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Neurocognition in congenital heart disease

Behavioral and neuroimaging studies in young adults

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Zusammenfassung

Eine kongenitale Herzkrankheit (KHK) gehört zu den häufigsten Geburtsfehlern überhaupt und betrifft neusten Schätzungen zufolge bis zu zwei Prozent aller neugeborenen Kinder. Dank dem medizinischen Fortschritt, und insbesondere dank der Erfindung der Herzlungenmaschine in der zweiten Hälfte des letzten Jahrhunderts, ist eine KHK heutzutage kein Todesurteil mehr. Die grosse Mehrheit der betroffenen Kinder überlebt mittlerweile bis ins Erwachsenenalter. Dennoch sind diese jungen Patienten nicht geheilt, sondern leiden unter verschiedenen Folgeerscheinungen. Zu nennen sind beispielsweise hirnanatomische Veränderungen (z.B. kleinere Hirnvolumen und Mikroblutungen) oder kognitive Defizite (z.B. psychomotorische und sprachliche Defizite). Letztere können die schulische und berufliche Entwicklung aber auch den Alltag und das private Leben der Betroffenen erheblich beeinflussen. Trotz den grossen Auswirkungen der kognitiven Defizite ist über die kognitive Leistungsfähigkeit von betroffenen Erwachsenen und die zugrundeliegenden neuronalen Korrelate noch wenig bekannt.

Diese Doktorarbeit hat zum Ziel, das „kognitive Leistungsprofil“ und die neuronalen Korrelate bei jungen Erwachsenen mit einer KHK zu identifizieren. Die Datenerhebung erfolgte mithilfe einer umfassenden neuropsychologischen Testbatterie und struktureller Magnet Resonanz Tomographie (MRT). Der Schwerpunkt liegt dabei auf dem Erfassen der kognitiven Verhaltensdaten. Im Rahmen dieser Doktorarbeit wurden drei Studien durchgeführt. Alle basieren auf einer grossen Stichprobe von 67 jungen Erwachsenen (18 bis 32 Jahre) mit einer KHK und 55 gesunden Kontrollpersonen.

Die erste Studie fokussierte sich auf die Identifikation von Unterschieden in verschiedenen kognitiven Funktionsbereichen. (1) Dabei konnte nachgewiesen werden, dass Patienten mit einer KHK in allen untersuchten Domänen (Exekutive, Gedächtnis, Aufmerksamkeit/Verarbeitungsgeschwindigkeit und allgemeine kognitive Leistungsfähigkeit) tiefere Werte erzielten. Insbesondere die Resultate bezüglich der Gedächtnisleistungen waren unerwartet, da in der bisherigen Literatur kaum über Gedächtnisdefizite bei jungen Erwachsenen mit einer KHK berichtet wurde. (2) Zudem wurde ein positiver Zusammenhang zwischen der Komplexität der KHK und dem Ausmass der kognitiven Einschränkungen gefunden.

Trotz der langsam wachsenden Anzahl an bildgebenden Studien in diesem Forschungsgebiet, ist uns keine Arbeit bekannt, die strukturelle Hirnveränderungen und deren Zusammenhang mit der allgemeinen kognitiven Leistungsfähigkeit gemessen mit dem Intelligenz Quotient (IQ) bei Patienten mit einer KHK untersuchte. Die zweite Studie sollte diese Forschungslücke füllen. (1) Strukturelle Hirnveränderungen wurden in der Mehrheit der Patienten mit einer KHK, aber bei keiner der Kontrollpersonen gefunden. Die häufigsten zerebralen Veränderungen waren Mikroblutungen, fokale Infarkte oder fokale Atrophien, Läsionen der weissen Substanz oder globale Atrophien. (2) Einen Zusammenhang zwischen diesen strukturellen Hirnveränderungen und dem IQ konnte hingegen nicht gefunden werden. Dieser ist offenbar auf andere Faktoren als strukturelle Hirnveränderungen zurückzuführen, die jedoch noch unbekannt sind.

