The Structural Connectome and Cognition in Early to Late Adolescents with Congenital Heart Disease

The Structural Connectome and Cognition in Early to Late Adolescents with Congenital Heart Disease

by

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ABSTRACT

Congenital heart defects are one of the most prevalent birth defects in the world, with the structural changes to the heart impacting oxygen capacity and brain development. Altered brain development and increased acquired brain injury risk from surgery (e.g., reduced brain volume, white matter injury, hemorrhage) put individuals with congenital heart disease (CHD) at increased risk of poor neurocognitive outcomes. Examining brain networks via graph theory analysis and how they relate to cognitive outcomes allows for an increased understanding of brain-behavior relationships in this at-risk population. To date, research utilizing graph theory in this population has been limited to one CHD diagnosis within a restricted age range. The current study examines how the structural connectome relates to cognitive outcomes in early to late adolescents with mixed CHD diagnoses. Thirty-seven participants with CHD and 38 healthy age- and gender-matched peers underwent neuroimaging and completed cognitive measures (processing speed, intelligence, informant-reported executive functioning). Analyses investigated group differences in global network metrics and relationships among five global network metrics and performance on select cognitive measures. Individuals with single-ventricle CHD, the group with the most severe disease types, showed significantly lower small-worldness compared to double-ventricle CHD and healthy peers with a large effect size (η^2=.15). Moderate correlations were observed between network metrics and cognitive measures, but they did not survive correction for multiple comparisons. In conclusion, small-worldness most robustly differed between groups, with single-ventricle CHD showing the lowest small-worldness values. While correlational relationships did not survive multiple comparisons, they provide preliminary evidence to guide future research on brain-behavior relationships in CHD. Larger multi-site studies are required to allow for further investigation of these potentially subtle differences between CHD severity groups.

INDEX WORDS: Congenital heart disease, Graph theory, Neurocognition, Neuroimaging, Diffusion tensor imaging, Connectome

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DEDICATION

This dissertation is dedicated to my husband, Patrick, and our dogs, Penny and Callie, who have been my unwavering support system throughout the graduate school process. We are in the home stretch.

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1 INTRODUCTION

1.1 Congenital Heart Disease

Congenital heart defects are present in approximately 8 per 1,000 live births worldwide (Bernier et al., 2010), making them one of the most prevalent birth defects in the world (Hoffman & Kaplan, 2002; Kirby, 2017; Van Der Linde et al., 2011). Individuals with congenital heart disease (CHD) are born with structural changes to their heart, which begin in the womb and can impact oxygen capacity and brain development. The number of individuals living with CHD is estimated to be over 1 million, with the population increasing at a rate of 5% per year, likely related to rising survival rates from medical advances in cardiology (Williams et al., 2006). Moreover, the total number of adults living with CHD is larger than that of children living with CHD (Williams et al., 2006), highlighting the importance of understanding the long-term outcomes in this aging population. As a group, emerging adults with CHD have worse educational attainment, underemployment, disability, and delayed progression into independent adulthood compared to their peers (Ilardi et al., 2017; Marelli et al., 2016). By utilizing a neurodevelopmental lifespan approach to understand how the disease impacts early brain development, there can be a better understanding of the neurocognitive outcomes across the lifespan, which can have cascading effects on academic, psychosocial, emotional, and occupational functioning (Kovacs & Bellinger, 2021).

As part of the disease and treatment, altered brain development and injury risk are multifactorial, including intrinsic, pre-operative, peri-operative, and post-operative factors that must be considered. Intrinsically, during the third trimester, fetuses with CHD have reduced brain volumes due to altered blood flow patterns of oxygenated and deoxygenated blood to the brain (Howell et al., 2019). Prior to surgery, up to 40% of infants with CHD show smaller total and regional brain volumes, higher cerebral spinal fluid volumes, lower fractional anisotropy, and higher rates of acquired ischemic lesions and strokes, similar to outcomes seen in the premature population without CHD (Howell et al., 2019; Peyvandi et al., 2019; Pulcine & deVeber, 2021). Operations are often crucial for the survival of an infant with CHD; however, they can also provide an increased risk for additional acquired brain injury. One study with a mixed sample of CHD types documented that up to 36% of children showed new post-operative white matter injury, infarction, or hemorrhage (Andropoulos et al., 2010). Moreover, these brain abnormalities persist throughout childhood and adolescence. Children, adolescents, and young adults with CHD show altered white matter microstructure, differences in network processes, and focal and multi-focal abnormalities compared to their healthy peers (Aleksonis & King, 2022; Bolduc et al., 2018; Marelli et al., 2016).

Research has established that individuals with CHD are at risk for altered brain development and acquired injury before and after surgery. Still, it is also important to know which individuals with CHD have the highest risk. The wide variety, combination, and complexity of possible congenital heart defects make forming risk categories difficult. CHD diagnoses are often categorized based on two factors: ventricle structural anatomy (single vs. double) and the presence of cyanosis. In general, single-ventricle structural abnormality, where one ventricle is non-functional (e.g., hypoplastic left heart syndrome, tricuspid atresia), is often thought to be more severe than double-ventricle anatomy due to the structural complications that often require multiple surgeries with cardiopulmonary bypass over several years, adding an increased risk of peri- and post-operative complications (Pulcine & deVeber, 2021). While often present in single-ventricle structural abnormalities but not exclusive to individuals with cyanotic CHD are at increased risk of brain insult, including stroke, hemorrhages, and thromboembolic events that result in focal or multi-focal abnormalities (Andropoulos et al., 2010; Marelli et al., 2016; Pulcine & deVeber, 2021). In cyanotic CHD, infants develop cyanosis, a bluish color to the skin, due to a mixture of oxygen-rich and oxygen-poor blood, causing less oxygen to be delivered to the tissues of the body and, notably, the brain. Less severe forms of CHD are often double-ventricle structural abnormality (e.g., atrial septal defect, ventricular septal defect, coarctation of the aorta) and/or acyanotic because they do not typically impact the amount of oxygen in the blood and are less likely to undergo repeat cardiac surgery with cardiopulmonary bypass (Huisenga et al., 2021; Marino et al., 2012; Pulcine & deVeber, 2021). In addition to disease and treatment considerations, prematurity and low birth weight can also put infants at risk for reduced brain volumes and acquired injuries such as ischemic stroke or hemorrhage and higher rates of developmental delay (Howell et al., 2019; Marino et al., 2012). Taken together, multiple disease and treatment factors increase the risk of altered brain development and white matter injury, which can impact cognitive development through childhood and beyond.

1.2 Neurocognitive Outcomes of Individuals with CHD Across the Lifespan

The culmination of premature birth, disease, and treatment factors put infants with CHD at increased risk of developmental disorders that require intervention and remediation for neurocognitive deficits that frequently carry into adulthood. As young as 18 months, infants with CHD show poorer psychomotor and mental developmental scores on the Bayley Scales of Infant Development compared to the normative mean (Huisenga et al., 2021). Psychomotor scores, but not mental developmental scores, were moderated by disease type, with infants with single-ventricle CHD showing lower scores than those with double-ventricle CHD (Huisenga et al., 2021). In infants with mixed CHD types born over 37 weeks gestation, poorer cognitive performances on the Bayley were associated with lower brain volumes in subcortical structures (i.e., caudate, thalamus) and cortical grey matter (Bonthrone et al., 2021). As children with CHD age into school and beyond, they continue to show poorer performance on neurocognitive measures compared to their peers.

Later in development, school-age children with mixed CHD types perform worse compared to their peers in neurocognitive domains of attention, processing speed, motor skills, memory, and areas of executive functioning, often requiring academic remediation (Cohen & Earing, 2018; Huisenga et al., 2021; Kovacs & Bellinger, 2021). In a recent meta-analysis, children with CHD after cardiopulmonary bypass surgery aged 5-17 collectively showed a mean full-scale intelligence quotient (IQ) in the average range; however, those with single-ventricle CHD had statistically lower IQs with high heterogeneity compared to those with double-ventricle CHD and healthy controls (Feldmann et al., 2021). Severity within CHD type may also factor into intelligence outcomes, with children with hypoplastic left heart syndrome, a single-ventricle cyanotic diagnosis, scoring lower than 80% of their peers with a large effect size and children with transposition of the great arteries scoring lower than 60% of their peers with a small effect size (Compas et al., 2017). In contrast, children with atrium and ventricular septum defects show intellectual outcomes in the average range (Compas et al., 2017). Similar variability in intelligence outcomes across disease severity ranges continues into adolescence and adulthood. In a small sample of tetralogy of Fallot and d-transposition of the great arteries, double-ventricle structural abnormalities, adolescents and young adults with CHD scored worse on measures of full-scale intelligence and processing speed compared to their healthy siblings (Murphy et al., 2017). In contrast, a meta-analysis of neuropsychological outcomes in mixed samples of CHD after childhood did not show overall differences in IQ compared to healthy controls from pooled effect sizes; however, the authors noted significant heterogeneity in effect sizes across studies

(Mills et al., 2018). Examining outcomes in mixed samples may mask poorer outcomes in more severe forms of CHD, such as single-ventricle and cyanotic disease types. Based on available meta-analyses with both specific and mixed samples of CHD, long-term intelligence outcomes are consistently poorer in individuals with severe disease types and less consistent in mixed samples, highlighting the importance of considering disease factors when examining outcomes. In addition to a general reduction in intelligence outcomes, the literature consistently reports that individuals with CHD show deficits in domains of executive function and processing speed.

As children age into adolescence and beyond, academic and adaptive functioning demands become more complex and can reveal difficulties in executive functioning, such as processing speed, cognitive flexibility, and working memory. Adolescents and young adults with CHD consistently show worse performance and higher dysfunction on informant- and self-report measures of executive function and poorer performance on measures of processing speed (Cohen & Earing, 2018; Klouda et al., 2017; Mills et al., 2018; Perrotta et al., 2020). On informant- and self-report measures of executive function, primarily using the Behavior Rating Inventory of Executive Function (BRIEF), adolescents and young adults with mixed CHD types showed higher overall executive functioning difficulties with large effect sizes, which in one study, related to the number of surgeries and more attention-deficit hyperactivity symptoms compared to siblings (Feldmann et al., 2021; Klouda et al., 2017; Murphy et al., 2017; Semmel et al., 2018). Importantly, measurable executive dysfunction in CHD is associated with worse psychosocial health and quality of life and is related to a reduced perceived ability to function in everyday life (Jacobsen, 2020). In a meta-analysis with mixed CHD types, adolescents and young adults with CHD performed worse on behavioral measures of executive function and processing speed when compared to their healthy peers, with some heterogeneity across studies but generally large effect sizes (Mills et al., 2018). It is important to remember that tasks designed to measure executive function and processing speed frequently include a psychomotor speed component, a domain often reduced in adolescents and young adults with CHD (Cohen & Earing, 2018; Mills et al., 2018; Semmel et al., 2018). As such, it is not surprising that individuals with CHD show poorer performance on processing speed measures involving a motor component, including sequencing, as measured by the Trail Making Test and Symbol Digit tasks (Mills et al., 2018; Perrotta et al., 2020). Similar to early developmental and intelligence outcomes, overall performance on measures of executive function and processing speed are poorer overall in mixed samples of CHD; however, the impact of disease severity and treatment factors on outcomes is less established.

1.3 Relationships Among Structural Neuroimaging and Cognitive Outcomes in Adolescents and Young Adults with CHD

A recent systematic review characterized the present state of the literature on structural brain-behavior relationships in adolescents and young adults with CHD, noting that current research shows consistent broad relationships between brain variables and performance on cognitive outcomes but that these relationships are primarily non-specific (Aleksonis & King, 2022). Structural neuroimaging methodologies included in the review were qualitative categorization of brain abnormalities, voxel-based morphometry, diffusion tensor imaging, and graph theory of structural white matter connections. Across methodologies, poorer brain outcomes (e.g., lower brain volumes, lower fractional anisotropy) relate to poorer outcomes across multiple cognitive domains (e.g., intelligence, processing speed, general memory, executive function). These relationships were often uniquely seen in the CHD samples, both of specific disorders (e.g., transposition of the great arteries) and mixed CHD sample types.

