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# Cerebellar Volume and Executive Function in Young Adults with Congenital Heart Disease

Eric Semmel

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CEREBELLAR VOLUME AND EXECUTIVE FUNCTION IN YOUNG ADULTS WITH  
CONGENITAL HEART DISEASE

by

ERIC S. SEMMEL

Under the Direction of Tricia Z. King, Ph.D.

ABSTRACT

This study investigates structural cerebellar correlates of executive function in adolescents and young adults (AYAs) with congenital heart disease (CHD). The sample includes 22 AYAs with CHD and 22 matched healthy controls. There were significant cerebellar volume differences between CHD patients and controls and CHD patients performed significantly more poorly on several measures of executive function (EF). Furthermore, we found a significant single dissociation such that EF measures were related to the posterior CB but not the anterior, lending support to previously established CB theories. We demonstrate that the posterior CB contributes to some aspects of EF above and beyond processing speed alone, suggesting a unique contribution that warrants further study. Exploratory analyses are discussed as well. A better understanding of these cognitive outcomes in CHD will allow us to identify patients at risk of poor functioning and to better understand the role of the CB in higher-order cognition.

INDEX WORDS: Congenital heart disease, Executive function, Cerebellum, Long-term outcomes, Magnetic resonance imaging

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by

ERIC S. SEMMEL

A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of

Master of Arts

in the College of Arts and Sciences

Georgia State University

2019

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CONGENITAL HEART DISEASE

by

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## **DEDICATION**

This proposal document is dedicated to my family and friends who have given me unwavering support during my time applying to and attending graduate school. I would not be here without their help and encouragement.

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## 1 INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect in the US, occurring in 1% of births each year (Hoffman, Kaplan, & Liberthson, 2004). It can arise as part of a genetic syndrome, such as Downs or DiGeorge's Syndromes, known single-nucleotide mutations, or subsequent to *de novo* mutations (in about 10% of cases) (Bruneau & Srivastava, 2014). Even though CHD remains the leading cause of infant death due to birth defect, advancements in pediatric cardiology have led to rapidly falling mortality rates, which have decreased by 24.1% between 1999 and 2006 (Gilboa, Salemi, Nembhard, Fixler, & Correa, 2010; Yang et al., 2006). Since these patients are living longer, there are now more than 1,000,000 adults with CHD in the United States, a number which is anticipated to grow by 5% each year (Jackson, Misiti, Bridge, Daniels, & Vannatta, 2015). This large and growing population of survivors necessitates the further study and understanding of long-term outcomes in CHD, a topic which until recently has been relatively neglected in the literature in favor of more short-term pediatric outcomes. As the CHD population ages, areas of concern for these patients include academic, occupational, and behavioral concerns as well as health-related quality of life. Underlying all of these are cognitive outcomes, particularly executive function (EF). Individuals with CHD are at risk for compromised EF, which can have detrimental effects on work and school performance and can create difficulties for young adults who are transitioning to managing their own medical care (e.g., making appointments, taking medication, etc.). In this study, we explore EF outcomes in a sample of adolescents and young adults in order to extend the literature and identify potential neuroanatomical correlates that predict risk for poor outcomes. It is our hope that a better understanding of these factors will allow providers to identify patients who are at risk for poor cognitive outcomes and intervene earlier.

## 1.1 Cognitive Outcomes in CHD

Within the CHD population, a range of severity in cognitive outcomes exists, with outcomes most closely related to the severity of the CHD itself. CHD as a category of defects is comprised of a variety of diagnoses, ranging in severity from mild (often requiring no intervention) to complex (often requiring multiple surgeries and cardiopulmonary bypass procedures). Another common method of describing diagnoses is specifying whether or not infants exhibit cyanosis, a blueish tint to the skin, lips, and nail beds that results from the mixing of oxygen-rich and deoxygenated blood. These cyanotic CHDs (e.g., pulmonary atresia, hypoplastic left heart syndrome, some cases of tetralogy of Fallot) are more severe and result in poorer outcomes than acyanotic CHDs (e.g., ventricular septal defect, atrial septal defect, aortic valve stenosis), as cyanotic forms result in suboptimal oxygen perfusion in the rest of the body. In the current study, we define severity based on whether the diagnosis is a single ventricle or biventricular diagnosis, meaning whether an individual is born with one or two functioning ventricles. Previous research has shown that single ventricle CHD results in poorer outcomes.

Already in the relatively young literature on outcomes in CHD, neurocognitive, behavioral, and quality of life difficulties have been widely noted in these patients (Karsdorp, Everaerd, Kindt, & Mulder, 2007; Mahle, 2001; Marino et al., 2012). One specific domain of cognitive functioning that is commonly found to be impaired in people with CHD is executive function (EF). Executive function generally refers to cognitive skills involved in top-down control of “lower-level” processes (for example, inhibition of prepotent responses) as well as cognitive flexibility, planning, organization, and goal-directed behaviors (Alvarez & Emory, 2006). EF deficits can have a wide range of impacts on day-to-day functioning and quality of life

including attention, academics, and occupational performance, making EF a particularly important cognitive domain for optimizing quality of life outcomes for these patients.

EF deficits have been found repeatedly in children with CHD, with some authors concluding that the rate of impairment is twice as high as in healthy controls (Bellinger et al., 2011; Bergemann et al., 2015; Cassidy, White, DeMaso, Newburger, & Bellinger, 2015; Gaynor et al., 2010). Cassidy and colleagues studied a sample of children aged 10-19 who were treated for critical cyanotic CHDs shortly after birth. The authors assessed EF with the Delis-Kaplan Executive Function System (D-KEFS) and found that rates of EF impairment (scores greater than 1.5 standard deviations below the mean) were nearly twice as high in individuals with CHD as in controls. Other studies have found that 4-6-year-old children perform worse than controls on the Stroop, a visual working memory block test, and a dimensional card sorting task. These authors also concluded that children whose CHD is identified earlier in the pregnancy exhibit more intact neurocognitive outcomes because it allows for more optimized cardiac care (e.g., delivery at a specialized cardiac center, administration of prostaglandin, and other specialized procedures when required) (Calderon et al., 2012; Calderon et al., 2010). Hovels-Gurich et al. (2007) found a significant deficit in executive control aspects of attention on the Attention Network Test in 5-11-year-old children as compared to controls. They demonstrated that this effect is particularly pronounced in individuals with cyanotic CHDs. Deficits in planning and cognitive flexibility, both domains of EF, were found in studies of 8-year-olds who were treated for d-transposition of the great arteries as infants. Patients from this study who were placed on cardiopulmonary bypass during their surgery were also significantly more impulsive responders on a vigilance task (Bellinger et al., 2003; Bellinger et al., 2011). As a final example, Miatton and colleagues evaluated 7-9-year-olds with Tetralogy of Fallot (TOF) and found significant



differences between TOF patients and healthy controls on the Tower and Design Copy from the NEPSY, two subtests that rely heavily on EF. They did not observe differences between TOF patients and those with acyanotic disease (Miatton, De Wolf, Francois, Thiery, & Vingerhoets, 2007).

Studies have shown that these deficits can persist into adolescence and adulthood as well, confirming the need for more research on older CHD patients (Klouda, Franklin, Saraf, Parekh, & Schwartz, 2017; von Rhein et al., 2015). While these deficits have been well documented in young children, little research exists on neurocognitive outcomes in adolescents and young adults (AYAs). In fact, one recent review of neurocognitive outcomes in this demographic found only five existing studies, out of which only one assessed any aspects of EF (Tyagi et al., 2014). The lone study in this review, conducted by Daliento et al. (2005), evaluated psychological and cognitive outcomes in an adult population (mean age = 32) who had been treated for tetralogy of Fallot, a moderate form of CHD. They administered a comprehensive neuropsychological battery that included several measures that are known to assess EF, including the Tower of London, Trail Making A and B, and a verbal fluency task. Patients performed significantly worse than controls on all of these tests, particularly on the Tower of London, a task which draws heavily on planning abilities.

In the time since the Tyagi review was published, a small number of new studies of EF in young adults with CHD have been published. Notable amongst these new additions to the literature include studies by King et al. (2016) and Klouda et al. (2017). King et al. studied CHD patients and controls (mean age = 18) using an n-back paradigm during a functional MRI session in conjunction with out-of-scanner administration of the Auditory Consonant Trigrams (ACT; a standardized and normative measure of memory and attention) assessment of working memory

and informant report on the Behavioral Rating Inventory of Executive Function (BRIEF). They found no significant differences between CHD patients and healthy controls on n-back performance; however, they did detect significant differences on the ACT and informant-report BRIEF, suggesting deficits in working memory and general behavioral aspects of EF. Klouda and colleagues recruited adults with moderate and severe CHD (mean age = 30) and assessed a variety of neurocognitive constructs using the computerized CNS Vital Signs battery, which includes seven widely used neurocognitive tests adapted for computer administration. Measures that tap EF included an attention-shifting task as well as measures of vigilance and verbal inhibition. These patients' data were compared to normative data acquired from 1069 participants during the development of the assessment. The participants also completed the BRIEF (self-report version). The authors found that there were no differences between those with moderate CHD and controls, but that individuals with severe CHD diagnoses exhibited an array of cognitive deficits, including worse performance on EF measures from the CNS Vital Signs battery and the BRIEF. They also found that the number of surgeries a participant had undergone was strongly related to EF performance.

Given the rapidly growing population of adult survivors, it is critical to better understand the causes and correlates of EF impairment so that we can improve screening and intervention procedures in the future. EF deficits have wide implications for academic and occupational success as well as general quality of life and health-related outcomes such as adherence to medication and attendance of follow-up appointments with physicians. Understanding which CHD patients are most at risk for suboptimal cognitive functioning is an important step towards ensuring best outcomes for these patients.

## 1.2 Mechanisms of Abnormal Neurodevelopment in CHD

Alongside cognitive impairment, patients with CHD are at high risk for abnormal brain development. One potential explanation for this is hypoxia, or an inadequate oxygen supply, which occurs as a result of structural heart abnormalities leading to suboptimal blood flow to the developing brain *in utero* (Mahle et al., 2000). A number of animal studies have demonstrated the detrimental effects of a hypoxic environment on neurological development. One study used a mouse model to study the impact of sublethal hypoxia on brain volumes and behavior (Lan et al., 2011). Notably, the authors found a sex difference, such that male mice who were exposed to hypoxia exhibited significantly smaller regional brain volumes as compared to control mice, while females did not show any significant differences. The abnormal volumes were found in total cortical volume, the cerebellum, and the hippocampus, however total cortical volume completely caught up to that of controls by 20 weeks of age. The cerebellum and hippocampal volumes remained significantly reduced, suggesting these regions might be particularly vulnerable. In another animal model study, researchers demonstrated a significant reduction in the number of hippocampal and cerebellar neurons in guinea pigs that were exposed to intrauterine growth-restriction via a unilateral ligation of the uterine artery (Mallard, Loeliger, Copolov, & Rees, 2000). They also noted a relative preservation of brain weight compared to body weight, a so-called “brain sparing” effect, which will be discussed in more detail shortly.