Menschen scheitern typischerweise systematisch beim Versuch eine zufällige Zahlenabfolge zu erzeugen. Die dritte Studie untersuchte zum ersten Mal das zufällige Generieren von Zahlen mithilfe des „Mental Dice Tasks“ und dessen neuronale Korrelate bei Patienten mit einer KHK. (1) Eine stärkere „Zähltendenz“ bei Patienten mit einer KHK im Vergleich zu den Kontrollprobanden wurde identifiziert. (2) Zudem konnte ein Zusammenhang zwischen der Leistung beim zufälligen Generieren von Zahlen und den Exekutivfunktionen nachgewiesen werden. (3) Die MRT Befunde wiesen ferner einen negativen Zusammenhang zwischen der Zähltendenz und dem Hirnvolumen hin.

Dank diesen drei Studien konnte das Wissen über das kognitive Leistungsprofil und dessen neuronalen Korrelate von jungen Erwachsenen mit einer KHK erweitert werden. Die vorliegende Doktorarbeit leistet dadurch einen wesentlichen Beitrag im klinisch hochrelevanten Gebiet der KHK.

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Acknowledgments

'A doctoral program is all about having a good stamina and keeping your nerve' is what I have heard from fellow PhD students who had already written their theses. I must admit that I was somewhat amused by these comments - after all, it cannot be that terrible after completing a bachelor's and master's degree, I thought. Spoiler alert: I was proven wrong. What it really feels like is that you want to throw your computer out of the window, escape to a desert island and cry out loud. However, at the same time you want to proudly pat yourself on the back and keep telling yourself that it will be over soon. You probably only know what I am talking about if you have dared to take this extraordinary roller coaster ride yourself. I would like to take this opportunity to thank all the people who have supported me on this journey.

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List of Abbreviations

ACHD	Adult congenital heart disease
BRIEF	Behavior Regulation Inventory for Executive Function
CHD	Congenital heart disease
FOD	First-order difference
GEF	Global executive function
IQ	Intelligence quotient
IQR	Inter quartile range
MDT	Mental Dice Task
MRI	Magnetic resonance imaging
RNG	Random number generation
SD	Standard deviation
SES	Socio-economic status

1 Introduction

> "(…) I had constantly in the back of my mind the idea of attempting to construct an extracorporeal blood circuit that would perform a part of the cardiorespiratory functions in animals and, hopefully, later in man."

With these words, John Heysham Gibbon described his thoughts after the death of a young patient who died of a pulmonary embolism despite emergency surgery (Gibbon, 1978). This was in 1931. Two decades later, he successfully applied a prototype to a cat and finally executed the first successful open-heart surgery in a female patient in 1953, using a cardio-pulmonary bypass (Hahn, 2005). This laid the foundation for the evolution of the modern heart-lung machine. The groundbreaking work of Gibbon, and many other pioneers in cardiology and heart surgery at their time, changed the fate of patients born with a congenital heart disease (CHD). The survival rate of children with CHD has improved significantly since the mid twentieth century, especially due to advances in surgical repair interventions. As a result, survival with a (complex) CHD no longer was an exception but became the rule and new areas of research evolved, exploring long-term consequences of childhood repair procedures. The main body of research to date focuses on the impact on the neurocognition of affected children and adolescents. However, how neurocognitive impairments change with the transition into young adulthood has hardly been investigated so far.

This doctoral thesis aims to expand our existing knowledge of the impact of a CHD on neurocognition in young adults. The focus lies on the examination of different neurocognitive domains in affected individuals. In addition, this thesis attempts to identify structural brain alterations as well as associations with neurocognitive performance. The following chapter, focuses on the definition and the prevalence of CHD. It provides an overview of the most common subtypes of CHD, outlines consequences of a CHD on brain development and highlights the current state of research on neurocognition of affected patients. Chapter 3 addresses the aims of the empirical work and emphasizes its importance. Chapter 4 describes the study population and gives

a brief introduction to the general methods. Chapter 5 presents the three empirical studies, including their methods in detail, their results, and discussions. Finally, Chapter 6 concludes this thesis with a general discussion on the potential impacts and some speculations for the future.

2 Theoretical background

This chapter serves as a brief introduction to the prevalence of CHD. Additionally, it provides an overview of the most common subtypes of CHD, discusses their impact on the brain development and neuroanatomical alterations that may occur. Finally, the latest scientific findings on the consequences of CHD in affected patients are presented.