However, relationships were not as consistent in the healthy control samples when analyzed separately. Overall, some broad patterns within and across methodology types emerged.

Cross-sectional studies using voxel-based morphometry to measure total and regional brain volumes and diffusion tensor imaging to measure fractional anisotropy, a measure of white matter integrity, generally showed non-specific patterns of brain-behavior relationships. Performance on measures of intelligence, processing speed, and executive functions showed a significant association with various brain regions (i.e., subcortical, temporal, frontal, motor cortex, and cerebellum) in at least one study included in the review (Aleksonis & King, 2022). These findings may partly be due to the multi-dimensional nature of these constructs, which means that multiple brain regions or systems support the cognitive skills of interest. This conclusion highlights a limitation of some of the structural methodologies used to examine these relationships, in that they looked at specific brain structures (univariate) or the integrity of the connections between two structures (bivariate) in isolation. However, the brain processes information much more dynamically (multivariate), utilizing a network holistically and in parallel to carry out tasks, especially complex ones (Bullmore & Sporns, 2009; Sporns, 2022). Thus, to better understand these relationships, it is crucial to employ a methodology that can characterize brain networks in this way. One such statistical method is graph theory; however, only a limited number of studies have utilized graph theory analysis in samples of adolescents with CHD.

Graph theory analysis may offer a unique perspective on subtle brain-behavior relationships in the CHD population due to its ability to examine brain networks across nodes - as part of a connectome, as opposed to viewing brain regions in isolation. Out of the twenty-two studies included in the above-mentioned systematic review, only two articles from the same research group used graph theory analysis to explore relationships among the structural connectome and cognitive outcomes in a target sample of 16-year-olds with d-transposition of the great arteries (Aleksonis & King, 2022). Briefly and further explained below, network metric differences (i.e., decreased global efficiency, increased modularity, and increased small-worldness in adolescents with CHD) between groups mediated worse performances on measures of intelligence (at age 8), memory, and visuospatial skills, as well as parent-reported problems of inattention and hyperactivity/impulsivity (Panigrahy et al., 2015; Schmithorst et al., 2016). Of note, these studies included a stringent age of 16-year-olds of only one CHD type (i.e., d-transposition of the great arteries, a double-ventricle CHD), which is beneficial to understanding outcomes and brain-behavior relationships of a specific group. While an essential initial step, it limits a more general understanding of outcomes of CHD across the developmental lifespan and the impact of disease severity. To better discern how adolescents with CHD may differ from their healthy peers, it is necessary to understand how brain networks in typically developing individuals are connected and change across the lifespan.

1.4 Benefit of Graph Theory as a Network Approach to Understanding Cognitive Outcomes

As described, structural neuroimaging studies of adolescents and young adults with CHD have primarily used univariate (i.e., brain abnormalities, voxel-based morphometry) and bivariate (i.e., tractography between two regions) methods to characterize regional differences from healthy controls as well as look at relationships with specific cognitions. However, these analyses employ the limited assumption that brain regions are responsible for specific functions in isolation. More advanced statistical methods, such as graph theory (or network analysis) with diffusion tensor imaging, allow the investigation of white matter connections across the entire brain to form a connectome. An expansive overview of the framework for applying this statistical analysis to brain networks has been previously described (Bullmore & Sporns, 2009; Sporns, 2022). In summary, graphs or networks are a collection of nodes and their links (edges, connections), which can be displayed as a connectivity matrix, defining the network's topology. These graphs can be investigated at two levels- local (nodal) and global (network-wide), with global networks made up of smaller modules of highly connected clusters that are weakly interconnected. These modules, measured as modularity, are thought to have significance in separating neural elements with specific functions (Sporns, 2022). Multiple metrics that describe both nodal and global aspects of the brain networks can be computed using this methodology.

A variety of graph analysis metrics can be computed to characterize global and nodal network properties and can be further classified into three broad categories: segregation, integration, and centrality. In structural networks, measures of segregation quantify the presence of highly interconnected groups of brain regions, known as clusters, in the network. High segregation equates to an increased number of triangles in the network and suggests the potential for high functional segregation. Integration is typically measured through the path length of connections between nodes and is interpreted as the brain's ability to communicate among regions quickly and efficiently. Shorter path lengths are interpreted to indicate a stronger potential for integration. Small-world networks are those that showcase a balance of highly segregated modules and a high number of integrated links. These networks are significantly more clustered than random networks, although they may have similar path lengths. Finally, centrality assesses how often brain regions interact with other regions, facilitates integration, and helps with network resilience. Nodes with high centrality often increase integration. Global and nodal graph theory metrics of interest to this study are summarized in Table 1 (Bassett & Bullmore, 2006; Bullmore & Sporns, 2009; Rubinov & Sporns, 2010; Sporns, 2022).

Table 1. Summary of global and nodal graph theory metrics

Category	Metric	Definition
Segregation	Clustering coefficient (Global and nodal)	Proportion of the number of connections between a node's neighbors and the maximum number of possible connections; can describe network region connectedness and local network connectedness
Integration	Shortest path length (Global and nodal)	For global, the average path length between all nodes; for nodal, the shortest given path length among a given node and all other nodes in the graph
	Global efficiency	The average inverse of the shortest path length describes the averaged efficiency among all network nodes
	Local efficiency	Measures how efficient communication is among the first neighbors of a given node when it is removed.
Segregation & Integration	Small-worldness	The ratio of standardized[1] clustering coefficient to standardized path length; Higher values indicate higher specialization and segregation of regions and are also thought to be efficiently connected for integration
Centrality (Nodal)	Betweenness centrality	The frequency that a given node is part of the shortest paths to all other network nodes
	Degree centrality	Total edge count for a given node

[1]Standardized z-scores based on randomly generated networks (i.e., N = 1,000).

When network properties are studied in healthy individuals across the lifespan, they can provide insight into how brain networks may change over development. Knowledge about typical development, differences, and the potential impact of those differences on cognitive outcomes in clinical populations, such as individuals with CHD, can be better characterized. From birth, healthy babies consistently demonstrate a small-world configuration similar to those seen across the lifespan, evidence of the formation of an initial foundation to help with the development of diverse connections (Cao et al., 2017; Khundrakpam et al., 2016; Zhao et al., 2015). Multiple studies with cross-sectional and longitudinal methods consistently show increases in global and local efficiency from birth to early adulthood, suggesting maturing of structural networks (Huang et al., 2015; Khundrakpam et al., 2013; Koenis et al., 2015; Zhao et al., 2015). One study of healthy individuals aged 9 – 85 demonstrated an inverted U-shaped trajectory of global and local efficiency and average path length across the lifespan, with global network efficiency peaking around the third decade (Zhao et al., 2015). In one review, the brain's projections and commissural tracts appear to mature around late adolescence. In contrast, association tracts, specifically the superior and inferior longitudinal and fronto-occipital fasciculi, continue to mature into young adulthood (Khundrakpam et al., 2016). In addition, the precuneus and precentral gyrus are consistently observed as centrally connected regions (Cao et al., 2017; Gong et al., 2009; Huang et al., 2015). Notably, changes in network metrics across the lifespan are not typically measured to be different between sexes (Gong et al., 2009; Zhao et al., 2015). Overall, brain network organization shows small-worldness from infancy, allowing for solid foundations for the maturation of other brain networks such as integration, segregation, and centrality.

Anatomically connected nodes in a structural connectome also tend to be strongly functionally connected (Meehan & Bressler, 2012). Termed neurocognitive networks, graph theory can be used to visualize and quantify large-scale brain networks that support cognitive function (Königs et al., 2021; Meehan & Bressler, 2012). Surprisingly, utilizing graph theory methods to investigate relationships among brain networks and cognitive performance has primarily been studied at the group level (healthy vs. clinical samples), with limited research in healthy control samples alone. Königs and colleagues (2021) argue that this helpful approach limits the ability to explore the inter-individual difference in network metrics and determine neurocognitive network organization in neurocognitive assessments. In healthy children and young adults, structural connectomes with higher clustering coefficient, local efficiency, and density are related to higher scores on intelligence testing (Suprano et al., 2020). Additionally, in a longitudinal study of adolescents over three years, increases in structural network efficiency were related to gains in IQ scores (Koenis et al., 2015). In contrast, individuals who showed a decrease in IQ scores displayed reductions or no change in efficiency levels, most evident in frontal and temporal areas (Koenis et al., 2015). On measures of processing speed, better performance on Weschler tests has been demonstrated to be related to better segregation, specifically transitivity (Suprano et al., 2020). On a global-local task designed to measure processing speed in healthy adults, higher structural global efficiency and path length was correlated with faster simple decision-making on the task (Imms et al., 2021). Although limited, current research suggests that better performance on intelligence and processing speed measures are related to higher integration and segregation structural graph theory metrics.

1.5 Graph Theory in Clinical Populations

Only two studies have investigated relationships between the structural connectome and cognitive outcomes in adolescents with CHD. As previously discussed, 16-year-olds with d-transposition of the great arteries showed reduced global efficiency, increased modularity, and increased small-worldness compared to healthy controls (Panigrahy et al., 2015). In addition, measures of connectivity, integration, and segregation mediated neurocognitive differences in intelligence, academic achievement, learning and memory, executive function, and visual-spatial performances, as well as Attention-Deficit/Hyperactivity Disorder symptoms on parent and teacher report Conners ADHD/DSM-IV Scales (Panigrahy et al., 2015; Schmithorst et al., 2016).

Although these studies could draw specific conclusions about brain-behavior patterns in one CHD diagnosis, more general conclusions about this diverse population cannot be inferred. In a study of neonates with mixed CHD types, structural network inefficiencies were shown pre- and postoperatively when controlling the number of connections in the network compared to healthy neonates (Schmithorst et al., 2018). While limited, the present research suggests that individuals with CHD, likely due to early brain insult, show differences in network metrics, which may mediate neurocognitive performance. Investigation of other clinical populations has established the utility of graph theory to characterize brain networks and relationships with cognitive performance.

Across clinical populations, including abnormal development, studies have shown disruptions in structural network metrics of segregation, integration, small-worldness, and centrality compared to healthy controls (Aerts et al., 2016; Vértes & Bullmore, 2015). In a meta-analysis of 26 neurological and psychiatric disorders, nodes with the highest proportion of lesion voxels were related to decreased global efficiency of structural brain networks (Crossley et al., 2014). In a meta-analysis of structural graph metrics in traumatic brain injury, higher clustering coefficient, longer path length, and reduced balance of the small-world network were seen in those with traumatic brain injury compared to healthy controls (Imms et al., 2019). In another study of children with mild traumatic brain injury and orthopedic injury compared to typically developing children examining the structural connectome, clinical groups showed lower network efficiency globally, segregation, degree centrality in the fusiform gyrus, and higher clustering coefficient and characteristic path length in the fusiform gyrus (Ware et al., 2022). Consistently, focal and diffuse brain insult has quantifiable impacts on the structural brain connectome.

Differences in the relationships among the structural connectome and neurocognitive outcomes in clinical populations compared to controls have been used to better characterize the impact of a brain insult on behavior. In a sample of children with fetal alcohol syndrome, parented-reported BRIEF General Executive Composite was positively correlated with characteristic path length using graph theory (Wozniak et al., 2013). In a sample of long-term survivors with a childhood brain tumor, global structural efficiency mediated differences in cognitive flexibility, measured by performance on the D-KEFS Color-Word Inhibition Switching task between groups (Na et al., 2018). In older adults (aged 70-90), better processing speed, as measured by Weschler Coding and Trail Making Part A, and executive function, as measured by Stroop interference, Trail Making Part B, and phonemic fluency, performance was shown to be related to higher global network efficiency when controlling for age, sex, and years of education (Wen et al., 2011). Across healthy and clinical samples, utilizing graph theory to compute structural brain network metrics has been demonstrated to be sensitive to differences in cognitive outcomes; however, this is still an understudied area, including in individuals with CHD. Several factors can impact white matter integrity and, thus, the structural connectome, with differences hypothesized to be related to cognitive outcomes.