A variety of studies have demonstrated a risk for abnormal blood flow and hypoxia in humans with CHD, a risk factor that could lead to a developmental environment similar to those seen in the animal studies above and lead to abnormal brain development. Heymann and Rudolph (1972) were among the first to study intrauterine blood flow dynamics in CHD, and their findings of abnormal fetal circulation have been supported by more recent work. Licht et al.

(2004) studied a group of term infants with CHD by assessing their preoperative cerebral blood flow with pulsed arterial spin-label perfusion MRI. The researchers found that overall cerebral blood flow was low compared to controls, with drastic reductions in some infants. Despite this finding of reduced cerebral perfusion, other researchers have identified in CHD patients what is known as a “brain sparing” effect (Donofrio & Massaro, 2010; Kaltman, Di, Tian, & Rychik, 2005). This phenomenon has also been observed in other intrauterine growth-restricted populations and involves the redistribution of fetal blood flow by reducing cerebrovascular resistance and therefore increasing cerebral perfusion. The discovery of this autoregulatory brain sparing effect in CHD is not necessarily at odds with the findings by Licht et al. outlined above, as several investigators have proposed that this process does not fully compensate for the reduced blood flow and still results in suboptimal cerebrovascular perfusion (Clouchoux et al., 2013; Kaltman et al., 2005).

Another potential source of brain injury for patients with CHD is the surgery that they undergo to repair their heart defects. Some lifesaving surgeries, especially more complex procedures, require the use of cardiopulmonary bypass. This procedure can result in further brain injury due to various types of emboli and inflammation, both of which are the result of the prolonged interface between the circulating blood and the artificial surfaces of the bypass machine (du Plessis, 1999; Wray, 2001). Wypij et al. (2003) conducted a study looking at neurodevelopmental outcomes in 8-year-olds who had undergone surgery for CHD as infants with either deep hypothermic circulatory arrest (DHCA) or low-flow bypass techniques. The authors found that there was a significant effect of being treated using DHCA after the duration of bypass had exceeded 41 minutes. This was a nonlinear relationship, with the influence of DHCA on outcomes worsening as the duration of the procedure became longer. A limitation of

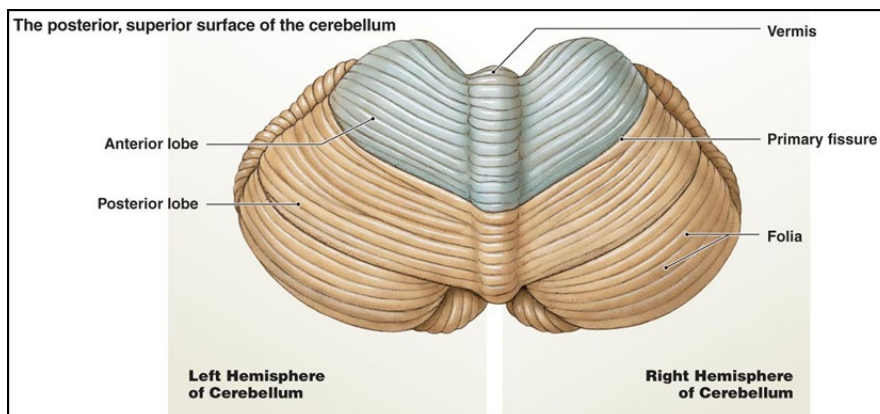
this study is that the authors did not take into account potential pre-surgical lesions that could have an impact on development; however, they did use a homogenous sample with respect to diagnosis, which increases the likelihood that baseline conditions were similar. A study by Mahle et al. (2002) served to address this limitation. MRI was conducted on 24 neonates before and after surgery to repair their CHD and the resulting images were used to quantify neurological injury. Prior to surgery, 16% of the patients presented with periventricular leukomalacia (PVL) and 8% showed infarct. Postoperatively, 48% of the neonates showed new PVL, 19% had new infarct, and 33% had a new parenchymal hemorrhage. In total 67% of the patients demonstrated either worsening of preexisting lesions or new lesions following surgery. This study corroborates claims that surgical treatment for CHD can itself cause neurological insult, above and beyond what already exists in these patients as a result of abnormal developmental processes.

Despite these risk factors associated with surgical intervention, researchers have found that many of the treatment-related brain injuries in the CHD population are associated with modifiable clinical risk factors. For example, the type of surgery, cooling duration, total support time, days in the cardiac ICU, and provider error have all been associated with cognitive outcomes (Dimitropoulos et al., 2013; Rivkin et al., 2013). Continuing to identify risk factors associated with medical treatment will further contribute to our understanding of best practices to minimize potential neurological injury in this already vulnerable population.

### **1.3 The Cerebellum as a Vulnerable Structure**

One area of the brain that is particularly vulnerable to hypoxic injury is the cerebellum (CB), which has been repeatedly documented as reduced in volume in the CHD population (Owen et al., 2014; von Rhein et al., 2015; Zeng et al., 2015). Multiple animal studies have shown anatomical differences in the CB of oxygen-deprived subjects on a cellular level. Mallard,

Rees, Stringer, Cock, and Harding (1998) found reduced length of neuronal processes within the molecular layer in fetal sheep that experienced hypoxia. Another study of fetal sheep found a 14% reduction in the length of granule cell dendrites as well as a 20% reduction in the area of the Purkinje cell dendritic field (Rees & Harding, 1988). These findings were supported more recently by a study, mentioned here previously, of guinea pigs exposed to sublethal hypoxic conditions, in which the authors found a reduction in the number of Purkinje cells, reduced length of neuronal processes in the molecular layer, and reduced volume of multiple fiber layers (suggesting a reduction in axonal and dendritic growth) (Mallard et al., 2000). Finally, Lan et al. (2011) found that overall CB volume reductions persisted in their hypoxia-exposed mouse sample even while cortical volume recovered to the point of being indistinguishable from controls. These studies provide strong evidence that CB development is vulnerable to hypoxic conditions, most likely more so than the cortex.



*Figure 1.1 CB Anatomy*

In typically developing human fetuses, the CB undergoes rapid development between 24 and 40 weeks gestation. In fact, CB volume increases five-fold during this time, a rate that is virtually nonexistent in other parts of the human brain (Volpe, 2009). At the end of normal development, the CB contains over half of the mature neurons in an adult brain (Butts, Green, & Wingate, 2014). Consequently, it has been proposed that the CB is particularly vulnerable to

hypoxic injury during development due to the high metabolic demands of such rapid growth (Limperopoulos, Soul, Gauvreau, et al., 2005; Owen et al., 2014). Abnormalities in CB structure have been noted frequently in the CHD population as well as the premature infant population, which is often cited in the CHD literature due to similar risk for hypoxia. One study of fetuses with CHD used 3D ultrasound techniques to measure brain volumes *in utero* (Zeng et al., 2015). The authors found that the fetuses with CHD had significantly smaller total CB volume than the healthy control subjects. Similarly, Ortinau et al. (2012) conducted a study with 67 infants with CHD, during which they assessed the size of the CB in these infants and controls. They concluded that infants with CHD had smaller CB measurements than controls. Owen et al. (2014) assessed 20 infants for CB volume and neurobehavioral status (using the Einstein Neonatal Neurobehavioral Assessment Scale; ENNAS) and found that reduced CB volume was significantly associated with abnormal behavioral state regulation. The authors propose that this is supportive of the evolving view of the CB's role in higher-order cognition and behavioral regulation abilities.

Studies of premature infants lend further support to findings of abnormal CB development in populations who are vulnerable to hypoxia. Limperopoulos, Soul, Haidar, et al. (2005) conducted term MRIs on 51 infants who were born prematurely. Mean CB volumes in these infants were significantly smaller than those of the 20 healthy infants who were used as controls. In a study by Allin et al. (2001), 76 children (mean age: 14.6 years old) born before 33 weeks gestation were assessed as part of a longitudinal outcomes study of premature births. The authors found that they had significantly smaller CB volume as compared to controls. This suggests that abnormalities in CB structure can persist long-term into adolescence. Furthermore, these differences persisted even when controlling for whole brain volume, sex, and

socioeconomic status. This robust finding strongly supports the proposition that CB structure is abnormal and particularly sensitive to developmental disruption in human populations that are susceptible to hypoxia, like CHD. As such, the CHD population is an ideal one in which to study the impact of abnormally developed CB.

#### **1.4 The Cerebellum and Cognition**

The cortico-centric view of cognition is the dominant framework for conceptualizing higher-order processes in the field of neuropsychology. However, many researchers have begun to argue that focusing exclusively on cortical bases of higher-order cognition neglects to recognize the important roles of more evolutionarily primitive subcortical structures like the CB, hippocampus, and basal ganglia. Among the first to advocate for the consideration of a role for the CB beyond motor coordination was Jeremy Schmahmann, whose 1991 paper on CB contributions to “higher function” is among the most often cited in the CB cognition literature (Schmahmann, 1991). In the paper, Schmahmann cites clinical observations of patients with localized CB lesions and accompanying cognitive deficits as well as referencing cerebellocortical connections putatively involved in communication between the CB and areas facilitating higher cognition. Schmahmann and Sherman (1998) followed up this initial paper by documenting what has become known as the *cerebellar cognitive affective syndrome*, a set of symptoms experienced by patients with CB lesions that are characterized by clinically significant behavioral changes, most prominently executive function deficits, and difficulty with spatial cognition, memory problems, and change in personality due to affective changes (Table 1.2). In a 2010 paper reviewing the role of the CB in expertise and giftedness, Koziol and colleagues continued to advance this new understanding of the CB by arguing that the cortico-centric approach is limited in its ability to fully understand the processes underlying adaptation (Koziol,



Budding, & Chidekel, 2010). They argue that, from an evolutionary perspective, cognition is an extension of the motor control system in that we think in order to deviate from routine, automatic behaviors that no longer satisfy the demands of a changing environment. Therefore, higher-order cognition evolved hand-in-hand with - and to improve the adaptability of - the motor control system, allowing for the most basic means of survival through successful interaction with the environment.

*Table 1.1 Deficits that Characterize the Cerebellar Cognitive Affective Syndrome*

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1. Executive function

Deficient planning, motor or ideational set-shifting, abstract reasoning, working memory. Decreased verbal fluency, sometimes to the point of telegraphic speech or mutism. Perseverative ideation in thought and/or action.

2. Spatial cognition

Visuospatial disintegration with impaired attempts to draw or copy a diagram. Disorganized conceptualization of figures. Impaired visual–spatial memory. Simultanagnosia in some.

3. Linguistic difficulties

Anomia, agrammatic speech, and abnormal syntactic structure, with abnormal prosody.