2.1 Congenital heart disease

Congenital heart diseases are the most common malformations in newborns (Moons et al., 2010). In a large meta-analysis (van der Linde et al., 2011), the authors reported a striking increase of the birth prevalence over the last centuries from 0.6 per 1000 live births in the 1930s to a relatively stable rate of 9.1 per 1000 live births since the 1990s. On one hand, this increased prevalence of newborns with CHD may be mainly caused by enhanced diagnostic methods and surgical advantages, on the other hand, also by an increased number of women with delaying childbearing, and the improved survival of premature infants (van der Linde et al., 2011). Either way, it is assumed that nowadays over one percent of live-borns are affected by a CHD. The latest estimations even assume a prevalence of up to two percent (Giang et al., 2022). With a worldwide estimated annual birth rate of 160 million live births in 2022 (www.countrymeters.info/de/World) this corresponds to 1.6 to 3.2 million newborns with a congenital heart malformation in only one year (and nearly 1’800 newborns with CHD in Switzerland)!

In about one third, no repair procedure is necessary. In another third, reparation is needed at some point in life, and in the last third, it is even necessary during the neonatal period (Warnes et al., 2001). Considering the prevalence figures, this results in a large number of individuals needing medical assistance during their lifetime due to a CHD. Approximately two thirds of CHDs occur isolated, meaning that only the heart is affected. One third occurs in combination with other syndromes or malformations, for example in the context of trisomy 21 (Keir et al., 2019; Marelli et al., 2016; Warnes et al., 2001).

Owing to the invention of the heart-lung machine and improvements in the interventional cardiology, the cardiac surgery and the intensive care medicine, the life expectancy of patients

with a CHD has increased significantly since the 1960s (Moons et al., 2010). While survival to adulthood was unlikely until repair procedures became available, especially with a severe defect complexity, it is nowadays expected that 85 % to 97 % of newborns with a CHD reach adulthood (Mandalenakis et al., 2016; Moons et al., 2010; Warnes et al., 2001), which leads to a fast-growing population of individuals with adult congenital heart disease (ACHD), sometimes also refers to grown-up congenital heart disease (GUCH). While the number of children with CHD remained relatively stable, the number of adults suffering from a CHD, increased strongly in the 2000s (Marelli et al., 2014, see Figure 2.1). Given that most adult cohorts of the different disease entities are just developing, exact estimates of life expectancy for different types of CHDs are not yet robust defined. In the following chapter, the most common CHD types are described.

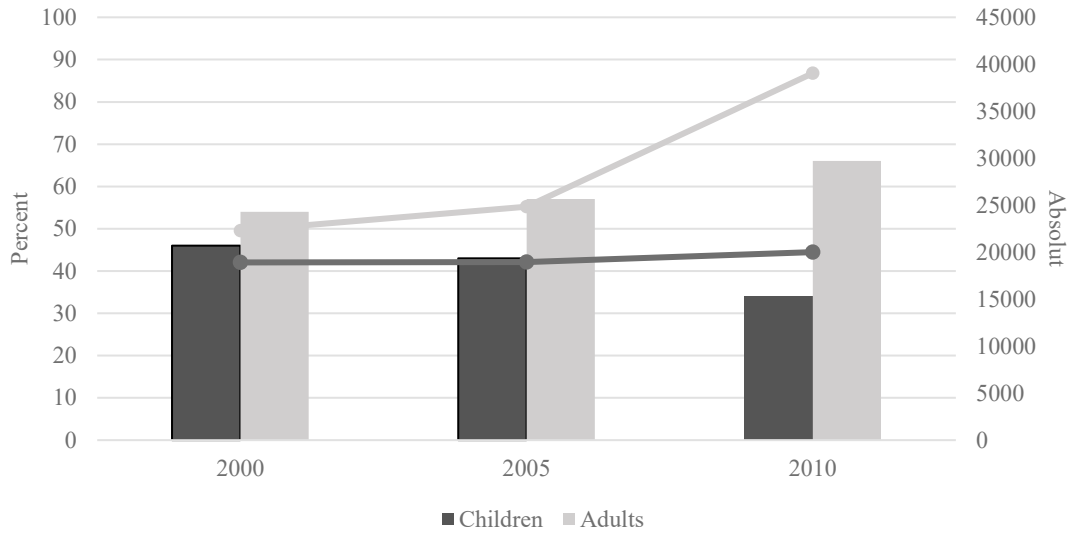

Figure 2.1. Prevalence of children and adults with CHD in Quebec in 2000, 2005 and 2010; in percent (pillars) and absolute (lines) figures, according to Marelli et al. (2014).