1.6 Specific Aims and Hypotheses

The primary aim of this study proposes to characterize and investigate the structural connectome and relationships with neurocognitive outcomes, specifically intelligence, processing speed, and parent-reported executive function, in early to late adolescents with CHD. Current knowledge about brain-behavior relationships in adolescents with CHD includes static univariate and bivariate relationships. However, these direct comparisons do not inform the understanding of the complex multi-dimensional nature of brain networks. Brain networks analyzed using graph theory provide an increased understanding of how brain regions (or nodes) work together holistically and in parallel. Thus far, only one research group has investigated how the structural connectome relates to behavior and informant-reported cognitive outcomes in a sample of 16-year-olds with d-transposition of the great arteries. This study fills an important gap in the literature about brain-behavior relationships using graph theory in a mixed sample of CHD types across a broad age range, allowing for more general conclusions about outcomes in this population. Furthermore, given the use of a sample with diverse CHD types, this study will be able to examine the impact of disease severity via broad ventricle structural abnormality (i.e., single-ventricle vs. double-ventricle) on the structural connectome and cognitive outcomes.

1.6.1 Aim 1

The purpose of the first aim is to utilize graph theory analysis of structural brain network connectivity to explore how the connectome is potentially altered in a sample of early to late adolescents with CHD compared to age-matched healthy controls.

Hypothesis 1: Measures of integration (i.e., shortest path length, global efficiency) will be lower in individuals with CHD compared to controls.

Hypothesis 2: Measures of segregation (i.e., clustering coefficient, small-worldness) will be higher in individuals with CHD compared to controls.

Hypothesis 3: Measures of centrality (i.e., betweenness centrality, degree centrality) will be lower in individuals with CHD compared to controls.

Hypothesis 4: Diagnosis risk factors (i.e., disease severity) will be associated with larger differences in measures of integration, segregation, and centrality.

1.6.2 Aim 2

The purpose of the second aim is to explore how network metrics relate to cognitive outcomes (i.e., intelligence, motor processing speed, and parent-reported executive functions) in both groups and to determine if network metrics highly related to cognitive outcomes mediate differences in cognitive performance between individuals with CHD and their healthy peers.

Hypothesis 1: Measures of integration, segregation, and centrality will significantly correlate with performance on cognitive measures.

Hypothesis 2: Brain network differences will underlie differences in cognitive outcomes between individuals with CHD and healthy controls. The differences in cognitive functioning between individuals with CHD and controls will be mediated by network metrics that are highly related.

1.6.3 Exploratory Aim 1

Currently, there is a lack of evidence about the impact of age and disease severity on the structural connectome. Exploratory aim 1 will investigate whether there is an interaction between age and disease severity, independent of site, related to network metric outcomes in adolescents with CHD.

Hypothesis 1: There will be an interaction of age by severity, where individuals with single-ventricle CHD will have lower network efficiency compared to those with double-ventricle CHD, and this difference will be larger in older individuals with CHD.

2 METHODS

2.1 Recruitment of Participants and Procedures

Participant data utilized in the present study were collected from two parent studies (A & B), each investigating outcomes in children, adolescents, and young adults with CHD. Specifics about procedures and recruitment, when different, are included below. Both studies were reviewed and approved by their local institutional review boards. All participants provided informed consent or parental permission and assent when the participant was under the age of 18.

2.1.1 Parent Study A

Adolescent and young adult participants with CHD were identified from the pediatric cardiology database at Children's Health Care of Atlanta in Atlanta, GA. Specific CHD diagnoses of interest that were eligible to be approached for recruitment included both double-ventricular anatomy (e.g., D-transposition of the great arteries, total anomalous pulmonary venous connection) and single-ventricular anatomy (e.g., double inlet left ventricle, hypoplastic left heart syndrome, tricuspid atresia, pulmonary atresia with hypoplastic right ventricle). Participants were eligible for the study if they were between the ages of 16 and 22 and could read English and complete self-report questionnaires. Ineligibility for recruitment in the parent study included severe mental or physical disability, prematurity (less than 34 weeks gestational age), history of cerebral vascular events, history of a brain tumor or traumatic brain injury, visual or hearing impairment, ferromagnetic implants or orthodontic devices, and residence of more than 60 miles from downtown Atlanta.

Screening of participants from an initial telephone interview with either the participant or, if under 18, a legal guardian, based on inclusion criteria, resulting in 45 eligible participants. Twenty-one participants agreed to enroll in the study and completed both neuroimaging and neuropsychological assessment procedures. The remaining 24 were not included in the sample for the present study due to missing either neuroimaging or neuropsychological assessment data or not participating due to lack of interest, scheduling conflicts, or not showing up to their appointment. The sample of individuals with CHD eligible for inclusion from parent study A includes 21 participants.

Healthy controls included in the present study were recruited through Georgia State University's psychology department research pool and fliers in the Atlanta community. All control participants had to meet the same inclusion (except CHD diagnosis) and exclusion criteria. In addition, potential control participants were administered the SCID-II (First et al., 2002) to ensure they did not meet the criteria for psychological or substance abuse disorder at the time of participation. Twenty-five age and gender-matched healthy control participants from parent study A were included.

Demographic characteristics for all participants of parent study A and diagnostic and treatment characteristics for CHD participants are presented in Tables 2 and 3. There is a comparable number of single- and double-ventricle CHD participants.

2.1.2 Parent Study B

Early adolescent and adolescent participants with CHD and healthy control peers were identified from an existing preliminary study of the social and emotional consequences of moderate to severe CHD. Participants with CHD who were part of the initial study were identified through the Nationwide Children's Hospital (NCH) electronic cardiac patient registry. Children with CHD were eligible for the study if they were between the ages of 10 and 15, were seen by a CHD cardiologist in the past three years, enrolled in school full time, were able to complete measures in English, and lived within 100 miles of NCH. Ineligibility for recruitment included a diagnosis of a genetic syndrome (e.g., Down Syndrome, Marfan Syndrome). CHD diagnoses included single-ventricle (i.e., hypoplastic left heart syndrome, coarctation of the aorta, tricuspid valve atresia) and double-ventricle (i.e., transposition of the great arteries, tetralogy of Fallot, ventricular septal defect) anatomy. Like parent study A, all, except one (28 weeks), were born over 34 weeks gestation with an average gestational age of 36.86 weeks (SD=3.16). Of the 62 children with CHD enrolled in the preliminary study, twenty enrolled in parent study B and completed neuroimaging and neuropsychological assessment procedures.

As part of the preliminary study, sociometric assessments in the classrooms of children with CHD were conducted, and one healthy peer classmate of the same age and gender was recruited to participate in additional measures. Healthy controls were eligible if they did not have a history of neurodevelopmental or chronic health condition. Of the 62 healthy controls enrolled in the preliminary study, fourteen enrolled in the parent study and completed both neuroimaging and neuropsychological assessment procedures.

Demographic characteristics for all participants of parent study B and diagnostic and treatment characteristics for CHD participants are included in Tables 2 and 3. There is a comparable number of single- and double-ventricle CHD participants.

2.1.3 Comparison of Participants Across Parent Studies

Participant groups were compared based on parent study enrollment. Participants from Parent Study A were significantly older with higher levels of education compared to Parent Study B due to the difference in targeted age for recruitment. Participants with CHD from each study did not differ in gender, race, handedness, age of first surgery, number of surgeries, or diagnostic group. Specific information comparing study participants across groups is included in Tables 2 and 3.

Table 2. Comparison of CHD demographics between parent studies

n (%)	**Parent Study A** **n=20**	**Parent Study B** **n=17**	χ^2
Female	5 (25.0)	8 (47.1)	.16
Race	Caucasian 17 (85.0) Black 2 (10.0) Asian 1 (5.0)	Caucasian 14 (82.4) Black 2 (11.7) Biracial 1 (5.9)	.56
Right-Handed	15 (76.2)	15 (85.7)	.31
	M (SD)	**M (SD)**	***p***
Age (years)	17.75 (1.52) Range:16-21	11.23 (0.84) Range: 10-12	<.001
Education (years)	11.50 (1.28) Range: 9-14	5.12 (0.93) Range: 4-6	<.001
Diagnosis & Treatment			χ^2
Diagnostic Group	Single Ventricle=9 Double Ventricle=11	Single Ventricle=8 Double Ventricle=9	.90
	M (SD)	**M (SD)**	***p***
Age at 1st surgery (days)	14.00 (22.33) Range:1-86	25.57 (34.49) Range: 0-124	.30
# of surgeries	1.85 (1.04) Range: 1-4	2.06 (1.75) Range: 1-8	.33

Table 3. Comparison of healthy control demographics between parent studies

n (%)	**Parent Study A** **n=25**	**Parent Study B** **n=13**	χ^2
Female	9 (36.0)	2 (15.4)	.18
Race	Caucasian 16 (64.0) Black 5 (20.0) Asian 3 (12.0) Hispanic 1 (4)	Caucasian 11 (84.6) Biracial 2 (15.4)	.06
Right-Handed	16 (64.0)	12 (92.3)	.06
	M (SD)	**M (SD)**	***p***
Age (years)	18.50 (1.64) Range: 16-21	11.14 (0.90) Range: 9-12	<.001
Education (years)	12.64 (1.15) Range: 10-14	5.00 (0.82) Range: 4-6	<.001

2.2 Participants

The combined sample of participants from each parent study includes 41 early to late adolescents with CHD and 39 healthy matched controls. After an initial review prior to neuroimaging processing, two participants were excluded due to severe motion (one CHD and one healthy control) and one CHD participant was excluded due to large artifact. All participants excluded from analysis due to image quality were from Parent Study B. After construction of connectivity matrices, two CHD participants (one from Parent Study A and one from Parent Study B) were excluded due to their connectivity matrices not being fully connected. The final sample of participants utilized in the present analyses includes 37 individuals with CHD and 38 healthy controls, for a total sample size of 75. Those excluded from the present analyses did not differ from those included in terms of age, sex, diagnostic group, or full-scale intelligence.

The CHD and healthy control groups did not differ in gender, race, handedness, age, or education. Demographics of the sample and group comparisons are presented in Table 4. Participants with CHD were also compared to each other based on the diagnostic group (i.e., single-ventricle, double-ventricle). The CHD sample includes 17 adolescents with single-ventricle disease anatomy and 20 with double-ventricle disease anatomy. The two diagnostic groups did not differ in gender, race, handedness, age, education, age at first surgery, or the total number of surgeries. Demographics and group comparisons for the CHD diagnostic groups are presented in Table 5.

Table 4. Demographics of controls, CHD, and group comparisons

n (%)	**Controls (n=38)**	**CHD (n=37)**	χ^2
Female	11 (28.9)	13 (35.1)	.57
Race	Caucasian 27 (71.1) Black 5 (13.2) Asian 3 (7.9) Hispanic 1 (2.6) Biracial 2 (5.3)	Caucasian 29 (78.4) Black 5 (13.5) Asian 1 (2.7)	.61
Right-Handed	28 (73.7)	30 (81.1)	.44
	M (SD)	**M (SD)**	***p***
Age (years)	15.99 (3.81)	14.75(3.52)	.15
Education (years)	10.03 (3.18)	8.57 (3.41)	.09

Table 5. CHD demographics and treatment characteristics by diagnostic group

n (%)	Double-Ventricle (n=20)	Single-Ventricle (n=17)	χ^2
Female	5 (25.0)	8 (47.1)	.16
Race	Caucasian 19 (95.0) Black 1 (5.0)	Caucasian 12 (70.6) Black 3 (17.6) Asian 1 (5.9) Biracial 1 (5.9)	.23
Right-Handed	17 (85.0)	13 (76.5)	.51
	M (SD)	**M (SD)**	***p***
Age (years)	14.99 (3.37)	14.48 (3.77)	.67
Education (years)	8.90 (3.39)	8.18 (3.50)	.53
Diagnosis & Treatment			***p***
Age at 1st surgery (days)	25.67 (55.77)	45.33 (56.50)	.36
# of surgeries	1.85 (1.63)	2.06 (1.09)	.66

2.3 Cognitive Measures

2.3.1 Intelligence

Intelligence was assessed with the 2-subtest version of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; Wechsler, 1999). The Vocabulary and Matrix Reasoning subtest scores are used to produce a 2-subtest full-scale intelligence quotient (FSIQ-2). In the Vocabulary subtest, participants are asked to define words that are presented visually and orally and are designed to measure a participant's word knowledge and concept formation. The WASI-II Vocabulary subtest has high reliability (.85-.95). The Matrix Reasoning subtest comprises a series of incomplete matrices in which participants are asked to select the correct response option from a set of five. This subtest measures nonverbal abilities and involves fluid intelligence, classification and spatial ability, knowledge of part-whole relationships, and perceptual organization (Wechsler, 1999). Matrix Reasoning also has high reliability (.85-.93). The WASI-II FSIQ-2 is shown to explain a significant amount of variance in performance on other Weschler intelligence scales (72-74%; Wechsler, 1999).