4. Personality change

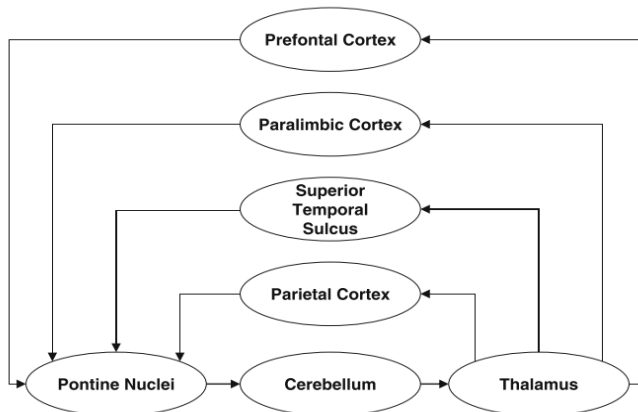
Aberrant modulation of behavior and personality with posterior lobe lesions that involve midline structures. Manifests as flattening or blunting of affect alternating or coexistent with disinhibited behaviors such as over-familiarity, flamboyant and impulsive actions, and humorous but inappropriate and flippant comments. Regressive, childlike behaviors and obsessive-compulsive traits can be observed

---

Koziol et al. (2014)

Much speculation has been made about the mechanisms by which the CB is involved in higher-order cognition and executive function. Some research has proposed that the CB facilitates “cognitive efficiency,” or the automation of cognitive processes. This can be estimated by proxy through measurements of processing speed, although it is unlikely that processing speed is all the CB contributes to cognitive function, cognitive efficiency requires an element of accuracy and task-specific skill (Ailion et al., 2016; Koziol et al., 2014). It is likely that the CB accomplishes this through the formation of internal models of movement and thought, in which the CB learns through repetition and stores the most efficient schematic for carrying out a given

movement or cognitive process (Koziol et al., 2014). This schematic can then be called upon by the cerebral hemispheres and retrieved from the CB so that the process can be carried out in the most efficient manner. In this way, the CB serves to refine cognitive processes in a similar way to how it is believed to make repeated and rehearsed movements automatic. As the CB adjusts and refines its internal models of higher-order processes, it can begin to perform these processes based on prediction and anticipation instead of direct cortical feedback. The similarities between how the CB interacts with motor function and higher-order cognitive processes can be attributed to the Dysmetria of Thought theory proposed by Schmahmann. This theory posits that the CB is a specialized structure involved in behavior modulation, “maintaining function automatically around a homeostatic baseline and smoothing out performance in all domains” (Schmahmann, 2004). It accomplishes this through the Universal Cerebellar Transform (UCT), a computational process which the CB is uniquely suited to perform based on its cytoarchitecture. Therefore, the CB’s role in refining behavior could be generally important for all brain processes.



*Figure 1.2 CB Circuitry (Koziol, Budding, & Chidekel, 2010)*

Neuroanatomically, the CB shares multiple, bidirectional connections with prefrontal regions, including the cortico-ponto-cerebellar and cerebello-thalamo-cortical loops (Figure 1.2). These circuits constitute feedforward and feedback limbs of the cerebrocerebellar system,

respectively. In the feedforward limb, outgoing signals from the cortex relay through the pontine nuclei before continuing on the pontocerebellar pathway to the CB. The feedback limb takes signals arising from the cerebellar corticonuclear projection and sends them to the thalamus by way of the red nucleus. From the thalamus, the signal is returned to the association cortices (Schmahmann, 1996). Previous findings specifically implicate the posterior lobe of the CB in cognitive processes, with anterior areas contributing to motor function (Stoodley & Schmahmann, 2010). Despite this apparent functional topography, the cellular structure of the CB is virtually uniform, a finding that serves to support the UCT hypothesis. This is because if the CB were contributing different types of processes to cognition and motor function independently, one would expect the cytoarchitecture of the anterior and posterior lobes to differ.

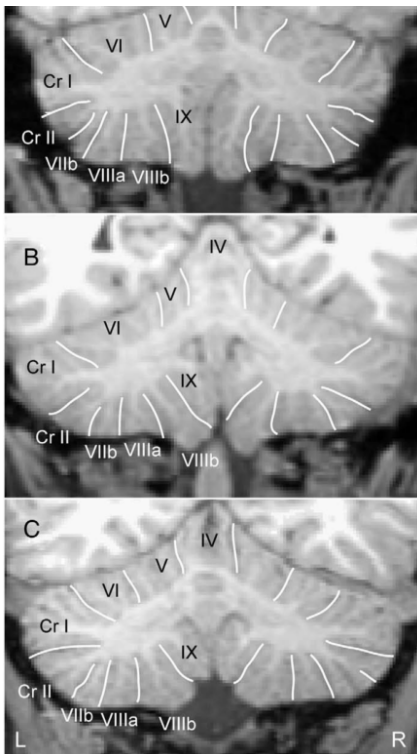
In addition to these theoretical and anatomical rationales for cerebellar involvement in higher-order cognition, there is a growing body of literature that has found associations between alterations in CB structure (e.g., differences in volume), connectivity, and EF performance in clinical samples (Allin et al., 2001; Bolduc et al., 2012; Koziol, Budding, & Chidekel, 2012; Limperopoulos et al., 2007; Stoodley & Schmahmann, 2010). In particular, Allin and colleagues (2001) found a relationship between CB volume and cognitive outcomes in preterm infants. These infants had significantly smaller cerebella than their term-born peers and CB volume was significantly associated with scores on EF and abstract reasoning-related subtests on the WISC-R (Similarities, Block Design, Object Assembly) as well as Digit Span. A study of children with ADHD, a disorder characterized by a variety of EF deficits, demonstrated that these children have significantly smaller CB volumes, as compared to healthy controls (Berquin et al., 1998). This difference was specifically located in the inferior posterior lobule, which is consistent with Stoodley and Schmahmann's assertion that higher order processes are mainly subserved by

posterior portions of the CB. Furthermore, a study conducted by Schall and colleagues utilized both fMRI and PET scans, during which participants completed the Tower of London task, a classic neuropsychological task used to elicit the use of EF. The two sets of imaging data provided convergent evidence of cerebellar involvement during the task, along with a task-difficulty-dependent increase in signal on both of these imaging modalities (Schall et al., 2003). Finally, our research group has previously found an association between reduced white matter integrity in the right middle cerebellar peduncle and poorer performance on an auditory attention task (Brewster, King, Burns, Drossner, & Mahle, 2015). This suggests that deficient white matter integrity in this tract that provides cortical input to the CB is related to poorer performance on tasks that draw heavily on EF. Few other studies have examined the relationship between the CB and EF abilities, and no volumetric studies exist in the CHD population, therefore this study may help to extend the literature on EF outcomes in AYAs with CHD.

## **1.5 Neuroimaging of the Cerebellum**

The CB presents unique challenges to neuroimaging researchers and methodologies for several reasons. First and foremost, the CB topography is extremely functionally diverse on a relatively small scale. This is because the CB receives inputs through the cortico-ponto-cerebellar path from almost every area of the cortex. These afferent pathways remain relatively segregated as they continue to specific regions of the CB. Because of this high-density functional heterogeneity, accurate localization and spatial discrimination are essential for neuroimaging analyses. In addition to the heterogeneity of functionally specialized regions of the CB, there is also remarkable heterogeneity in the structure of the human CB between individuals. Despite the fact that Schmahmann developed the first atlas of human CB anatomy in 1996, his atlas is susceptible to human error in misidentification of structures and is, therefore, most useful in

posthoc labeling of images as opposed to group-level analyses (Schmahmann, 1996). In fact, the high spatial variability of CB structures in one study resulted in differences in primary fissure alignment of up to 1.5 centimeters between individuals once registered to MNI space (Figure 1.3) (Diedrichsen, 2006). In the neocortex, this problem was originally solved by developing probabilistic atlases based on differential cytoarchitecture. However, the CB consists of relatively homogenous cytoarchitecture, making it difficult to differentiate structure on this basis.



*Figure 1.3 Parcellation of three individual cerebella (Diedrichsen et al., 2009)*

Diedrichsen and colleagues set out to create a probabilistic atlas of the CB modeled after existing neocortical atlases, but given this homogeneous cytoarchitecture, it was implausible to base it on histological differences (Diedrichsen, Balsters, Flavell, Cussans, & Ramnani, 2009). Therefore, the developers relied on the macro-anatomical subdivisions of the CB into 10 lobules, which remains a relatively consistent characteristic of mammalian CBs across individuals. Based on these lobular anatomical differences, they created a probabilistic CB atlas by averaging 20

neurologically normal adult participants' MRI images, which yielded statistical probabilities that each voxel in MNI space would occupy a given structure of the CB. The final atlas, the Spatially Unbiased Infratentorial Template (SUIT), consists of 28 probabilistic maps and a maximum-probability map, which indicates the lobule that has the highest probability of occupying a given voxel and can be used to delineate regions of interest (ROIs). After testing SUIT against several other whole brain normalization methods in other popular software packages, it was determined that SUIT's cerebellum-only probabilistic template was the most valid method for correctly labeling cerebellar anatomy. SUIT has previously been used by our research team with other complex clinical populations, such as survivors of childhood brain tumors (Ailion et al., 2016).

## 1.6 Specific Aims

To date, no studies have evaluated the relationship between CB volume and EF in the CHD population. As such, this study utilized structural MRI analysis with the SUIT Toolbox to analyze total and lobular CB volumes in a sample of AYAs with CHD and healthy controls. We assessed group differences in brain volume and performance on neuropsychological measures of EF and processing speed. Next, we computed correlations between cerebellar volume and EF performance. Finally, we conducted a hierarchical regression to see if the CB contributes to EF above and beyond processing speed alone, which would suggest that it plays a role in facilitating efficient EF in a more nuanced way than by just speeding up processing.

### 1.6.1 *Specific Aim 1*

Evaluate CB structure (using MRI), executive function, processing speed, and motor function in the CHD population compared to healthy controls.

**Hypothesis 1:** AYAs with CHD have significantly reduced total and lobular (anterior and posterior) cerebellar volumes compared to healthy controls.

**Hypothesis 2:** The CHD population perform significantly more poorly on measures of executive function, processing speed, and motor function than their healthy peers.

### 1.6.2 *Specific Aim 2*

Determine which substructures/lobules of the cerebellum are most involved in executive function (Table 1.2).

**Hypothesis 1:** Posterior cerebellar volumes will be correlated with EF as measured by the D-KEFS, BRIEF, and Matrix Reasoning significantly more highly than with motor function as measured by Grooved Pegboard.

**Hypothesis 2:** Anterior cerebellar volumes will be correlated with motor function significantly more highly than with EF.

*Table 1.2 Double Dissociation Effect Predicted in Aim 2*

	Executive Function				Motor Function
	Trail Making Test	Verbal Fluency	Color-Word Interference	Matrix Reasoning	Grooved Pegboard
Posterior Volume	*	*	*	*	-
Anterior Volume	-	-	-	-	*

\*Denotes where we expect significantly higher correlations by lobule

### 1.6.3 *Specific Aim 3*

Investigate whether posterior CB volume contributes to EF above and beyond processing speed alone.