2.2 Types of congenital heart diseases and their epidemiology

In utero, the blood flows from the placenta through the right to the left ventricle of the baby's heart and then out the aorta to ensure oxygenated and nutrient-rich blood to reach the brain and other organs, resulting in a so-called right-to-left-shunt (Claessens et al., 2017). In many CHDs, anatomical alterations of this right-to-left shunt occur, leading to an undersupply of oxygenated blood in the brain. Types of CHD are often classified according to their anatomical complexity.

The present thesis is based on the classification of complexity by Warnes et al. (2001) according to the 28th Bethesda Conference. The classification differs between simple (prevalence rate 2.2 per 1000), moderate (prevalence rate 2.5 per 1000) and severe (prevalence rate 1.5 per 1000) CHD complexity. Simple CHDs include isolated or simple atrial septal defects or ventricular septal defects, and moderate CHDs prominently include aortic isthmic stenosis or tetralogy of Fallot. Complex CHDs include, in particular, cyanotic[1] vitiations, such as hearts with only one ventricle or transpositions of the great vessels. But, for example, simple CHDs can also become clinically complex (e.g., atrial septal defect with additional pulmonary hypertension). While most patients affected by CHDs of moderate or severe complexity require life-long specialist care at dedicated tertiary care centers, some patients with simple CHDs may be treated at non-specialist centers, though often in collaboration with referral centers.

There is a great variety of different CHDs and even combinations thereof. Their detailed description is beyond the scope of this thesis. In the following section, some of the most common types of CHDs are briefly illustrated. Figure 2.2 shows the anatomy of a normal heart and Figure 2.3 illustrates an overview of the anatomical alterations of the respective subtypes.

[1] Bluish skin discolouration caused by a high concentration of deoxygenated haemoglobin (Warnes et al., 2001).

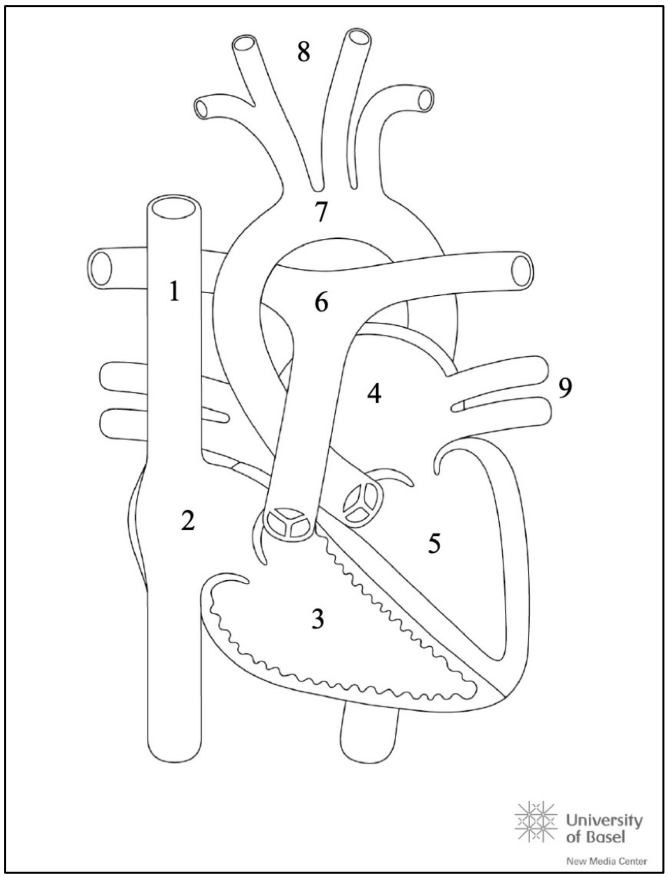

Figure 2.2. Anatomy of a normal heart. 1 Caval vein; 2 right atrium; 3 right ventricle; 4 left atrium; 5 left ventricle; 6 Pulmonary artery; 7 Aorta; 8 Carotid arteries; 9 Pulmonary veins. Illustration according to http://www.chd-diagrams.com.