2.3.2 Processing Speed

Motor processing speed was assessed with either the Symbol Digit Modalities Test (SDMT; Smith, 1982) or the Wechsler Intelligence Scale for Children, Fifth Edition Coding subtest (Wechsler, 2014). The two tasks are similar in that they are both timed tasks where participants are given a key with symbols and a corresponding number. On the same page, there is a sequence of boxes with either a symbol (SDMT) or number (Coding) at the top, with an empty box underneath. Based on the provided key, participants are given a time limit (90 or 120 seconds) to fill in as many boxes as possible. Each task has a high test-retest reliability of .76 and .81 for the SDMT and Processing Speed Index, respectively (Smith, 1982; Wechsler, 2014). For the SDMT, raw scores were converted into age-normed z-scores. For the Coding subtest, raw scores were first converted into age-normed scaled scores and then converted into z-scores to compare to SDMT scores.

2.3.3 Informant Reported Executive Function

Executive function was assessed via informant or parent report on the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000). The BRIEF is an 86-item questionnaire completed by either a parent or someone who knows the participant well (e.g., significant other, roommate) and includes eight clinical scales (Inhibit, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor), two broader indices (Behavioral Regulation (BRI) and Metacognition (MI)), and an overall score (Global Executive Composite (GEC)). For the purposes of this study, the two broader indices, BRI and MI, were used in analyses to characterize informant-reported day-to-day executive function. The questionnaire has high internal consistency (αs=.80-.98) and test-retest reliability (r=.82 for parents; (Gioia et al., 2000)).

2.4 Neuroimaging Parameters

2.4.1 Parent Study A

Participants were scanned in a 3 Tesla Siemens Trio magnetic resonance imaging (MRI) scanner at the Center for Advanced Brain Imaging in Atlanta, Georgia. Diffusion-weighted images were acquired using a spin echo EPI sequence with 2 $b = 0$ s/mm^2 volumes and 30 gradient directions at $b = 1000$ s/mm^2, TR/TE = 7700/90 ms, isotropic resolution = 2.0 mm, FOV = 204 mm, 60 contiguous slices, and scan duration = 8:22 min.

2.4.2 Parent Study B

Participants were scanned in a 3 Tesla Siemens Prisma MRI scanner at Nationwide Children's Hospital in Columbus, Ohio. Diffusion-weighted images were acquired using a spin echo EPI sequence with 2 $b = 0$ s/mm^2 volumes and 64 gradient directions at $b = 700$ s/mm^2, TR/TE = 8300/85 ms, isotropic resolution = 2.0 mm, FOV = 280 mm, 66 contiguous slices.

2.5 Neuroimaging Processing

Neuroimaging processing of diffusion-weighted images for whole brain fiber tractography, network construction, and calculation of network metrics will be conducted based on the methods described by Ware and colleagues (2022) and outlined below.

2.5.1 Quality Assessment

An initial visual review of diffusion-weighted images was conducted to identify and exclude any data with scanner artifacts or incomplete or partially acquired images. As previously mentioned, two participants were excluded due to severe motion and one participant was excluded due to large artifact.

2.5.2 Tractography and Network Construction

Diffusion-weighted DICOM data were converted into NIfTI format and then imported into ExploreDTI in MATLAB for pre-processing, including corrections for motion, eddy current distortions, and Gibb's ringing (Leemans et al., 2009). Calculation of the diffusion tensor, whole brain fiber tractography via a deterministic streamline approach, and computation of a connectivity matrix for each participant was conducted with ExploreDTI in MATLAB (Leemans et al., 2009). To ensure that fiber pathways terminate in gray matter, fiber tracking was initiated using randomized seed points in the brain mask with a 0.10 seed and tractography FA threshold with a 0.5 mm step size, 30° angle threshold, and 50-500 mm streamline length (Long et al., 2019; Thomas et al., 2014). A connectivity matrix for each participant was computed using the extracted whole brain fiber tractography.

The automated anatomical labeling (AAL-90) template was used to define 90 nodes from supratentorial brain regions in native space (Long et al., 2019) using Analysis of Functional Neuroimages (AFNI) and FMRIB Software Library (FSL) in MATLAB (Cox, 1996; Jenkinson et al., 2002; Smith et al., 2004). A standardized Montreal Neurological Institute (MNI) template and each AAL-90 atlas brain region was registered individually to the FA map of each participant in native space using FMRIB's Linear Image Registration Tool (FLIRT; (Collins et al., 1994; Jenkinson et al., 2002). A 90 x 90 connectivity matrix for each participant was constructed in ExploreDTI (Leemans et al., 2009). All connectivity matrices were checked to ensure that they are fully connected. As previously mentioned, two participants were excluded from statistical analyses because their connectivity matrices were not fully connected.

2.5.3 Calculation of Graph Theory Metrics

GRaph thEoreTical Network Analysis (GRETNA) toolbox was used to calculate the theoretical graph metrics for each participant's connectivity matrix (Wang et al., 2015).

Weighted connectivity matrices were calculated and examined to optimize ability to identify statistical relationships. Initial global metrics calculated included clustering coefficient, shortest path length, small-worldness, and global and local efficiency (see Table 1). Standardized z-scores for the computation of small-worldness was based on 1,000 randomly generated networks. To decrease the number of analyses (thus, the chance of spurious findings) and due to the small sample size, statistical relationships and analyses outlined in the Statistical Analyses section were completed for global metrics only.

2.6 Statistical Analyses

Statistical analyses were computed in RStudio 2023.03.0+386. Graph metrics were harmonized across the two parent studies using the neuroCombat package for R (https://github.com/Jfortin1/neuroCombat_Rpackage; (Johnson et al., 2007). Sample demographic information were analyzed using *t*-tests, analysis of variance (ANOVA) and chi-square techniques. Test of normality and linearity were conducted to ensure assumptions were met.

2.6.1 Specific Aim 1

The purpose of the first aim was to utilize graph theory analysis to explore how structural network metrics are altered in the sample of adolescents with CHD compared to healthy controls.

t-tests were conducted to determine if there were significant group differences in five global network metrics of interest, including clustering coefficient, shortest path length, small-worldness, global efficiency, and local efficiency. Effect sizes were also calculated. A sensitivity power analysis was conducted using G*Power v3.1, indicating that the sample size (n = 75) is sufficiently powered to large effects (effect size d = 0.84). The false discovery rate (FDR) correction was applied to control for multiple comparisons at $p<.05$.

An ANOVA was conducted to determine if there were statistically significant differences in global network metrics between CHD severity groups (i.e., single- vs. double-ventricle) and controls. Gabriel's post hoc test was used to determine which groups were significantly different. A sensitivity power analysis was conducted using G*Power v3.1, indicating that the proposed sample size (n = 75) was sufficiently powered to detect large effects (effect size f = 0.46).

2.6.2 Specific Aim 2

The purpose of the second aim was to explore how network metrics correlate with cognitive outcomes (i.e., intelligence, motor processing speed, and parent-reported executive function) in both groups and to determine if network metrics highly related to cognitive outcomes mediate differences in cognitive performance between CHD and their healthy peers.

First, bivariate Pearson correlations were conducted to determine significant associations among network metrics of interest, described in the previous aim, and performance calculated as age-normed z-scores on cognitive measures (i.e., intelligence, motor processing, informant-reported executive function). A sensitivity power analysis was conducted using G*Power v3.1, which indicated that the proposed sample size (n = 75) is sufficiently powered to detect medium effects (r = 0.39). The false discovery rate (FDR) correction was applied to control for multiple comparisons at $p<.05$.

To investigate the potential mediating effect of network metrics on the relationship between group and performance on cognitive measures, a mediation analysis using PROCESS v4.1 model 4 was conducted with bootstrapping (Hayes, 2017). To limit the number of analyses, mediation analysis was only performed on correlations between network metrics and performance with the highest correlation coefficient.

2.6.3 Exploratory Analysis 1

The purpose of exploratory aim 1 was to investigate if age at different levels of CHD disease severity (i.e., single- vs. double-ventricle) significantly contributes to network metrics in the structural connectome. A hierarchical regression tested for interactions between age and CHD disease severity. To help reduce the number of analyses, hierarchical regression was only performed for network metrics that were significantly different between groups in Aim 1. A sensitivity power analysis was performed using G*Power v3.1, which indicated that the proposed sample size ($n = 75$) is sufficiently powered to detect medium to large effects (effect size $f = 0.42$).

3 RESULTS

3.1 Descriptive Analyses

Tests of normality, linearity, heteroscedasticity, and independence were not violated for all variables of interest, and the sample was normally distributed. To help characterize the sample and understand relationships of the cognitive variables among the groups, descriptive statistics and groups differences were assessed. Age was tested as a potential covariate and was found not to be significantly correlated with *harmonized* network metrics or cognitive variables, and thus was not included as a covariate in subsequent analyses. Means and standard deviations of each cognitive measure based on group are reported in Table 6. An independent samples *t*-test showed that participants with CHD had poorer FSIQ and higher informant-reported executive dysfunction on the metacognitive and behavioral regulation indices of the BRIEF compared to their healthy peers with large effect sizes.

Table 6. Group comparison of cognitive measures

Cognitive Measure	**Controls (n=38) M (SD)**	**CHD (n=37) M (SD)**	***t***	***p***	***d***
Motor Processing Speed[1]	-0.12 (0.96)	-0.15 (1.14)	0.13	.90	0.03
WASI-II FSIQ	0.50 (0.59)	0.00 (1.11)	2.42	.02	0.89
BRIEF					
Metacognition	0.02 (1.02)	1.03 (1.32)	-3.55	<.001	1.19
Behavioral Regulation	-0.23 (0.98)	0.53 (1.21)	-3.01	.003	1.11
Global Executive Composite[2]	-0.10 (1.02)	0.93 (1.33)	-3.62	<.001	1.19

[1]Motor processing speed measure was either WISC-V Coding or Written Symbol Digit Modalities Test [2]BRIEF Global Executive Composite is a composite score of the Metacognition and Behavioral Regulation indices *Note*. Means and standard deviations are in z-scores. WASI-II FSIQ = Weschler Abbreviated Scale of Intelligence, 2nd Edition 2-subtest Full Scale Intelligence Quotient; BRIEF = Behavior Rating Inventory of Executive Function, Parent or Information Report

To further characterize the sample, rates of individual performances that fell within the clinically impaired range (i.e., a z-score < -2.0 for processing speed and FSIQ, and >2.0 for the

BRIEF) were tabulated (Table 7). The CHD group had higher rates of impairment on motor processing speed and BRIEF metacognition index compared to healthy controls.