**Hypothesis 1:** Posterior CB volume will predict a significant amount of variance in EF above and beyond processing speed alone.

## 2 METHODS

### 2.1 Procedures

#### 2.1.1 *Participant Screening and Recruitment*

Potential adolescent and young adult (AYA) participants were identified from the pediatric cardiology database at Children's Healthcare of Atlanta and Emory University. CHD diagnoses were limited to biventricular anatomy, including D-transposition of the great arteries and total anomalous pulmonary venous connection, as well as single ventricle anatomy, including a double inlet left ventricle, hypoplastic left heart syndrome, tricuspid atresia, and pulmonary atresia with a hypoplastic right ventricle. Participants with diagnoses listed above were eligible to be included in the study if they were between the ages of 16 and 22 and were able to read English and complete questionnaires. The heterogeneity of diagnoses in our sample is an advantage, as it captures a large range of severity and outcomes. Participants were excluded due to severe mental or physical disability, prematurity (less than 34 weeks gestational age), history of cerebral vascular events, history of brain tumor or TBI, visual or hearing impairment, ferromagnetic implants or orthodontic devices, or residence more than 60 miles from downtown Atlanta.

Recruitment consisted of a telephone interview with eligible AYAs (or family members authorized to give consent for individuals under the age of 18), which was outlined by an IRB approved script and conducted by physicians from Children's Healthcare of Atlanta and Emory University. The script outlined the details of participation and participants were screened for MRI eligibility. 45 participants met the requirements for CHD anatomy and inclusion criteria and were contacted by phone. 26 participants agreed to enroll in the study (58%), while 19 did not participate due to lack of interest, scheduling conflicts, or not showing up for their appointment.



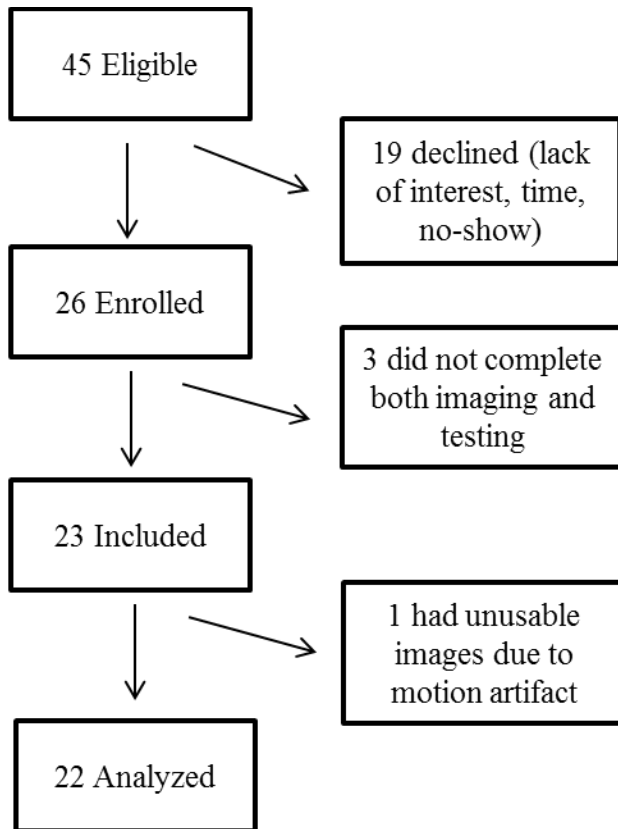
Twenty-three participants completed both neuroimaging and neuropsychological assessment. Eight controls were recruited for this study, in addition to another 15 being selected from a larger study of individuals from the Atlanta community. Controls were matched as closely as possible by age, sex, and race to the CHD participants. Subjects provided written consent prior to completing the study protocol. Upon inspection, one CHD participant and one control participant had unusable imaging data due to motion artifact. Therefore, the final sample was comprised of 22 participants in each group. 48% of our CHD group carried single ventricle diagnoses (diagnoses in which only one functioning ventricle), which are typically more severe, while the remaining 52% had been diagnosed with the typically mild-moderate biventricular diagnoses (in which both ventricles function properly). See Table 2.1 for a summary of participant demographic information. Group differences in demographic data were analyzed using either independent samples *t*-tests or chi-square tests and are discussed in the Results section.

*Table 2.1 Participant Characteristics*

	<b>CHD</b>	<b>Controls</b>	<b><i>p</i></b>	<b><i>d</i></b>
N (# of participants)	22	22	-	-
Sex (% Male)	69.6	69.6	1.000	0.000
Race (% White)	73.9	60.9	0.747	0.097
Age at examination (SD)	18.05 (1.618)	18.53 (1.686)	0.336	0.290
Handedness	86.4% right	72.7% right	0.262	0.343
Mean years education (SD)	11.74 (1.421)	12.70 (1.146)	0.054	0.601
WASI 2-Scale IQ	101.65 (15.66)	111.61 (6.330)	0.013	0.834
Diagnosis groups	48% single ventricle, 52% biventricular	-	-	-

\**p*<.05; \*\**p*<.01

Note: CHD = congenital heart disease; WASI = Wechsler Abbreviated Scale of Intelligence



*Figure 2.1 Participant Exclusion Tree*

### **2.1.2 Imaging Parameters**

Participants were scanned in a 3 Tesla Siemens Trio magnetic resonance imaging (MRI) scanner. Anatomical scans were high-resolution ( $1\text{mm}^3$ ) T1-weighted structural images in the sagittal plane. Specifically, images were acquired with a three-dimensional magnetization-prepared rapid gradient echo sequence using the following parameters: acquisition matrix =  $256 \times 256$ , TR = 2,250 ms, TE = 3.98 ms, inversion time = 850 ms, flip angle =  $9^\circ$ .

### **2.1.3 Image Processing**

Total intracranial volume (ICV) was calculated in SPM8 by summing the total volume of gray and white matter and cerebral spinal fluid. This ICV value was considered as a potential

covariate to account for individual difference in cranial size more generally (Sanfilipo, Benedict, Zivadinov, & Bakshi, 2004). Cerebellar volumes were analyzed using the SUIIT toolbox for SPM (Diedrichsen, 2006). Preprocessing was done according to recommendations documented by the SUIIT developers, beginning with the conversion of original image files to SPM format in MRIcron's DICOM to NIFTI converter, dcm2nii. The remainder of preprocessing functions took place in SUIIT, including isolation, normalization, and segmentation. Finally, SUIIT provided total cerebellar volumes as well as the volumes of individual lobules through the use of a probabilistic atlas, which automatically defined the ROIs. We combined posterior lobules to create a Posterior CB volume total and similarly combined anterior lobules to create an Anterior CB volume variable. This is according to previous findings that implicate the posterior CB in cognitive processes and the anterior CV in motor function (Stoodley & Schmahmann, 2010). Resulting volume data were entered into SPSS for statistical analysis.

#### ***2.1.4 Assessment of Executive Function***

Executive function was assessed with the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001) and the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia, Isquith, Guy, & Kenworthy, 2000). Participants completed the Verbal Fluency, Trail Making, and Color-Word Interference subscales from the D-KEFS, a widely used neuropsychological assessment of executive function. During the Verbal Fluency subscale, participants are told that they are to generate as many words as possible that begin with a given letter in a one minute period. Subsequently, they list as many words as possible that fall into a given category (e.g., *animals*). Finally, the participant is asked to generate words while switching between categories. For the Trail Making subscale, participants trace paths on paper in number and then letter order and then are asked to trace them while switching back and forth between

numbers and letters (i.e., 1, A, 2, B...). The Trail Making test also has the Visual Scanning and Motor Speed subtests which are measures of visual and motor processing speed. The Color-Word Interference subscale is essentially a Stroop test, where participants are asked to identify colors, read words, and then state the color of printed words while inhibiting the dominant response of reading the word aloud. Finally, they are asked to switch between naming the color of the word and reading the word aloud, as prompted by the presence or absence of a box around the word.

We used the BRIEF informant-report version, which asks a person close to the enrolled subject to report on observed day-to-day behaviors that indicate the degree to which that person is able to exhibit effective executive function. An informant (e.g., a roommate, significant other, or parent) completed the BRIEF survey. These inventories take 10-15 minutes to complete and yield a variety of subscales, including a Global Executive Composite, Metacognitive Index, and Behavioral Regulation Index. For the proposed study, we will focus on the Global Executive Composite (GEC) for our analyses.

Finally, we elected to use the Matrix Reasoning subscale from the Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II) (Wechsler, 2011). This tests abstract problem solving and non-verbal reasoning skills, which both depend heavily on EF abilities. The participant is presented with a matrix of figures with one figure missing and is asked to select from a number of choices which figure should go in the blank space. This task depends on recognizing patterns in the matrix in order to choose the correct figure. The reason we elected to use this task as an indicator of EF is because it is not a timed task, like the tasks on the D-KEFS. Measuring EF with timed tasks presents a challenge in that it is also related to an individual's processing speed. We decided to examine Matrix Reasoning in order to obtain a measure of

cognitive flexibility and EF that is not scored partially based on the amount of time to complete the task. Also from the WASI-II, we will be looking at group differences in the Vocabulary subtest as a way to show that these deficits are specific to EF as opposed to a more global “bad brain” phenomenon whereby CHD patients have a general reduction in cognitive function that applies broadly to various domains. The Vocabulary subtest simply consists of asking participants to define the meanings of verbally presented words and therefore tests their knowledge of word meanings. The absence of significant differences on Vocabulary would lend support to the hypothesis that CHD patients are particularly at increased risk for EF deficits.

### ***2.1.5 Assessment of Processing Speed***

Processing speed was assessed with the Symbol Digit Modalities Test (SDMT) (Smith, 1982). While there is both a written and oral form of this test, we will only be using the oral form due to the commonly documented motor deficits in the CHD population potentially interfering with participants’ abilities to draw small symbols accurately and quickly. In the oral version of this test, the participant is shown a series of symbols that are numbered in a key. As they look at each symbol in order, they are asked to say aloud which number corresponds to each symbol as quickly as possible.

### ***2.1.6 Assessment of Motor Function***

Motor function was assessed using the Grooved Pegboard task, a commonly used test of finger manipulation, dexterity, and motor coordination (Lafayette Instrument Company Inc., 2002). The participant is asked to insert a number of grooved pegs into a board with holes in it. The grooves require that the participant rotates the pegs appropriately so that they fit into the holes. This test is scored according to the amount of time the participant takes to insert all of the

pegs into the holes on the board. In an effort to reduce the number of analyses, we will only use scores from performance with the dominant hand.

