to study the impact of the current scientific context on behaviour and brain development. The political climate, the effects of systemic inequities, racism, and microaggressions on minoritized youth are areas of research that need imminent consideration for future research (Paradies et al., 2015).

Conclusion

The current study integrated a brain-behaviour approach as outlined in the RDoC framework to investigate EF challenges in children with ADHD compared to typically developing peers using both objective measures and parent ratings of EF. The study also examined the neuroanatomical volumetric difference in the caudate and putamen in children with ADHD compared to their peers. Lastly, the current study was interested in understanding the clinical relevance of structural differences with EF performance to identify biomarkers of ADHD. Overall, this study showed significant EF difficulties based on parent ratings, but no statistically significant volumetric difference was observed in the caudate or putamen. However, the right caudate was correlated to parent ratings of emotional regulation in the ADHD participant group and predicted 26.3% of the variability in parent ratings. These findings highlight the need to consider emotional regulation difficulties in ADHD not just for diagnostic purposes, but also for targeted treatment options. As well, the current study recommends assessing EF using a variety of assessment tools such as informant rating scales and neuropsychological measures for best practice. Given the exploratory nature of the findings, future studies are required to replicate current results and determine if the right caudate volume can be a possible biomarker of ADHD.

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