Table 7. Rates of impairment on cognitive measures

Cognitive Measure	Controls (n=38)	CHD (n=37)	χ^2	*p*	*OR*
Motor Processing Speed[1]	0%	5.6%	4.40	.04	1.13
WASI-II FSIQ	0%	2.7%	1.01	.31	1.03
BRIEF					
Metacognition	3.0%	37.1%	11.70	<.001	18.32
Behavioral Regulation	3.0%	16.8%	3.51	.06	3.51
Global Executive Composite[2]	3.0%	28.6%	8.17	.004	12.80

[1]Motor processing speed measure was either WISC-V Coding or Written Symbol Digit Modalities Test [2]BRIEF Global Executive Composite is a composite score of the Metacognition and Behavioral Regulation indices *Note.* Means and standard deviations are in z-scores. CHD = congenital heart disease; OR = Odds ratio; WASI-II FSIQ = Weschler Abbreviated Scale of Intelligence, 2nd Edition 2-subtest Full Scale Intelligence Quotient; BRIEF = Behavior Rating Inventory of Executive Function, Parent or Information Report

3.2 Results for Specific Aim 1

Healthy controls and individuals with CHD did not statistically differ on any of the network metrics, prior to multiple comparisons correction. Although not statistically significant, global shortest path length and global efficiency had small effect sizes. Results are presented in Table 8.

Table 8. Group comparisons of global brain network metrics

Network Metric	Controls (n=38) M (SD)	CHD (n=37) M (SD)	*t*	*p*	*d*
Clustering Coefficient	0.176 (0.007)	0.175 (0.009)	0.27	.79	0.06
Shortest Path Length	1.932 (0.078)	1.969 (0.095)	-1.85	.07	-0.43
Global Efficiency	0.115 (0.004)	0.113 (0.005)	1.72	.09	0.40
Local Efficiency	0.142 (0.005)	0.142 (0.006)	-0.20	.84	-0.05
Small-Worldness	0.577 (0.047)	0.571 (0.052)	0.48	.63	0.11

An ANOVA examined whether global brain metrics differed among severity groups (i.e., single ventricle CHD, double ventricle CHD, and healthy controls). Gabriel's post-hoc test was used to explore group differences. Results showed that individuals with single-ventricle CHD had significantly lower small-worldness values compared to both healthy controls and individuals with double-ventricle CHD, $F(2, 72) = 6.56$, p=.002, with a large effect size (η^2=.15). This relationship survived FDR correction with a p-value of .01. Individuals with double-ventricle CHD did not differ from healthy controls. Figure 1 shows boxplots as a visual representation of differences in small-worldness across groups. No other significant group differences for global brain network metrics were found.

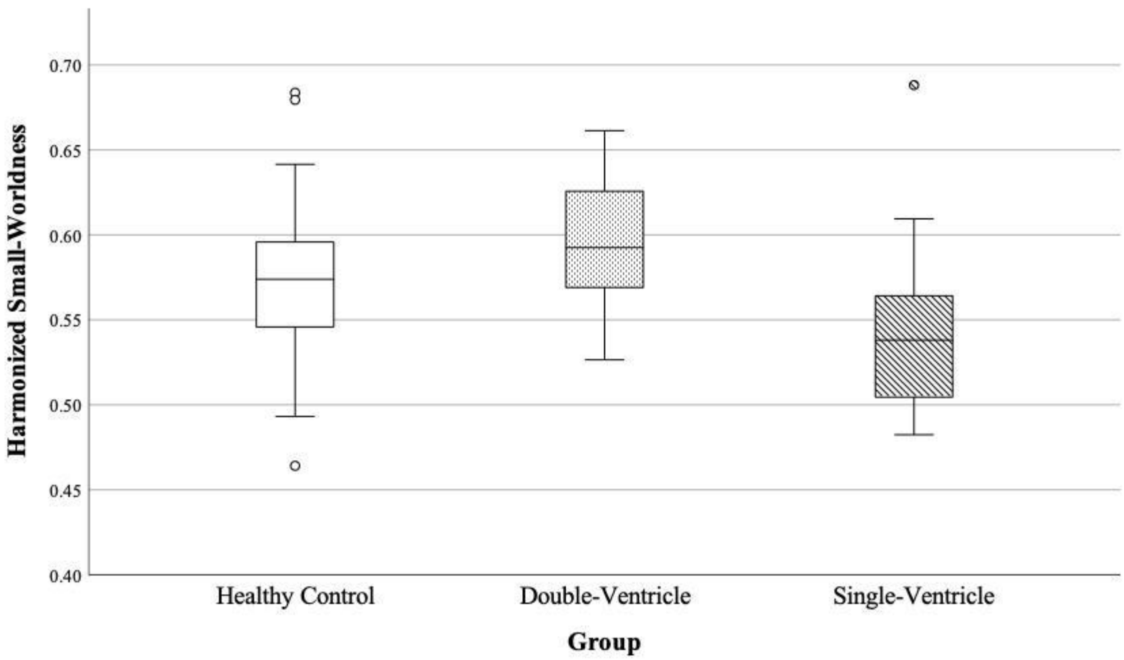


Figure 1. Boxplot representation of group comparisons of small-worldness

3.3 Results for Specific Aim 2

Bivariate correlations examined associations among brain network metrics and performance on cognitive measures. Results prior to FDR correction are presented in Table 9. Scatterplots for each of the global metrics and cognitive measures are included in Appendix A. Longer shortest path length was moderately associated with lower FSIQ and higher concerns with metacognition on the BRIEF. Higher global efficiency was moderately correlated with higher FSIQ, and lower concerns with metacognition and overall executive functioning on the BRIEF. Higher local efficiency was moderately correlated with better performance on processing speed and higher FSIQ. While not statistically significant, intelligence showed a moderate positive correlation with clustering coefficient and a moderate negative correlation with small-worldness. Unfortunately, no significant correlations survived FDR correction for multiple comparisons or when using a somewhat less stringent correction, Holm's sequential Bonferroni procedure (Holm, 1979).

Table 9. Associations among global network metrics and cognitive measures

	Processing Speed	**WASI-II FSIQ**	**BRIEF BRI**	**BRIEF MI**	**BRIEF GEC**
Clustering Coefficient	.128	.204	-.151	-.037	-.089
Shortest Path Length	-.127	**-.257***	.100	**.244***	.159
Global Efficiency	.171	**.333****	-.183	**-.302***	**-.240***
Local Efficiency	**.246***	**.245***	-.085	-.137	-.110
Small-Worldness	.000	-.201	.069	.098	.084

Note. **p*<.05*;* ***p*<.01 before FDR correction

As the strongest relationship with FSIQ, global efficiency was included in a mediation analysis as a potential mediator in the relationship between group and FSIQ. Global efficiency was not shown to be a significant mediator of the relationship between group and FSIQ.

3.4 Results for Exploratory Aim 1

A regression analysis tested the effect of age, CHD severity (i.e., single-ventricle CHD, double-ventricle CHD, and healthy controls), and their centered interaction on unharmonized small-worldness. Analyses did not reveal a significant interaction of age by CHD severity, $F(3, 71) = 1.76$, $p=.16$, with a small effect (Cohen's $f^2=0.07$) and accounting for about 7% of unexplained variance ($R^2=.069$).

4 DISCUSSION

4.1 Group Differences in Cognitive Measures

Group differences and rates of impairments were explored to characterize the sample and better understand overall cognitive performance across groups. Individuals with CHD showed significantly lower scores on intelligence; however, the average 2-subtest FSIQ for individuals with CHD as a group was in the average range with only 2.7% of participants scoring in the impaired range. These results are in line with a previous meta-analysis that showed that mixed-samples of individuals with CHD did not differ from their peers on intelligence scores (Mills et al., 2018). In this study, individuals with CHD as a group performed in the average range and similar to their peers on a performance-based measure of motor processing speed. Overall, results from this study showed that on two performance-based measures of intelligence and motor processing speed, a sample of individuals with mixed CHD types performed in the average range with relatively low rates of impairment.

The biggest differences between groups with the largest effect sizes was seen on informant-reported day-to-day executive function, with about a third of individuals with CHD having scores in the impaired range on the Metacognition Index and the Global Executive Composite. High rates of informant-reported executive dysfunction in samples of CHD have been reported in the literature (Feldmann et al., 2021; Klouda et al., 2017; Murphy et al., 2017; Semmel et al., 2018). Executive functioning is essential for activities of daily living that could impact this group negatively as they age into adulthood and require increased independence skills. It will be important for future research to explore if this executive dysfunction is also seen on performance-based measures.

4.2 Group Differences in Global Brain Networks

The purpose of Aim 1 was to investigate the difference in global brain metrics between individuals with CHD and healthy controls. In this sample of 37 individuals with CHD and 38 healthy controls, the groups did not significantly differ in the five measured global brain metrics of clustering coefficient, shortest path length, global efficiency, local efficiency, or small-worldness. When examining effect sizes, although not statistically significant, global metrics of shortest path length and global efficiency had small effect sizes.

Importantly, when exploring the potential influence of disease severity, CHD groups did show significant differences in small worldness. Specifically, individuals with single ventricle CHD showed lower small-worldness than both healthy controls and individuals with double-ventricle CHD, with a large effect size. Simply put, small-worldness is the ratio of integration and segregation with higher values indicating higher specialization of regions and increased efficiency. These results suggest that disease severity, likely due to the increased risk and medical intervention required, may play a role in overall balance of integration and segregation, such as those with more severe CHD types have a less optimal balance. Interestingly, another study examining the structural connectome in 16-year-olds with d-transposition of the great arteries (cyanotic CHD) showed small-worldness as being significantly higher in this group compared to a healthy reference group (Panigrahy et al., 2015). Differences in the variables used to calculate small-worldness could explain differences in findings across the studies. In the present study, when looking at group level means, small-worldness values were highest in individuals with double ventricle CHD, followed by healthy controls, and then individuals with single-ventricle CHD (Figure 1). Panigrahy and colleagues' (2015) calculation of small-worldness was difference from the present study and was calculated as the ratio of transitivity (i.e., the proportion of triangles relative to incomplete triangles in a network) and characteristic path length. In contrast, the calculation of small-worldness is the present study was the ratio of standardized clustering coefficient to standardized shortest path length. Unfortunately, the methods of the current study did not allow for calculation of small-worldness based on Panigraphy and colleagues' definition. In conclusion, while the sample of individuals with mixed-types of CHD did not differ from their healthy peers on global network metrics, differences in small-worldness were seen between CHD severity groups and their healthy peers with a large effect size.

4.3 Relationships Among Global Brain Networks and Cognition

The purpose of Aim 2 was to investigate relationships among the connectome and cognitive measures. Our hypothesis was somewhat supported, showing moderate strength correlations between some variables of interest prior to correction for multiple comparisons. In particular, the two-subtest WASI-II FSIQ was moderately correlated with higher local and global efficiency and lower shortest path length. As a multi-modal construct, it makes sense that intelligence performance would be linked to global efficiency metrics and better performance would require more integrated networks. In the literature, intelligence performance with individuals with CHD has been robustly related to white matter structure, including various tracts such as the inferior-occipital fasciculus, inferior longitudinal fasciculus, corticospinal tract and others (Aleksonis & King, 2022).

Some of the strongest relationships seen were among lower global efficiency and higher informant-reported concerns of metacognition and overall executive dysfunction. Global efficiency is important for parallel processing in the brain and completing complex tasks often involved in executive functioning. However, in this sample, global efficiency did not differ between groups and was not shown to have a significant indirect effect on the relationship between group and informant-reported executive function. Other studies, appearing more exploratory in nature and with a sample of individuals with severe CHD, have shown that multiple network metrics significantly mediate cognitive performance across measures of intelligence, memory, executive function, and parent-reported Attention-Deficit/Hyperactivity Disorder symptoms (Panigrahy et al., 2015; Schmithorst et al., 2016). Specifically, increased small-worldness was shown to mediate intelligence and executive function, while decreased global efficiency mediated intelligence and rating of inattention and hyperactivity/impulsivity (Panigrahy et al., 2015; Schmithorst et al., 2016). As mentioned in the previous section, small worldness was calculated differently between the present and cited studies, which could contribute to differing results. Findings with other global metrics were not replicated in the present study, potentially in part due to the utilization of a mixed CHD sample compared to a sample with severe CHD in the cited study. In present study, individuals with double-ventricle CHD, as a group, tended to show more subtle differences with controls and could have masked some of the group differences that are more apparent between single-ventricle CHD and their healthy peers.