## **2.2 Analyses**

### **2.2.1 *Confound Analysis***

Confounding variables are those which are related to both the independent variable and the outcome variable and negatively impact the validity of an experiment. These present a problem because it makes it difficult to determine whether the effect that we observe is due to the independent variable itself or differences in the confounding variable in each of our IV groups. For example, if performance on the Category Fluency subtest from the D-KEFS is significantly related to our independent variable (posterior CB volume) and our dependent variable (EF), it is impossible to determine whether the differences in the DV stem from the differences in the IV or whether they are actually due to the differences in the confound which just happens to be related to the IV. It is important to statistically control for confounds in order to adjust for their effect. Alternatively, a covariate is a variable that is related only to the dependent variable. While covariates do not impact the validity of conclusions drawn about the relationship between the independent and dependent variable, it can still be advantageous to control for covariates, especially if they are of particular interest to the researcher and strongly related to the dependent variable. This allows us to increase the specificity of the statistical prediction and create a better model of the dependent variable.

Potential confounds were analyzed in order to more specifically plan the analyses outlined below. Candidates included ICV as well as several non-EF-related subtests from the D-KEFS: Category Fluency, Visual Scanning, Color Naming, and Word Reading. ICV was considered as a covariate due to the potential need to control for differences in CB volume

associated with cranial size more generally (i.e., individuals with higher ICV would be expected to have proportionally larger CB volumes). The non-EF-related subtests from the D-KEFS were analyzed because they measure the non-EF components of the EF-related tasks on the D-KEFS. That is, they measure constructs such as processing speed, which are necessary for completing timed measures of EF, but do not measure EF itself.

In order to determine whether each of these variables were confounds, we analyzed whether they were significantly related to the IVs and DVs for each aim. If we found that one of the above variables was related to both the IV and DV, we determined that this was a confounding variable and noted that it should be controlled for in the final analyses. If a variable was a covariate (it was related to a DV but not IV), we decided to covary for it when conducting our analyses on its related subtest, as there would be the highest shared variance between tasks that come from the same subtest (e.g., Category Fluency and Category Switching both come from the Verbal Fluency subtest of the D-KEFS). We did not analyze IQ as a potential confound, following concerns raised by Dennis et al. (2009) in which the authors conclude that covarying for IQ overcorrects and leads to an inaccurate characterization of neurocognitive functioning.

For Aim 1, there were no confounds, therefore we opted not to covary for any of the existing covariates since this aim uses simple independent samples *t*-tests and there were no significant differences in extraneous variables. For Aim 2, there were also no confounds and therefore, correlations were carried out without inclusion of covariates. Finally, Aim 3 had two confounding variables: Category Fluency and Visual Scanning, both of which are significantly correlated with both Processing Speed and at least one dependent variable. We controlled for these confounds in the respective Aim 3 analyses in order to reduce the effect of the confounding variable on the interpretability of the relationship between the IV and DV.

Table 2.2 Confound Analysis for Aim 1

	Independent Variables	Dependent Variables					
	<i>d</i> (CHD vs. Controls)	Category Switching	LNS	Inhibition	IS	Matrix Reasoning	GP
ICV	.04	.13	.07	.19	.10	.08	.12
Category Fluency	.54	.32*	.22	.43**	.43**	.39**	.22
Visual Scanning	.17	.29	.46**	.12	.17	.31*	.20
Color Naming	.32	.20	.34*	.61**	.30*	.48**	.43**

\* $p < .05$ , \*\* $p < .01$

Note: *d* = Cohen's *d* effect size; ICV = intracranial vault; CHD = congenital heart disease; LNS = Letter-Number Sequencing; IS = Inhibition-Switching

Table 2.3 Confound Analysis for Aim 2

	Independent Variables		Dependent Variables					
	Post. CB Volume	Ant. CB Volume	Category Switching	LNS	Inhibition	IS	Matrix Reasoning	GP
ICV	.22	-.26	.13	.07	.19	.10	.08	.12
Category Fluency	.21	.07	.32*	.22	.43**	.43**	.39**	.22
Visual Scanning	.08	.19	.29	.46**	.12	.17	.31*	.20
Color Naming	.23	.14	.20	.34*	.61**	.30*	.48**	.43**

\* $p < .05$ , \*\* $p < .01$

Note: Post. = posterior; Ant. = anterior; CB = cerebellar; ICV = intracranial vault; LNS = Letter-Number Sequencing; IS = Inhibition-Switching; GP = Grooved Pegboard

Table 2.4 Confound Analysis for Aim 3

	Independent Variables		Dependent Variables				
	Post. CB Volume	Processing Speed	Category Switching	LNS	Inhibition	IS	Matrix Reasoning
ICV	.22	.16	.13	.07	.19	.10	.08
Category Fluency	.21	.32*	.32*	.22	.43**	.43**	.39**
Visual Scanning	.08	.39*	.29	.46**	.12	.17	.31*
Color Naming	.23	.09	.20	.34*	.61**	.30*	.48**

\* $p < .05$ , \*\* $p < .01$

Note: Post. = posterior; CB = cerebellar; ICV = intracranial vault; LNS = Letter-Number Sequencing; IS = Inhibition-Switching



### 2.2.2 *Analyses for Specific Aim 1*

Based on past research findings that CHD increases the risk for smaller CB volume, suggesting abnormal development (Lan et al., 2011; Owen et al., 2014; von Rhein et al., 2015; Zeng et al., 2015), the first hypothesis of Aim 1 is that we will find significant differences in total and lobular cerebellar volumes between CHD patients and healthy controls. However, to date, no studies have evaluated CB volumes in adolescents and young adults over the age of 17. If our hypothesis proves to be true, this suggests that the structural cerebellar abnormalities observed so far in mouse models, infants, and early adolescents may persist into young adulthood. We conducted one-tailed independent samples *t*-test to determine whether any significant differences in volume exist between CHD patients and healthy controls at the  $p=0.05$  level. We elected to use one-tailed tests, as we expect CHD patients will have smaller CB volumes based on previous research findings. We also calculated Cohen's *d* as an indicator of the effect size of these potential differences.

The second hypothesis for Aim 1 is that AYAs with CHD perform significantly more poorly on measures of executive functioning measures, processing speed, and motor function. All analyses of these measures in this proposed study used Z scores calculated on normative data in order to take into account demographic factors such as age and gender. For the D-KEFS, we analyzed group differences for the Verbal Fluency (Total Switching Accuracy score), Trail Making (Letter-Number Sequencing score), and Color-Word Interference subscales (Inhibition and Inhibition-Switching scores). Secondly, we tested group differences on the BRIEF Global Executive Composite (a summary composite score of all BRIEF scales). Group differences in performance on Matrix Reasoning were tested similarly. For our assessment of processing speed with the Symbol Digit Modality Test, we analyzed group differences in the oral form score.

Finally, group differences on Grooved Pegboard dominant hand scores were tested. All of these analyses were carried out with one-tailed independent samples *t*-tests to determine whether any significant differences in scores differ at the  $p=0.05$  level. We used one-tailed tests since we predict that the CHD sample will exhibit poorer outcomes on all of these measures. We also calculated Cohen's *d* as an indication of effect size.

In addition to analyzing overall group differences for our neuropsychological data, we wanted to determine what proportions of our groups were considered normatively impaired, that is 1.5 standard deviations below the normative mean. This stems from a recognition that there tends to be a great deal of variability in neuropsychological outcomes in medical populations that would not necessarily be reflected by overall means and group difference analyses. To do this, we created a dichotomous variable for each of the variables listed above that indicated whether or not each individual's scores fell in the impaired range. We then conducted a chi-square test to determine whether there was a significant difference in the proportion of impairment between the CHD and control groups for each variable.

### ***2.2.3 Analyses for Specific Aim 2***

Our second aim is to demonstrate a functional dissociation between the posterior and anterior CB (Table 1.2). The first hypothesis for Aim 2 proposes that there will be significant positive correlations between EF scores and posterior cerebellar volumes and that these correlations will be significantly greater than those with motor function. We used Pearson's bivariate correlations to test the relationship between CB volume and EF measures as well as motor function. Secondly, we used Fisher's *Z* Transformation to test whether the correlations between the posterior CB and EF are significantly greater than the correlation between the posterior CB and motor function. This test transforms *r* values into *z*-scores in order to test

significant differences between each  $r$  value. We will use the one-tailed  $p$  values for both calculating the significance of our correlations and for Fisher's  $Z$  Transformation, as we have hypothesized specific directions of effects based on theories in the existing literature.

The second hypothesis for Aim 2 states that anterior CB volumes will be more significantly correlated with motor function and that this correlation will be significantly higher than those between the anterior CB and EF scores. This is in line with Stoodley and Schmahmann's assertion that the anterior lobe of the CB is involved with motor control, while the posterior areas are more involved in cognition. In order to test this hypothesis, we used the same methods as outlined above. If our hypotheses are confirmed, this would lend support to the theory that posterior CB areas are more related to higher-order cognitive functions and that anterior areas are less related to these processes.

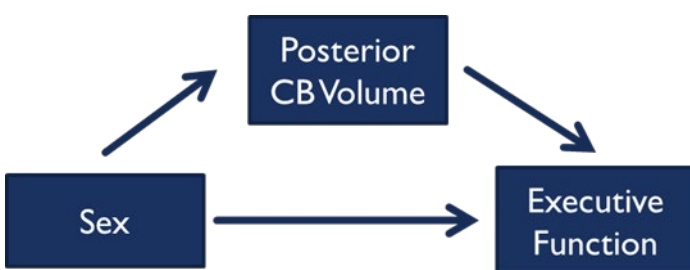
#### ***2.2.4 Analyses for Specific Aim 3***

Our third aim is to investigate whether the posterior CB contributes uniquely to EF above and beyond oral processing speed alone. This hypothesis stems from the theory that the CB aids in cognitive processes by allowing for more efficiency and automaticity. It has been proposed previously that due to this role in cognitive efficiencies, the CB is indirectly related to general speed of processing (Ailion et al., 2016; Koziol et al., 2014). However, cognitive efficiency as a construct is not equivalent with processing speed. In order to demonstrate cognitive efficiency, one needs to demonstrate both processing speed as well as an added element of skill and accuracy. This additional element could be derived from the learned automaticity facilitated by the CB. Therefore we hypothesize that the CB contributes to effective EF in a unique way and predicts EF performance above and beyond processing speed alone.

In order to test this hypothesis, we used hierarchical linear regression. We entered processing speed (Oral SDMT  $z$ -score) in the first step of the regression, followed by the posterior CB volume in the second step for each of the EF outcome variables. For those D-KEFS subtests with relevant covariates discussed previously, we ran these regressions with those covariates entered alongside processing speed in the first step. First, we checked for issues with multicollinearity to ensure unbiased results. According to commonly observed guidelines, assuming the variance inflation factor (VIF) was less than 10, we proceeded to interpret the results of the regression accordingly. We report  $R^2$  and  $\Delta R^2$  values to indicate what percentage of the variance is explained by the predictors as well as  $p$  values to indicate whether or not the addition of the posterior CB volume predictor resulted in a statistically significant increase in predictive power. In the case(s) that this  $p$  value is significant, this would indicate that posterior CB volume is predicting a unique portion of variance in EF above and beyond processing speed and any covariates alone.

### 2.2.5 *Planned Supplemental Analysis 1*

As additional analyses, we tested whether a sex effect exists such that males are more susceptible to poorer EF function and smaller CB volumes than females. This is included as an



*Figure 2.2 Exploratory Analysis 1*

additional analysis, as it is largely

exploratory. Lan et al. (2011) found that in mice exposed to hypoxic conditions, only the males demonstrated observably different brain volumes, while the females were indistinguishable from

controls. Previous work has identified a similar sex effect in the premature infant population, where males suffer from poorer outcomes and a higher incidence of complications (Ingemarsson, 2003; Stevenson, 2000). However, no work has looked specifically at sex effects on brain structure and cognitive outcomes in CHD. To do so, we first examined sex differences in intracranial vault volume (ICV) to determine whether it would be necessary to covary for this variable in our indirect effect analysis. Subsequently, we checked for an indirect effect of sex on EF through (or, mediated by) CB volume (Figure 2.2). We expected that sex differences in CB volumes due to differential vulnerability might account for any differences in EF outcomes for males versus females. This analysis was carried out using the PROCESS macro for SPSS (Hayes, 2013). This method is advantageous in calculating indirect effects, as it utilizes a resampling with replacement bootstrapping method to construct confidence intervals around likely effect sizes. Bootstrapping is significantly more powerful, reduces the number of tests necessary to make inferences about the indirect effect, tests the quantitative representation of the indirect effect itself (i.e.,  $ab$ ) as opposed to testing each path separately, and has been shown in simulation studies to be more valid than other methods of detecting indirect effects (Hayes, 2013; MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). This is preferable over Barron and Kenny's method utilizing the Sobel Test because in small samples the calculation of the product term (i.e.,  $ab$ ) often results in a skewed distribution. PROCESS overcomes this problem by creating a new approximation of the sampling distribution of the  $ab$  product term by repeatedly resampling the dataset (for the current study, we will resample 10,000 times). Additionally, bootstrapping does not require an assumption of normally distributed data. The investigator is aware that this is not mediation in the traditional sense, as these data are not longitudinal; however, a test of indirect effects (or a test to see whether CB volume accounts for

variance in the relationship between sex and EF) is still plausible, given the theoretical grounding of the research question.

### ***2.2.6 Planned Supplemental Analysis 2***

Finally, we investigated potential differences in outcomes by diagnosis severity. As mentioned previously, the severity of cognitive outcomes has been shown to depend heavily on the severity of the heart defect. Therefore, we aimed to determine whether our sample shows significant differences in CB volumes, EF, processing speed, and motor function outcomes amongst our three diagnosis groups: single ventricle diagnoses, biventricular diagnoses, and controls. Generally, the literature has established that patients with single ventricular diagnoses experience the most severe outcomes, therefore we expect these patients in our sample to have the smallest CB volumes and poorest performance on EF, processing speed, and motor function. This analysis was carried out using analysis of variance (ANOVA), for which we reported effect sizes due to our small sample size. We also conducted the Least Square Difference (LSD) post-hoc test to further probe any significant omnibus effects. This post-hoc analysis was chosen because it is less conservative than other options and our sample size is modest.

## 3 RESULTS

### 3.1 Demographics

The only significant group difference noted in our demographic variables was in IQ (previously shown in Table 1.3). We believe this difference is mainly driven by the high performing control group (mean IQ = 111.61). The finding that our groups had comparable years of education helps to lessen our concern about this difference, although we do not have socioeconomic status or parental education data to serve as a proxy indicator of education quality. Notably, our CHD sample's mean IQ is higher than one would expect based on previous research, which helps to close this gap between CHD and controls. Additionally, our IQ assessment was based on the two-subscale WASI, which is comprised of Vocabulary and Matrix Reasoning. As discussed below, there were no group differences on Vocabulary, but Matrix Reasoning was different, as hypothesized. Therefore, we believe this IQ difference to be mainly the result of differences on Matrix Reasoning, which we expected to be significantly poorer in the CHD population, and it therefore reflects mostly an EF impairment, not IQ overall. This line of reasoning is consistent with Dennis et. al (2009), who caution against controlling for IQ in neurodevelopmentally impaired populations for similar reasons.

### 3.2 Aim 1 Results: Group Differences

#### 3.2.1 Volumetric Differences

Individuals with CHD had significantly smaller total CB volumes than healthy controls ( $t=2.56, p=.007$ ). Additionally, posterior CB volumes ( $t=2.12, p=.020$ ) and anterior CB volumes ( $t=1.71, p=.048$ ) were significantly smaller in CHD patients (Cohen's  $d$  from .52-.78).

### 3.2.2 *Neuropsychological Differences*

CHD patients performed significantly more poorly on two measures of EF: the Color-Word Interference Inhibition subscale from the D-KEFS ( $t=2.59, p=.007$ ) and the Matrix Reasoning subscale from the WASI ( $t=2.89, p=.004$ ). The CHD sample was also reported to have poorer EF on the BRIEF General Executive Composite ( $t=-3.15, p=.002$ ). Motor function as measured by the Grooved Pegboard test was significantly poorer for individuals with CHD ( $t=2.49, p=.010$ ). A trend-level difference between groups emerged on our measure of processing speed ( $t=-1.65, p=.053$ ), indicating poorer performance and there was a medium effect size for this comparison.

On average, neither group was normatively impaired on any of our neuropsychological measures. However, our analysis of impairment shows that there were individuals within each group who fell into the impaired range. Table 3.3 shows rates of impairment on each measure for our CHD and control groups as well as the results from our chi-square comparison of proportions between groups. The only significant group difference in the proportion of individuals falling into the impaired range was for Grooved Pegboard, however even in the case of nonsignificant findings there were consistently more CHD participants who were considered impaired. Notably, there was one individual (4.5% of the control group) who was impaired on three of the subtests. We checked our data and were able to verify that these were different individuals for each variable, which reflects natural variability in performance as opposed to one specific control individual with EF impairment.



Table 3.1 Aim 1 Results: Group Differences

Test	Variable	CHD	Control	<i>t</i>	<i>d</i>
CB Volumes	Total CB Volume	-0.36 (0.80)	0.36 (1.06)	2.56**	0.78
	Posterior CB Volume	-0.31 (0.82)	0.31 (1.08)	2.12*	0.64
	Anterior CB Volume	-0.25 (0.96)	0.25 (1.00)	1.71*	0.52
D-KEFS	Category Switching	0.07 (1.16)	0.30 (0.96)	0.71	0.22
	Letter-Number Sequencing	-0.39 (1.28)	0.03 (0.90)	1.27	0.39
	CWI Inhibition	-0.17 (0.90)	0.44 (0.64)	2.59**	0.79
	CWI Inhibition-Switching	-0.17 (0.88)	0.23 (0.93)	1.44	0.44
WASI	Matrix Reasoning	-0.21 (1.13)	0.55 (0.49)	2.89**	0.94
	Vocabulary	0.45 (1.03)	0.80 (0.53)	1.42	0.45
BRIEF	General Executive Composite	0.72 (1.34)	0.84 (0.19)	-3.15**	1.01
SDMT	Oral Subscale	0.89 (2.04)	0.01 (1.42)	-1.65	0.51
Grooved Pegboard	Dominant Hand	-1.06 (1.66)	0.70 (0.15)	2.49**	0.81

\* $p < .05$ , \*\* $p < .01$

Note: CHD = Congenital heart disease; CB = cerebellar; D-KEFS = Delis-Kaplan Executive Function System; WASI = Wechsler Abbreviated Scale of Intelligence; BRIEF = Behavior Rating Inventory of Executive Function; SDMT = Symbol Digit Modalities Test

*Table 3.2 Impairment Rates by Group and Chi-Square Comparison*

Test	Variable	CHD (%)	Control (%)	X <sup>2</sup>	p
D-KEFS	Category Switching	13.6	4.5	1.10	0.294
	Letter-Number Sequencing	18.2	4.5	2.03	0.154
	CWI Inhibition	4.5	0.0	1.02	0.312
	CWI Inhibition-Switching	9.1	4.5	0.36	0.550
WASI	Matrix Reasoning	13.6	0.0	3.22	0.073
	Vocabulary	0.0	0.0	-	-
BRIEF	General Executive Composite	0.0	0.0	-	-
SDMT	Oral Subscale	4.5	9.1	0.31	0.578
Grooved Pegboard	Dominant Hand	27.3	0.0	6.95	0.008**

\* $p < .05$ , \*\* $p < .01$

Note: CHD = Congenital heart disease; D-KEFS = Delis-Kaplan Executive Function System; WASI = Wechsler Abbreviated Scale of Intelligence; BRIEF = Behavior Rating Inventory of Executive Function; SDMT = Symbol Digit Modalities Test

### 3.3 Aim 2 Results: Correlations

#### 3.3.1 *Brain-Behavior Correlations*

Pearson's correlations were carried out to test the relationships between CB volumes and our EF and motor variables in an effort to demonstrate a functional dissociation between the anterior and posterior lobes. Significance values for correlation coefficients indicate the results of a one-tailed significance test, given that our hypotheses specified directions for these relationships.

First, there were significant correlations between the following D-KEFS subscales and only the posterior CB: Letter-Number Sequencing ( $r=.286, p=.030$ ), Color-Word Interference Inhibition ( $r=.483, p<.001$ ), and Color-Word Interferences Inhibition-Switching ( $r=.292, p=.027$ ). Similarly, the BRIEF General Executive Composite was significantly correlated only with the posterior CB ( $r=-.253, p=.049$ ). The WASI Matrix Reasoning subscale was correlated with both the posterior ( $r=.557, p<.001$ ) and anterior ( $r=.307, p=.021$ ) CB. The only measure of EF to have no significant relationships with CB volumes was the D-KEFS Category Switching subscale. Finally, our measure of motor function, the Grooved Pegboard, was correlated only with the posterior CB ( $r=.348, p=.010$ ). See Table 3.3 for all correlation coefficients.

#### 3.3.2 *Fisher's Z Transformation*

Fisher's Z Transformation was used to assess whether the strength of correlations significantly differed between the posterior and anterior CB for each measure. There were two significant results, indicating that both the D-KEFS Color-Word Inhibition ( $p=.018$ ) and Color-Word Inhibition-Switching ( $p=.048$ ) subscales were significantly more strongly associated with the posterior CB than with the anterior CB. See Table 3.3 for complete results.