Exploratory analyses were conducted to better understand the relationships among global network metrics and cognitive measures at the severity group level. Interestingly, several stronger relationships were found, but patterns were different across severity groups and not consistent. Due to the sample size of each group and increased chance of spurious findings, these analyses were merely exploratory and are not reported in the document. Importantly, they do suggest that larger multi-site studies with increased power are necessary to continue to identify a clearer and more stable pattern.

4.4 Age, Disease Severity, and the Structural Connectome

A supplemental analysis was conducted to test whether there was an interaction between age and disease severity on unharmonized brain network metrics. As the only difference between groups was shown in small-worldness, this metric was used to investigate this potential interaction. This hypothesis was not supported, suggesting that the structural connectome may not significantly change at different rates across adolescence depending on CHD disease severity, with a small effect size. Brain network metrics are associated with age over the lifespan (Zhao et al., 2015). In our own sample, age was correlated with all unharmonized brain network metrics, except small-worldness. As such, it appears that while brain networks change over adolescence, based on this sample, they may not change in significantly different ways depending on CHD disease severity.

4.5 Limitations and Strengths

The proposed study should be considered within the context of its limitations. This study is cross-sectional, examining the structural connectome during only one point in time. However, the structural makeup of an individual's brain over the lifespan changes, and relationships with cognitive outcomes likely also change. As such, this study cannot provide information about developmental change across time frames at the individual level. Exploratory analyses were conducted to investigate how network metrics may change across age based on disease severity, one benefit of a broad age range. The small clinical sample size limits the power to identify relationships with small effects and also limits the generalizability of these results. Although small for general graph theory analyses, the current sample size is on par with previously published articles on adolescents with CHD. Given the limited age and CHD types included in studies using graph theory so far, the proposed study contributes important additional knowledge regarding mixed CHD types across adolescence. In addition, this study used limited performance-based cognitive measures, namely intelligence, a multidimensional construct, and motor processing speed. While high rates of impairment in the CHD sample were seen in an informant-report of day-to-day executive function, performance-based measures of executive function will need to be utilized in future studies to determine if these relationships are replicated.

Methodologically, there are inherent limitations to using deterministic tractography and graph theory analysis. White matter networks were constructed using deterministic tractography, which can result in the loss of existing fibers due to fiber crossing compared to other methods such as probabilistic tractography and has the potential to produce false-positive connections or missed connections (Bucci et al., 2013). In addition, while nodes with similar connection patterns exhibit similar functionality, it is not a one-to-one relationship (Bullmore & Sporns, 2009). The use of multimodal techniques in the future could provide a fuller picture of the relationships between functional and structural outcomes. Graph theory is inherently limited by the metrics utilized and their interpretation. Many graph theory metrics are highly correlated due to how they are calculated (e.g., the relationship of small-worldness to measures of both segregation and integration). Finally, it is plausible that the large age range (ages 10-22) of the participants may have reduced our sensitivity to detect relationships between graph theory metrics and cognition due to the changing network structure across this period of development. However, given the limited number of studies using graph theory analysis to investigate outcomes in CHD, increasing our sample size for generalizability across CHD types and ages is advantageous to report on long-term outcomes.

This study contributed to a gap in the literature on the structural connectome of early to late adolescents with CHD by utilizing graph theory analysis to compute a variety of network metrics and explore relationships with common cognitive outcomes, specifically intelligence, motor processing speed, and informant-reported executive function. Multivariate methods such as graph theory provide more comprehensive information about brain networks in an analysis that more closely encapsulates how the brain functions across regions, compared to univariate and bivariate methods. The generalizability of the structural brain connectome and relationships on cognitive outcomes with a sample of individuals with mixed CHD types informs the larger research and clinical community about outcomes in this population during adolescence. As this population ages, it is crucial to understand how brain networks may change and differ from their peers across development.

4.6 Conclusions and Future Directions

Overall, results from this study revealed that individuals with mixed types of CHD differ from their healthy peers in intelligence and executive functioning outcomes; however, brain network differences, if present, are potentially more subtle. Importantly, disease severity may be a particular important factor in long-term outcomes of individuals with CHD, as lower small-worldness was seen in individuals with single-ventricle CHD compared to both individuals with double-ventricle CHD and their healthy peers. This suggests connectome differences for those who have the most neurological risk, as expected. In addition, the present study showed that multiple brain network metrics were moderately correlated with important cognitive outcomes that we examined, namely intelligence and executive function.

This preliminary study highlights the importance of investigating differences in brain-behavior relationships among individuals with mixed CHD types. An important conclusion of this population may be that individuals with less severe forms of CHD have lower risk for poorer neurocognitive and neurological outcomes compared to their peers. However, as expected, given the higher rates of surgery and brain insult in the single-ventricle CHD population, individuals with more severe forms of CHD show increased risk of poor outcomes. Studies examining outcomes of adolescents and young adults with single-ventricle CHD are more prevalent compared to mixed-severity CHD samples and double-ventricle CHD (Aleksonis & King, 2022), potentially making it appear as though CHD as a group shows poorer outcomes. It will be important for future research to continue to explore nuanced differences in these two severity groups, which could have different risk levels in cognitive outcome and graph theory metrics.

As previously describe, the current literature on individuals with CHD through adolescence, young adulthood, and beyond is extremely limited. Continued research in this population is essential to better characterize outcomes as this vulnerable population continues to age. Much of the present research has focused on outcomes of specific CHD diagnoses, often the most severe. While these are important due to being the highest risk, further research across the severity spectrum can provide better understanding of this group overall and help inform medical professionals and patient families about expected outcomes, potentially based on myriad of disease factors. To achieve this goal, future research should employ larger multi-site data collection to better generalize and characterize outcomes. Larger sample sizes will allow for more power to examine potential outcome differences among severity groups and differences that may be more subtle, especially in those with less severe forms of CHD. Furthermore, reporting of effect sizes will be essential to understand the strength of statistical relationships and benefit future researchers conducting meta-analyses and planning for prospective studies. Finally, important socioeconomic variables (e.g., income, household material hardship, education quality), should also be collected to better understand how these factors may contribute to outcomes.

Research on brain-behavior relationships in adolescence and young adults with CHD is still in its beginning stages. This study sought to make an important step in filling the gap of knowledge about brain networks and relationships with cognitive measures in a sample of individual with mixed CHD types. Results revealed that CHD severity may be an important variable in brain network outcomes, namely small-worldness. While other group differences were detected, further research with larger sample sizes is warranted to examine potentially subtle brain network differences in less severe forms of CHD.

REFERENCES

Aerts, H., Fias, W., Caeyenberghs, K., & Marinazzo, D. (2016). Brain networks under attack: robustness properties and the impact of lesions. *Brain*, *139*(12), 3063-3083.

Aleksonis, H. A., & King, T. Z. (2022). Relationships Among Structural Neuroimaging and Neurocognitive Outcomes in Adolescents and Young Adults with Congenital Heart Disease: A Systematic Review. *Neuropsychology Review*, 1-27.

Andropoulos, D. B., Hunter, J. V., Nelson, D. P., Stayer, S. A., Stark, A. R., McKenzie, E. D., . . . Fraser Jr, C. D. (2010). Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring. *The Journal of thoracic and cardiovascular surgery*, *139*(3), 543-556.

Bassett, D. S., & Bullmore, E. (2006). Small-world brain networks. *The neuroscientist*, *12*(6), 512-523.

Bernier, P.-L., Stefanescu, A., Samoukovic, G., & Tchervenkov, C. I. (2010). The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual,

Bolduc, M. E., Lambert, H., Ganeshamoorthy, S., & Brossard-Racine, M. (2018). Structural brain abnormalities in adolescents and young adults with congenital heart defect: a systematic review. *Developmental Medicine & Child Neurology*, *60*(12), 1209-1224.

Bonthrone, A. F., Dimitrova, R., Chew, A., Kelly, C. J., Cordero-Grande, L., Carney, O., . . . Simpson, J. (2021). Individualized brain development and cognitive outcome in infants with congenital heart disease. *Brain communications*, *3*(2), fcab046.

Bucci, M., Mandelli, M. L., Berman, J. I., Amirbekian, B., Nguyen, C., Berger, M. S., & Henry, R. G. (2013). Quantifying diffusion MRI tractography of the corticospinal tract in brain tumors with deterministic and probabilistic methods. *NeuroImage: Clinical, 3*, 361-368.

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature reviews neuroscience*, *10*(3), 186-198.

Cao, M., Huang, H., & He, Y. (2017). Developmental connectomics from infancy through early childhood. *Trends in neurosciences*, *40*(8), 494-506.

Cohen, S., & Earing, M. G. (2018). Neurocognitive impairment and its long-term impact on adults with congenital heart disease. *Progress in Cardiovascular Diseases*, *61*(3-4), 287-293.

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of computer assisted tomography*, *18*(2), 192-205.

Compas, B. E., Jaser, S. S., Reeslund, K., Patel, N., & Yarboi, J. (2017). Neurocognitive deficits in children with chronic health conditions. *American Psychologist*, *72*(4), 326.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical research*, *29*(3), 162-173.

Crossley, N. A., Mechelli, A., Scott, J., Carletti, F., Fox, P. T., McGuire, P., & Bullmore, E. T. (2014). The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain*, *137*(8), 2382-2395.

Feldmann, M., Bataillard, C., Ehrler, M., Ullrich, C., Knirsch, W., Gosteli-Peter, M. A., . . . Latal, B. (2021). Cognitive and Executive Function in Congenital Heart Disease: A Meta-analysis. *Pediatrics*, *148*(4).

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. (2002). Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition (SCID-I/P). *New York: Biometrics Research, New York State Psychiatric Institute*.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). *Behavior rating inventory of executive function: BRIEF*. Psychological Assessment Resources Odessa, FL.

Gong, G., Rosa-Neto, P., Carbonell, F., Chen, Z. J., He, Y., & Evans, A. C. (2009). Age-and gender-related differences in the cortical anatomical network. *Journal of Neuroscience, 29*(50), 15684-15693.

Hayes, A. F. (2017). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. Guilford Publications.

Hoffman, J. I., & Kaplan, S. (2002). The incidence of congenital heart disease. *Journal of the American college of cardiology*, *39*(12), 1890-1900.

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scandinavian journal of statistics*, 65-70.

Howell, H. B., Zaccario, M., Kazmi, S. H., Desai, P., Sklamberg, F. E., & Mally, P. (2019). Neurodevelopmental outcomes of children with congenital heart disease: A review. *Current Problems in Pediatric and Adolescent Health Care*, *49*(10), 100685.

Huang, H., Shu, N., Mishra, V., Jeon, T., Chalak, L., Wang, Z. J., . . . Peng, Y. (2015). Development of human brain structural networks through infancy and childhood. *Cerebral Cortex*, *25*(5), 1389-1404.

Huisenga, D., La Bastide-Van Gemert, S., Van Bergen, A., Sweeney, J., & Hadders-Algra, M. (2021). Developmental outcomes after early surgery for complex congenital heart disease: A systematic review and meta-analysis. *Developmental Medicine & Child Neurology, 63*(1), 29-46.

Ilardi, D., Ono, K. E., McCartney, R., Book, W., & Stringer, A. Y. (2017). Neurocognitive functioning in adults with congenital heart disease. *Congenital heart disease, 12*(2), 166-173.

Imms, P., Clemente, A., Cook, M., D'Souza, W., Wilson, P. H., Jones, D. K., & Caeyenberghs, K. (2019). The structural connectome in traumatic brain injury: A meta-analysis of graph metrics. *Neuroscience & Biobehavioral Reviews*, *99*, 128-137.

Imms, P., Domínguez D, J. F., Burmester, A., Seguin, C., Clemente, A., Dhollander, T., . . . Caeyenberghs, K. (2021). Navigating the link between processing speed and network communication in the human brain. *Brain Structure and Function*, *226*(4), 1281-1302.

Jacobsen, R. M. (2020). Outcomes in adult congenital heart disease: neurocognitive issues and transition of care. *Pediatric Clinics, 67*(5), 963-971.

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*(2), 825-841.