Table 3.3 Aim 2 Results: Correlations and Fisher's Z Transformation

	Pearson's <i>r</i>		Fisher's Z Test
	Posterior CB Vol.	Anterior CB Vol.	<i>p</i>
D-KEFS Category Switching	-0.034	0.089	0.2877
D-KEFS Letter-Number Sequencing	0.286*	0.15	0.2578
D-KEFS CWI Inhibition	.483**	0.063	0.0179*
D-KEFS CWI Inhibition-Switching	0.292*	-0.067	0.0475*
WASI-Matrix Reasoning	.557**	.307*	0.0793
BRIEF General Executive Composite	-0.253*	-0.105	0.2451
Grooved Pegboard	.348*	0.184	0.2119

\* $p < .05$ ; \*\* $p < .01$

Note: D-KEFS = Delis-Kaplan Executive Function System; CWI = Color-Word Interference; WASI = Wechsler Abbreviated Scale of Intelligence; CB = cerebellar; Vol. = volume

### 3.4 Aim 3 Results: Regression

Our regression analyses examined whether posterior CB volumes predicted EF performance above and beyond processing speed alone. There were no issues with multicollinearity, so all results were interpreted in a routine manner. Two significant results emerged, whereby posterior CB volume accounted for a significant amount of variance above and beyond processing speed in predicting the D-KEFS Color-Word Interference Inhibition and the WASI Matrix Reasoning subscale. There were no other significant regression analyses. See Table 3.4 for the results of our significant regression findings.

Table 3.4 Aim 3 Results: Regression

Variable	D-KEFS Color-Word Interference: Inhibition				WASI Matrix Reasoning			
	Model 1		Model 2		Model 1		Model 2	
	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>	<i>B</i>	<i>SE</i>
Processing Speed	.027	.073	-.040	.067	.157	.079	.084	.072
Posterior CB Vol.	-	-	.427	.120	-	-	.474	.128
$R^2$	.003		.243		.089		.322	
$F$	.132		6.41**		4.00		9.48**	

\* $p < .05$ ; \*\* $p < .01$

Note: D-KEFS = Delis-Kaplan Executive Function System; CB = cerebellar; Vol. = volume; WASI = Wechsler Abbreviated Scale of Intelligence

### 3.5 Planned Supplemental Analysis 1

Our first analysis assessed whether there was an indirect effect such that posterior CB volumes accounted for a significant amount of variance in the relationship between sex and EF. First, we checked for a sex difference in a potential covariate, ICV. There was a significant difference such that males had significantly larger ICV volumes, therefore we opted to covary for ICV in the indirect effect analyses ( $t=2.30, p=.037$ ). However, upon further inspection, we found that there was a significant difference in the distribution of severity among males and females, such that the female group had significantly more severe diagnoses according to a chi-square test. Therefore, we decided not to proceed with the indirect effect analyses, as there is a confounding factor.

*Table 3.5 Chi-Square Results for Differences in Severity by Sex*

	Male	Female	$\chi^2$	$p$
Control	15	7		
Biventricular	11	1	6.71	0.04
Single Ventricle	4	6		

*Note:* Single ventricle diagnoses are our most severe group, while biventricular are typically mild-moderate in severity.

### 3.6 Planned Supplemental Analysis 2

Our second analysis aimed to determine whether there were significant differences in CB volumes, EF performance, processing speed, and motor function when our CHD sample was further broken down into groups based on disease severity. There were three significant omnibus effects: D-KEFS Color-Word Interference Inhibition ( $F(2, 41), p=.026$ ), WASI Matrix Reasoning ( $F(2, 41), p=.012$ ), and the BRIEF General Executive Composite ( $F(2, 41), p=.003$ ). Additionally, there were medium-to-large effect sizes for differences in anterior and posterior CB volumes and Grooved Pegboard. See Table 3.6 for effect sizes.

For the statistically significant omnibus effects, we performed a Least Square Difference (LSD) post hoc test to probe for specific group differences. For all three significant omnibus effects, there were significant differences only between controls and our single ventricle (most severe) group. Specifically, for D-KEFS Color-Word Interference Inhibition  $p=.009$ , for WASI Matrix Reasoning  $p=.004$ , and for the BRIEF General Executive Composite  $p=.001$ . A similar pattern was observed for the anterior and posterior CB volumes, whose omnibus effects were trending significant and showed medium-to-large effect sizes. However, specific differences between controls and single ventricle CHD patients for anterior CB volumes had a  $p$  value of .030, while for posterior CB volumes  $p=.01$ .

*Table 3.6 Exploratory Analysis 2 Results: ANOVA Omnibus Effects*

	Controls (N=22)	Group A (N=12)	Group B (N=10)	F	$\eta^2$	<i>p</i>
Posterior CB Vol.	0.31 (1.08)	-0.06 (0.53)	-0.61 (1.03)	3.18	0.13	0.052
Anterior CB Vol.	0.25 (1.00)	-0.53 (0.86)	0.08 (1.00)	2.59	0.11	0.087
D-KEFS Category Switching	0.30 (0.96)	-0.22 (1.05)	0.43 (1.24)	1.33	0.07	0.277
D-KEFS Letter-Number Sequencing	0.03 (0.90)	-0.25 (1.37)	-0.57 (1.20)	1.02	0.05	0.369
D-KEFS CWI Inhibition	0.44 (0.64)	0.00 (0.57)	-0.37 (1.18)	3.97	0.16	0.026*
D-KEFS CWI Inhibition-Switching	0.23 (0.93)	-0.14 (0.48)	-0.20 (1.24)	1.03	0.05	0.366
WASI Matrix Reasoning	0.55 (0.49)	-0.01 (0.99)	-0.45 (1.28)	4.94	0.19	0.012*
BRIEF GEC	-0.38 (0.84)	0.33 (1.26)	1.20 (1.33)	7.00	0.26	0.003**
Oral Systems Digit Modalities	0.01 (1.42)	1.17 (2.04)	0.58 (2.11)	1.64	0.08	0.206
Grooved Pegboard	-0.10 (0.70)	-1.15 (1.83)	-0.96 (1.51)	3.10	0.13	0.056

Note: CB = cerebellar; Vol. = volume, D-KEFS = Delis-Kaplan Executive Function System; CWI = Color-Word Interference; WASI = Wechsler Abbreviated Scale of Intelligence; BRIEF GEC = Behavior Rating Inventory of Executive Function General Executive Composite

## 4 DISCUSSION

### 4.1 Discussion of Aim 1 Results

The results of our Aim 1 analyses partially support our hypotheses that CHD patients would exhibit poorer outcomes on all of our measures. All measurements of CB volumes, both total and lobular, were significantly reduced in CHD patients as compared to healthy controls, confirming that this population is at risk for abnormal CB development. This finding is strengthened by the fact that there were no differences in intracranial vault volume, which suggest that this vulnerability is specific to the CB and is not the result of whole-brain volume reductions. Additionally, three out of our six measures of EF indicated significantly poorer outcomes for our CB sample as compared to healthy controls. Specifically, these poorer outcomes fell into the domains of inhibition, abstract reasoning, and informant-reported executive function. This supports previous research which has suggested that EF impairments that are present in childhood can persist into adolescence and young adulthood, confirming the importance of continued screening and follow-up with neuropsychological services for this population. Additionally, there was no significant group difference on the WASI Vocabulary subtest, which adds further support to the notion that CHD patients are particularly susceptible to EF deficits and are not displaying a cognitive disruption more generally. Finally, CHD patients performed significantly more poorly on the GP test, indicating reduced motor function, a finding that has been frequently documented in this population. While there was not a statistically significant difference at the  $p=.05$  level, there was a trend and moderate effect size for a difference in oral processing speed, suggesting that CHD patients have slightly reduced capabilities in this core skill.



Notably, despite the fact that there were significant differences between CHD patients and controls on several measures, none of the CHD group means were greater than 1.5 standard deviations below the normative mean, suggesting that this group is not impaired on average. As a follow-up to our group difference analyses, we calculated proportions of impairment for each measure in each group and assessed whether there were group differences in rates of impairment. While there were no significant differences in rates of impairment between our groups, the trend reflected higher rates of impairment for the CHD group across the board. Overall, the highest rate of impairment for CHD was in motor function (27.3% were impaired, compared to 0% of controls). The highest rate of cognitive impairment in CHD relative to controls was for Letter-Number Sequencing (18.2% vs. 4.5%), a measure of cognitive flexibility, followed by Matrix Reasoning (13.6% vs. 0%), a measure of abstract reasoning. These results show that, while on average the CHD group was not impaired, there was clinical significant impairment at the individual level. This speaks to the variability in outcomes for this population and that the majority of the individuals are doing well relative to their peers, however it also emphasizes the importance of continuing to examine CHD patients for cognitive performance difficulties.

#### **4.2 Discussion of Aim 2 Results**

Our initial correlation analyses for Aim 2 resulted in a consistent pattern whereby EF measures were significantly correlated with the posterior CB but not the anterior CB. In total, four out of our six EF assessments were significantly associated with posterior CB volume only. Specifically, measures of inhibition, cognitive flexibility, abstract reasoning, and informant-reported executive function were correlated with the posterior CB only. This constitutes robust evidence that there is a role for the CB in EF and that there is some degree of specificity to the posterior lobe. The only measure of EF that was associated with the anterior CB as well was the

WASI Matrix Reasoning subscale, a measure of abstract reasoning. This finding could be because this test is not as pure of a measure of EF as the other assessments we used in this study. According to the WASI-II manual, the Matrix Reasoning subtest taps fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing, and perceptual organization (Wechsler, 2011). Therefore, given the broad range of abilities necessary to complete this assessment, it seems plausible that there could be anterior CB involvement in some capacity.

Our analysis of motor function and its relationship to the CB did not confirm our original hypothesis that these functions are subserved by the anterior CB. In fact, we found the exact opposite relationship, with Grooved Pegboard being significantly correlated with the posterior CB but not anterior CB. Similar to our speculations about Matrix Reasoning above, this could be due to the fact that our chosen measurement of motor function, the Grooved Pegboard task, requires elements of planning and visual processing that might be related to posterior CB function. It is possible that a more appropriate assessment of motor function for the purposes of this study would have been Finger Tapping or a similar, more automatic motor task. Regardless of potential measurement error accounting for the relationship between the Grooved Pegboard and the posterior CB, this does not explain the lack of an association with the anterior CB. Out of curiosity, we conducted a post-hoc correlation between the anterior CB and the Motor Speed subtest of the D-KEFS (also referred to as Trails 5), as this is an alternative motor measurement in our data. There was no significant correlation for these variables either. Therefore, it could be that there is no relationship between motor function and the anterior CB, which would contradict Stoodley and Schmahmann's model of CB function, or it could be that we were insufficiently powered to detect an existing relationship due to our modest sample size (although  $r=.184$  is not

a negligible effect size). Alternatively, there could be motor disruption occurring in another part of the brain, which would lead to poorer motor performance while obscuring the motor-CB relationship in our data. Speculating further, volumetric assessment might not be the most effective method in neuroimaging to elucidate the neuroanatomical relationships between the CB and functional outcomes. Future research should utilize complementary neuroimaging methods, such as functional magnetic resonance imaging and diffusion tensor imaging, to further investigate CB involvement in cognitive and motor function.