Johnson, W. E., Li, C., & Rabinovic, A. (2007). Adjusting batch effects in microarray expression data using empirical Bayes methods. *Biostatistics*, *8*(1), 118-127.

Khundrakpam, B. S., Lewis, J. D., Zhao, L., Chouinard-Decorte, F., & Evans, A. C. (2016). Brain connectivity in normally developing children and adolescents. *Neuroimage*, *134*, 192-203.

Khundrakpam, B. S., Reid, A., Brauer, J., Carbonell, F., Lewis, J., Ameis, S., . . . Das, S. (2013). Developmental changes in organization of structural brain networks. *Cerebral Cortex*, *23*(9), 2072-2085.

Kirby, R. S. (2017). The prevalence of selected major birth defects in the United States. Seminars in perinatology,

Klouda, L., Franklin, W. J., Saraf, A., Parekh, D. R., & Schwartz, D. D. (2017). Neurocognitive and executive functioning in adult survivors of congenital heart disease. *Congenital heart disease*, *12*(1), 91-98.

Koenis, M. M., Brouwer, R. M., van den Heuvel, M. P., Mandl, R. C., van Soelen, I. L., Kahn, R. S., . . . Hulshoff Pol, H. E. (2015). Development of the brain's structural network efficiency in early adolescence: a longitudinal DTI twin study. *Human Brain Mapping*, *36*(12), 4938-4953.

Kovacs, A. H., & Bellinger, D. C. (2021). Neurocognitive and psychosocial outcomes in adult congenital heart disease: a lifespan approach. *Heart*, *107*(2), 159-167.

Königs, M., Verhoog, E. M., & Oosterlaan, J. (2021). Exploring the neurocognome: Neurocognitive network organization in healthy young adults. *Cortex*, *143*, 12-28.

Leemans, A., Jeurissen, B., Sijbers, J., & Jones, D. K. (2009). ExploreDTI: a graphical toolbox for processing, analyzing, and visualizing diffusion MR data. Proc Intl Soc Mag Reson Med,

Long, X., Kar, P., Gibbard, B., Tortorelli, C., & Lebel, C. (2019). The brain's functional connectome in young children with prenatal alcohol exposure. *NeuroImage: Clinical*, *24*, 102082.

Marelli, A., Miller, S. P., Marino, B. S., Jefferson, A. L., & Newburger, J. W. (2016). Brain in congenital heart disease across the lifespan: the cumulative burden of injury. *Circulation*, *133*(20), 1951-1962.

Marino, B. S., Lipkin, P. H., Newburger, J. W., Peacock, G., Gerdes, M., Gaynor, J. W., . . . Johnson Jr, W. H. (2012). Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. *Circulation*, *126*(9), 1143-1172.

Meehan, T. P., & Bressler, S. L. (2012). Neurocognitive networks: findings, models, and theory. *Neuroscience & Biobehavioral Reviews*, *36*(10), 2232-2247.

Mills, R., McCusker, C. G., Tennyson, C., & Hanna, D. (2018). Neuropsychological outcomes in CHD beyond childhood: a meta-analysis. *Cardiology in the Young*, *28*(3), 421-431.

Murphy, L. K., Compas, B. E., Reeslund, K. L., Gindville, M. C., Mah, M. L., Markham, L. W., & Jordan, L. C. (2017). Cognitive and attentional functioning in adolescents and young adults with Tetralogy of Fallot and d-transposition of the great arteries. *Child Neuropsychology*, *23*(1), 99-110.

Na, S., Li, L., Crosson, B., Dotson, V., MacDonald, T. J., Mao, H., & King, T. Z. (2018). White matter network topology relates to cognitive flexibility and cumulative neurological risk in adult survivors of pediatric brain tumors. *NeuroImage: Clinical*, *20*, 485-497.

Panigrahy, A., Schmithorst, V. J., Wisnowski, J. L., Watson, C. G., Bellinger, D. C., Newburger, J. W., & Rivkin, M. J. (2015). Relationship of white matter network topology and cognitive outcome in adolescents with d-transposition of the great arteries. *NeuroImage: Clinical*, *7*, 438-448.

Perrotta, M. L., Saha, P., Zawadzki, R., Beidelman, M., Ingelsson, E., Lui, G. K., & Priest, J. R. (2020). Adults With Mild-to-Moderate Congenital Heart Disease Demonstrate Measurable Neurocognitive Deficits. *Journal of the American Heart Association*, *9*(19), e015379.

Peyvandi, S., Latal, B., Miller, S. P., & McQuillen, P. S. (2019). The neonatal brain in critical congenital heart disease: insights and future directions. *Neuroimage*, *185*, 776-782.

Pulcine, E., & deVeber, G. (2021). Neurologic complications of pediatric congenital heart disease. In *Handbook of Clinical Neurology* (Vol. 177, pp. 1-13). Elsevier.

Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: uses and interpretations. *Neuroimage*, *52*(3), 1059-1069.

Schmithorst, V. J., Panigrahy, A., Gaynor, J. W., Watson, C. G., Lee, V., Bellinger, D. C., . . . Newburger, J. W. (2016). Organizational topology of brain and its relationship to ADHD in adolescents with d-transposition of the great arteries. *Brain and behavior*, *6*(8), e00504.

Schmithorst, V. J., Votava-Smith, J. K., Tran, N., Kim, R., Lee, V., Ceschin, R., . . . Blüml, S. (2018). Structural network topology correlates of microstructural brain dysmaturation in term infants with congenital heart disease. *Human brain mapping*, *39*(11), 4593-4610.

Semmel, E. S., Dotson, V. M., Burns, T. G., Mahle, W. T., & King, T. Z. (2018). Posterior cerebellar volume and executive function in young adults with congenital heart disease. *Journal of the International Neuropsychological Society*, *24*(9), 939-948.

Smith, A. (1982). *Symbol digit modalities test*. Western Psychological Services.

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., . . . Flitney, D. E. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage*, *23*, S208-S219.

Sporns, O. (2022). Graph theory methods: applications in brain networks. *Dialogues in clinical neuroscience*.

Suprano, I., Kocevar, G., Stamile, C., Hannoun, S., Fourneret, P., Revol, O., . . . Sappey-Marinier, D. (2020). White matter microarchitecture and structural network integrity correlate with children intelligence quotient. *Scientific reports*, *10*(1), 1-10.

Thomas, C., Ye, F. Q., Irfanoglu, M. O., Modi, P., Saleem, K. S., Leopold, D. A., & Pierpaoli, C. (2014). Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. *Proceedings of the National Academy of Sciences*, *111*(46), 16574-16579.

Van Der Linde, D., Konings, E. E., Slager, M. A., Witsenburg, M., Helbing, W. A., Takkenberg, J. J., & Roos-Hesselink, J. W. (2011). Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. *Journal of the American College of Cardiology*, *58*(21), 2241-2247.

Vértes, P. E., & Bullmore, E. T. (2015). Annual research review: growth connectomics–the organization and reorganization of brain networks during normal and abnormal development. *Journal of Child Psychology and Psychiatry*, *56*(3), 299-320.

Wang, J., Wang, X., Xia, M., Liao, X., Evans, A., & He, Y. (2015). GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. *Frontiers in human neuroscience*, *9*, 386.

Ware, A. L., Yeates, K. O., Geeraert, B., Long, X., Beauchamp, M. H., Craig, W., . . . Zemek, R. (2022). Structural connectome differences in pediatric mild traumatic brain and orthopedic injury. *Human Brain Mapping*, *43*(3), 1032-1046.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence manual*. Psychological Corporation.

Wechsler, D. (2014). Wechsler intelligence scale for children-fifth edition. In. Bloomington, MN: Pearson.

Wen, W., Zhu, W., He, Y., Kochan, N. A., Reppermund, S., Slavin, M. J., . . . Sachdev, P. (2011). Discrete neuroanatomical networks are associated with specific cognitive abilities in old age. *Journal of Neuroscience*, *31*(4), 1204-1212.

Williams, R. G., Pearson, G. D., Barst, R. J., Child, J. S., Del Nido, P., Gersony, W. M., . . . Neish, S. R. (2006). Report of the National Heart, Lung, and Blood Institute Working Group on research in adult congenital heart disease. *Journal of the American College of Cardiology*, *47*(4), 701-707.

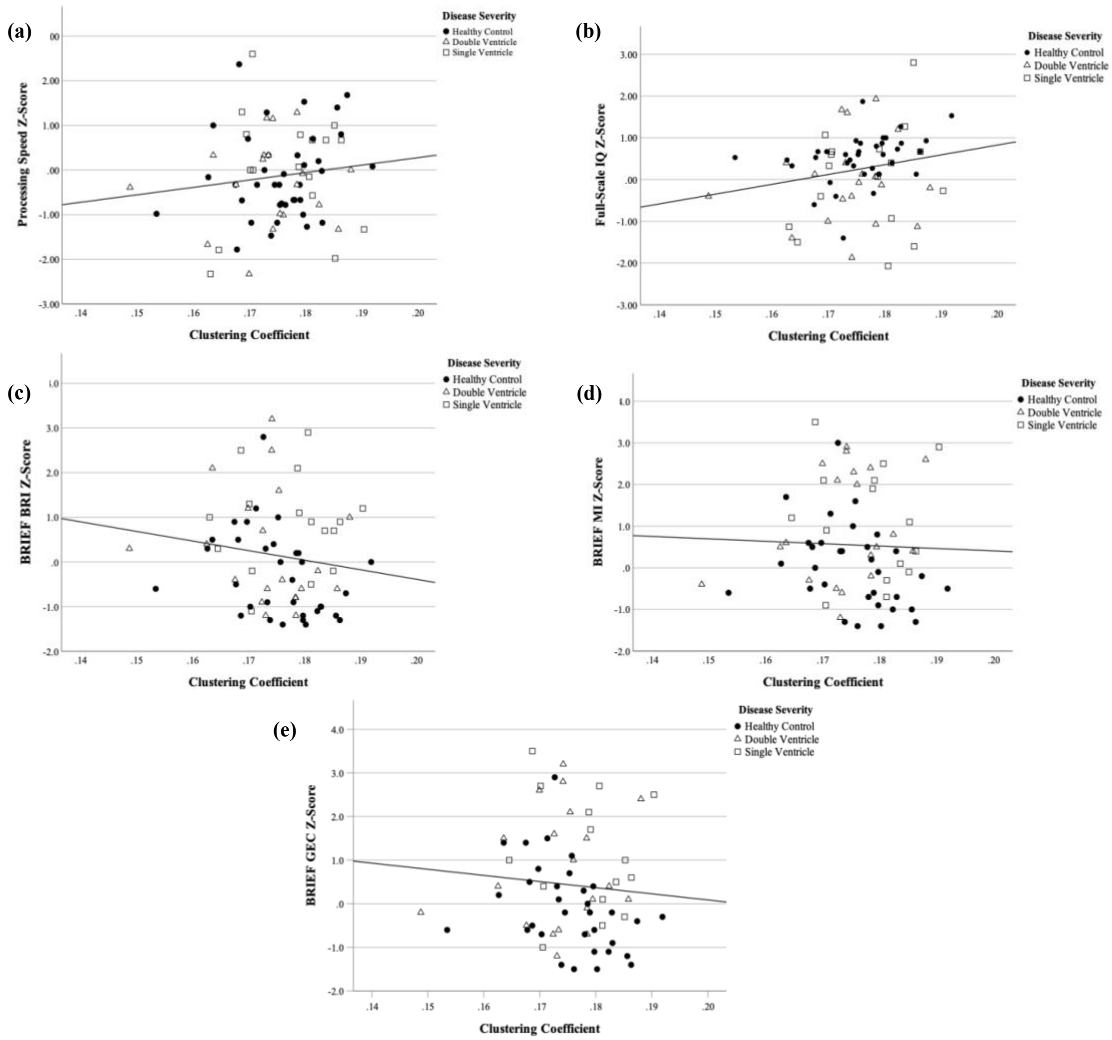
Wozniak, J. R., Mueller, B. A., Bell, C. J., Muetzel, R. L., Hoecker, H. L., Boys, C. J., & Lim, K. O. (2013). Global Functional Connectivity Abnormalities in Children with F etal A lcohol S pectrum D isorders. *Alcoholism: Clinical and experimental research*, *37*(5), 748-756.

Zhao, T., Cao, M., Niu, H., Zuo, X. N., Evans, A., He, Y., . . . Shu, N. (2015). Age-related changes in the topological organization of the white matter structural connectome across the human lifespan. *Human brain mapping*, *36*(10), 3777-3792.

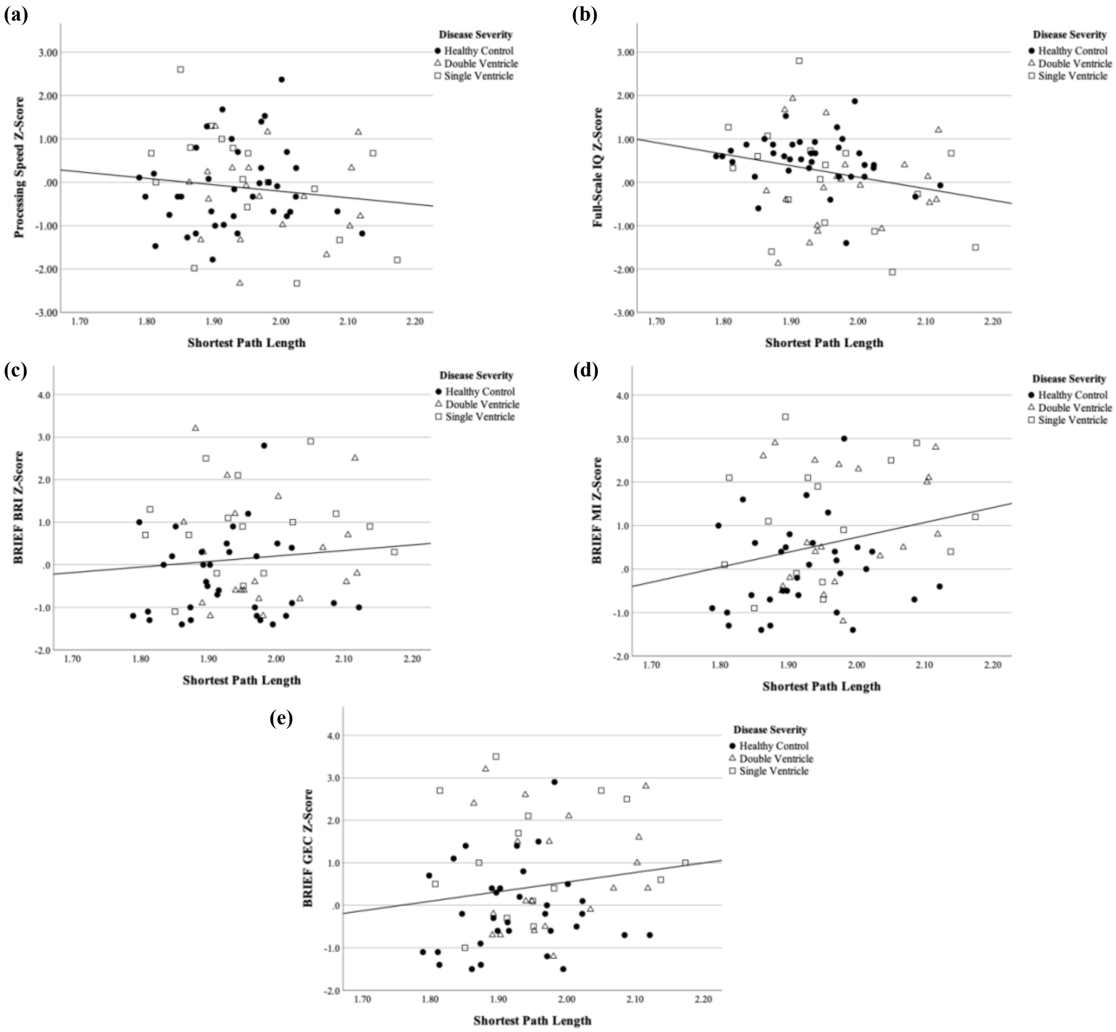
APPENDICES

Appendix A

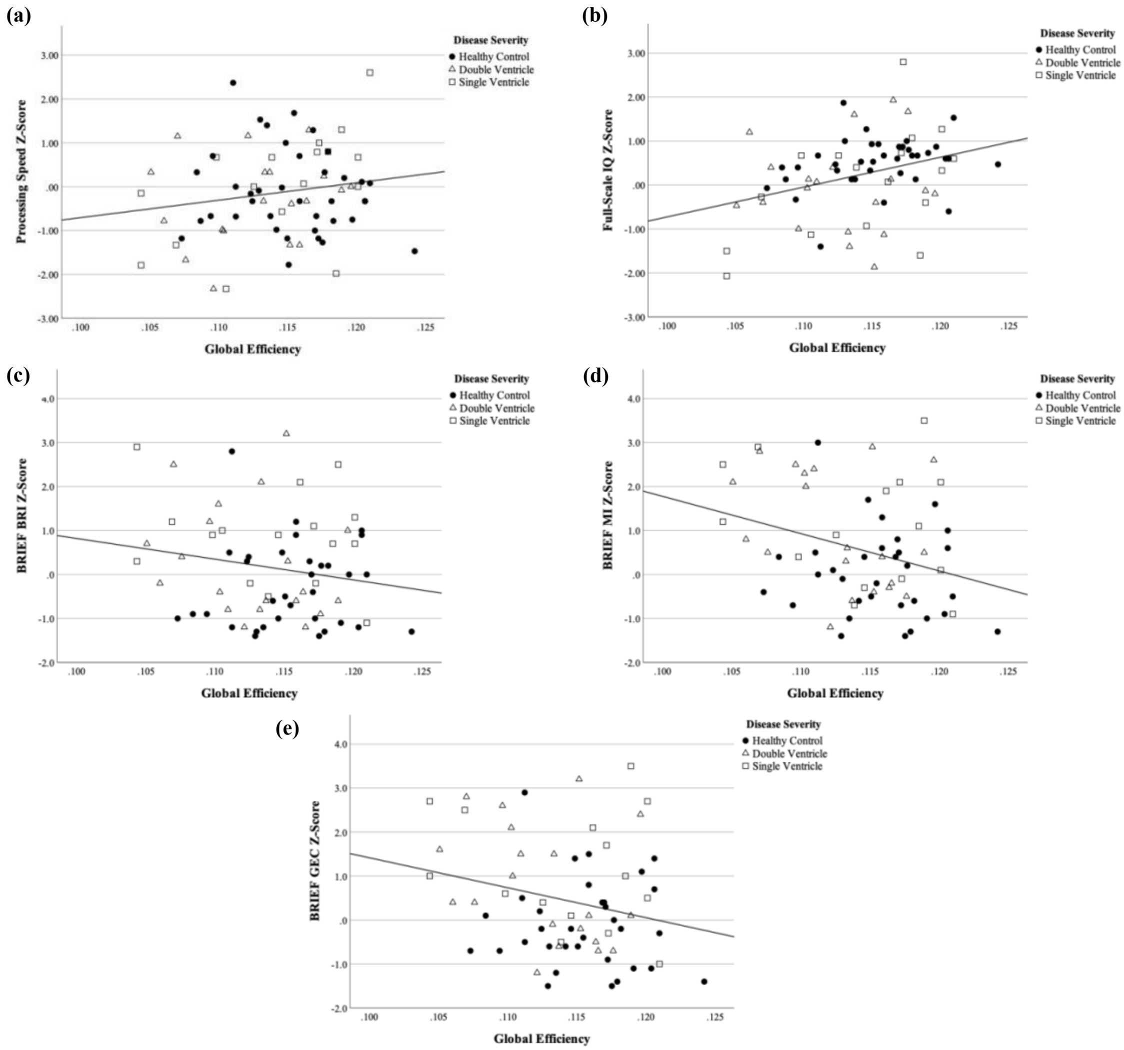
Appendix A.1 - Scatterplots of Clustering Coefficient with Cognitive Measures



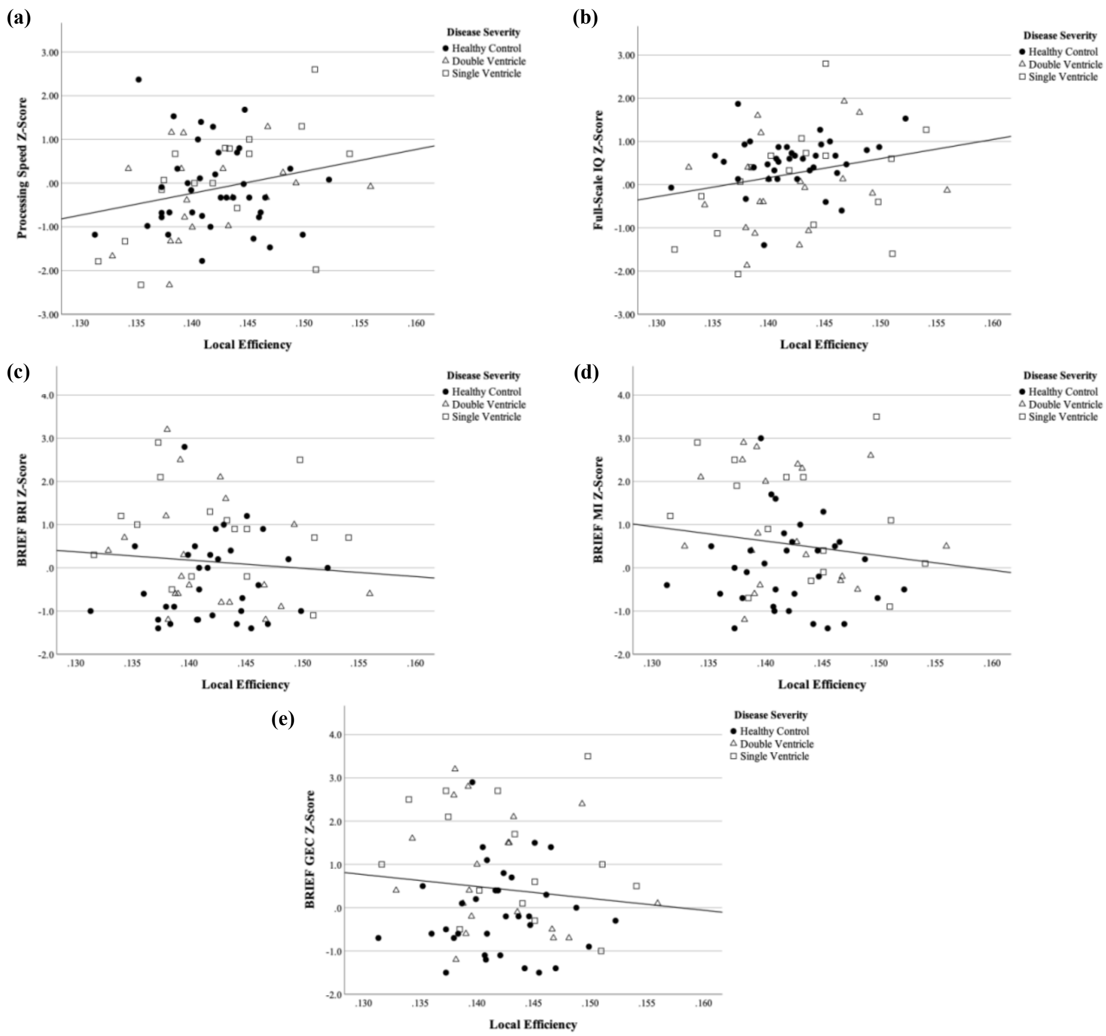
Appendix A.2 - Scatterplots of Shortest Path Length with Cognitive Measures



Appendix A.3 - Scatterplots of Global Efficiency with Cognitive Measures



Appendix A.4 - Scatterplots of Local Efficiency with Cognitive Measures



Appendix A.5 - Scatterplots of Small Worldness with Cognitive Measures