As a test for significance in the difference in sizes of correlation coefficients, we conducted Fisher's Z Transformations. This test allowed us to determine whether there were meaningful differences in the sizes of correlation coefficients for the posterior CB versus the anterior CB. There were two significant results, which showed that both D-KEFS Color-Word Interference subtests were significantly more highly correlated with the posterior CB than with the anterior CB. This suggests that these two tests have the strongest specificity to the posterior CB out of all our EF assessments. What these tests have most in common (and what most differentiates them from our other measures of EF) is that they draw heavily on the ability to inhibit a prepotent response in favor of a different, correct response. While these tests also employ a degree of cognitive flexibility (especially Inhibition-Switching), there are other tests on the D-KEFS that draw just as heavily on cognitive flexibility and were not as robustly related to the posterior CB. Therefore, it appears likely that the posterior CB may be participating in inhibitory mechanisms through which a participant is able to abstain from responding in an impulsive fashion and provide a correct response. No other differences in correlations were statistically significant per the Fisher's Z Transformation, however there are still large and meaningful differences as mentioned above, in which there were significant correlations for the

posterior CB and not the anterior CB. These findings lend support to our hypotheses despite not reaching the significance threshold.

### **4.3 Discussion of Aim 3 Results**

Expanding on our Aim 2 analyses that supported our hypothesis that the posterior CB is involved in EF outcomes, Aim 3 investigated whether posterior CB volumes predict EF outcomes above and beyond processing speed alone. In the past, the CB has been conceptualized as facilitating automatic processing of rehearsed functions and therefore has been associated with cognitive efficiency. Accordingly, past studies of the CB's involvement in cognitive efficiency have used processing speed as a proxy indicator of this construct. However, as mentioned here previously, cognitive efficiency is comprised of more than just processing speed. There are elements of skill, accuracy, and task-specific abilities that are necessary to exhibit cognitive efficiency – speed of processing does not suffice on its own. Therefore, we wanted to explore whether the CB contributes any of these task-specific elements to EF performance above and beyond processing speed.

Our results indicate that, when added to a model with processing speed, the posterior CB contributes a significant amount of additional predictive power when predicting D-KEFS Color-Word Interference Inhibition and the WASI Matrix Reasoning, which are measures of inhibition and abstract reasoning. These results help to support our hypothesis that the posterior CB contributes a unique, EF-specific function in addition to simple processing speed. Particularly notable was that the regression predicting D-KEFS Color-Word Interference Inhibition was significant, as this lends further support to our conclusion in Aim 2 that the posterior CB may be contributing to inhibitory abilities. A potential mechanism for this involvement in response inhibition was noted by Bellebaum and Daum (2007), who noted the strong reciprocal

connections between the CB and the lateral prefrontal cortex. A frequent finding in individuals with lesions to the lateral prefrontal cortex is reduced response inhibition. One study found that individuals with a variety of selective frontal lesions performed more poorly on the Stroop, a classic measure that is similar to the Color-Word Interference tests on the D-KEFS, and that this association was the strongest for individuals with lateral prefrontal lesions (Vendrell et al., 1995). Similar findings on other neuropsychological tests requiring inhibitory abilities support the importance of the lateral prefrontal cortex (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Burgess & Shallice, 1996). Studies of inhibition in individuals with CB lesions have been less conclusive, however one group found impaired Stroop performance in a sample with acute CB injury. These individuals were found to have recovered at a later time point (Neau, Arroyo-Anllo, Bonnaud, Ingrand, & Gil, 2000). Another study of CB lesions found intact inhibition performance (Heyder, Suchan, & Daum, 2004). These inconsistent findings point to a need for further work to understand the CB's role in inhibition. Notably, these inconsistent findings were in samples with acute injury to normally developed CBs, while our findings pertain to individuals with abnormally developed CBs. It is possible that these different conditions result in different cognitive outcomes.

Concerning the significant regression predicting performance on the Matrix Reasoning subscale from the WASI, it is possible that participants with smaller posterior CB volumes performed more poorly due to compromised visuo-spatial processing, which is essential to successful Matrix Reasoning performance and has been noted as commonly impaired in individuals with lesions in the CB (Petrosini, Leggio, & Molinari, 1998). Kalbfleisch, Van Meter, and Zeffiro (2007) found BOLD responses in lobule VI of the CB (part of the posterior lobe) during a Matrix Reasoning task and proposed an alternative theory. They suggest that the

CB is important in reasoning in the absence of explicit external feedback about performance, and that under such conditions of uncertainty, the CB forms internal models of response correctness, serving as a guide to the brain during complex and novel problem solving. They note that this is particularly true under time-pressured conditions. This is consistent with previously mentioned theories about internal model formation for automation of function in the CB.

#### **4.4 Discussion of Planned Supplemental Analyses**

Our first supplementary analysis was based in past research that has found sex differences in outcomes for populations experiencing hypoxia during development. Specifically, it has been proposed that males are more vulnerable to hypoxia than females and experience poorer outcomes. We expected that there would be an indirect effect of sex on EF through posterior CB volume, suggesting that posterior CB volume partially accounts for any relationships between sex and EF. However, due to an unequal distribution of severity of diagnosis in our male versus female groups (such that there were significantly more females who fell into the more severe diagnosis group), we decided not to proceed with these analyses.

Our second exploratory analysis aimed to investigate differences in our variables of interest by diagnosis severity. Differences were tested between controls, biventricular diagnoses (mild-moderate severity), and single ventricle diagnoses (typically most severe). Results indicate that several factors seem to be impacted by the severity of the CHD diagnosis, including inhibitory and global EF abilities as well as CB volumes and motor function. For all significant and trend-level omnibus effects, a similar pattern was found in the post-hoc analyses, such that only controls and single ventricle patients were significantly different from one another. This finding is consistent with previous research that has found mild-to-moderate CHD diagnoses to result in cognitive outcomes that are similar to healthy controls while more severe diagnoses

result in more profound impairment (Karsdorp et al., 2007). Therefore, it would appear that a subset of CHD patients is at relatively low risk for cognitive impairment, while others are more likely to experience difficulty. While the most severe diagnosis group was not impaired on average on any measures, it did tend to have the greatest number of impaired individuals out of all three groups. One consideration to keep in mind while interpreting these data is that there is potentially a sex effect influencing these analyses, given the unequal severity distribution between sexes mentioned earlier as our reason for not conducting Exploratory Analysis 1. That being said, more research is needed given the potentially subtle differences in EF outcomes in less severe CHD diagnoses. These findings are not surprising, given the increased likelihood that children with severe CHD diagnoses are exposed to risk factors outlined earlier in this manuscript (e.g., hypoxia during development, larger number of surgeries, chromosomal abnormalities). Future studies should explore these differences and other factors that influence outcomes in larger samples.

#### **4.5 Limitations and Strengths**

The current study's findings should be considered within the context of its limitations. First, these are pilot study data, meaning that this was an initial exploration of outcomes in this population aimed at laying the groundwork for potential future studies. Related to this, we collected data on a relatively small sample, which may have resulted in underpowered statistical analyses (n=44). However, despite the fact that this might appear to be a relatively small sample, this is in fact respectable sample size in the context of neuroimaging studies of medical populations. Furthermore, these data are cross-sectional, making it difficult to draw any firm conclusions about causality or the direction of effects other than those based in theory.

Many strengths of the current study should be highlighted to emphasize its contribution to the field. First, we excluded individuals who were born premature in our sample. This is not always a consideration in studies of the CHD population and can prove to be a serious confound when evaluating neurological effects, as prematurity confers risk for similar hypoxic environments as seen in CHD as well as intraventricular hemorrhage. We also excluded individuals with developmental disorders (many of which are due to genetic disorders that also lead to associated CHD). Excluding premature and developmentally disabled individuals reduced a great deal of additional variance that would have been difficult to control for and allows us to more confidently make conclusions about our findings being related to CHD-specific impairment as opposed to confounding factors. That said, our findings may have been more robust if we had included a group of individuals with CHD who were also born premature or developmentally disabled, as there likely would have been greater variability and more severe outcomes. Our second major strength is that our hypotheses are theory-driven and firmly based in the current literature. It also aims to extend knowledge on a relatively new and poorly understood area of study: the involvement of the CB in cognition. Our analyses are laid out specifically and suit the research questions well. Additionally, we utilized a method of image analysis that has been specifically developed to study the CB, which maximizes accuracy in the calculation of CB volumes. Finally, given that EF is a broad domain of cognitive functions, we examined multiple subtypes of EF (e.g., inhibition, cognitive flexibility, fluency) from both performance and survey methods in an effort to determine whether the CB is related to one specific type over others.

#### **4.6 Conclusions and Future Directions**

This study adds to the sparse literature on adolescent and young adult neurocognitive outcomes in CHD. As compared to healthy controls, these individuals are at risk for a variety of



negative outcomes, including reduced CB volumes, impaired EF abilities, and poorer motor function. We also used this CB-compromised sample to explore the contribution of the CB to higher-order cognition, as has been proposed in previous research. Our findings of a single dissociation such that our EF measurements were related to the posterior CB but not the anterior CB suggest a role for the CB in higher order cognition in our sample overall. We were unable to confirm our hypothesized double dissociation between the posterior and anterior CB, as the posterior CB was related to motor function and the anterior was not. As previously discussed, this could be due to measurement error. Furthermore, we found that posterior CB volumes were able to predict two measures of EF above and beyond processing speed, suggesting that the CB adds an element EF other than simply subserving that automation of cognitive functions. Finally, in our exploratory analyses we were unable to draw conclusions about a sex effect given the characteristics of our sample. However, we were able to show that patients with severe CHDs fare the worst and accounted for the majority of individuals falling into the normatively impaired range in our sample, while more moderate CHDs can result in more subtle impairment. In the future, clinicians assessing CHD patients should be mindful of the potential for subtle effects that nevertheless could have important impacts on daily functioning and quality of life.

These findings help to lay the groundwork for more research. Future work should explore CB anatomy in this population and relationships between the CB and cognitive outcomes using complementary techniques. Volumetric analyses are an important starting point for neuroimaging research, but they do not capture the whole picture of brain-behavior relationships. Therefore, studies using methods such as fMRI and diffusion tensor imaging are needed. Second, investigators should seek to determine specifically what the CB contributes to EF above and beyond processing speed. We demonstrated that the CB is not merely responsible for the

automation of cognitive function through our regression analyses, and our findings are suggestive of a CB contribution to inhibitory processes and cognitive control. However, the mechanisms behind these contributions to EF remain unclear and would benefit from further study. Third, future work should aim to identify more specific medical and treatment factors and their relationship to CB and EF outcomes. These factors could include the number of surgeries a patient undergoes, the number of days they stay in the hospital, whether or not they undergo cardiopulmonary bypass, etc. The identification of modifiable risk factors is essential to reducing the burden of poor long-term outcomes. Finally, future studies should focus on developing EF interventions in the CHD population and determine what services would be beneficial to improve quality of life and ease the transition into adulthood for these patients.

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