Ventricular septal defect

With an incidence of 2.62 per 1000 live births, ventricular septal defect (Figure 2.3 A) is by far the most common type of CHD with a prevalence of 30-35 % and it is considered a simple CHD. With a ventricular septal defect, oxygen-rich blood passes from the left to the right ventricle due to a hole between the two ventricles, leading to a left-to-right shunt. To ensure an adequate supply of oxygen, the heart pumps more strongly, which can lead to heart insufficiency in the long-run (Claessens et al., 2017; van der Linde et al., 2011). Estimates suggest that 70 % of all ventricular septal defects close spontaneously during childhood, if not, surgical closure of the leak is often required within the first year of life (Hoffman et al., 2004). When large defects are left untreated, severe, typically irreversible pulmonary hypertension may ensue with the result that long-term survival is significantly impaired.

Atrial septal defect

Atrial septal defect (Figure 2.3 B) is another type of a simple and the second most common CHD (1.64 per 1000 live births, 10 % of all CHDs) (van der Linde et al., 2011). It is characterized by a defect between the two atria. Some small defects do not require repair while large defects need closure by interventional device or surgery (Claessens et al., 2017; Hoffman et al., 2004). As atrial septal defects often remain asymptomatic during childhood, it is frequently diagnosed during adulthood.

Patent ductus arteriosus

In utero, the ductus arteriosus (Figure 2.3 C) is part of the fetal circulation and connects the pulmonary artery with the aorta. The ductus arteriosus normally closes spontaneously after birth. In a patent ductus arteriosus, a simple CHD, this connection remains open (0.87 per 1000 live births, 10 % of all CHD) and blood flows from the aorta directly into the pulmonary artery. If the defects is large, heart failure or pulmonary hypertension may occur and a surgical intervention is needed (Hoffman et al., 2004; van der Linde et al., 2011).

Pulmonary valve stenosis

The pulmonary valve stenosis (Figure 2.3 D) refers to a condition in which the pulmonary valve is narrowed. Its incidence is around 0.5 per 1000 live births with a prevalence of 5 % of all CHD (van der Linde et al., 2011). The severity of the stenosis dictates the timing and type of the repair. Most (also non-operated) pulmonary valve stenoses are classified as simple CHD (Hoffman et al., 2004). However, if a severe stenosis is left untreated, it may lead to increased blood pressure, an enlargement of the right ventricle and in extreme forms, it may even lead to right heart failure.

Tetralogy of Fallot

The tetralogy of Fallot (Figure 2.3 E) includes four anatomical abnormalities: a ventricular septal defect, a pulmonary stenosis, the overriding of the aorta and the hypertrophy of the right ventricle. It is classified as a CHD of either moderate complexity when it occurs isolated, or severe complexity when it is associated with complete pulmonary atresia (Hoffman et al., 2004; Warnes et

al., 2001). Depending on the severity of the pulmonary outflow tract obstruction, right-to-left-shunting with cyanosis may occur. This condition represents the most common cyanotic CHD (Claessens et al., 2017). Survival to adulthood without surgical repair is unlikely and affected patients may die from hypoxemia, strokes, or heart collapses (Hoffman et al., 2004). According to van der Linde et al. (2011), 0.34 out of 1000 live born children (5 % of all CHD) suffers from tetralogy of Fallot.

Coarctation of the aorta

The caorctation of the aorta (Figure 2.3 F) accounts for approximately 5 % of all CHDs (0.34 per 1000 live birth) and is a narrowing of the aorta to the left subclavian artery (van der Linde et al., 2011). This causes high proximal blood pressure and often leads to early left ventricular failure. If left unrepaired, long-term prognosis is poor. In case of extensive collaterals, it may be diagnosed in adulthood only, when patients suffer from untreatable systemic arterial hypertensions. The caorctation of the aorta is typically considered a CHD of moderate complexity (Hoffman et al., 2004; Warnes et al., 2001).

Transposition of the great arteries

The transposition of the great arteries (Figure 2.3 G) is a severe form of a CHD (Warnes et al., 2001). Its prevalence is estimated at about 5 % of all CHDs (0.31 per 1000 live birth) and it is the most common cyanotic CHD in neonatal life (van der Linde et al., 2011). In patients with a transposition of the great arteries, the pulmonary and the systemic circulation are not in sequence but run ‘parallel’. A transposition of the great arteries is a deadly condition and without surgical repair, all affected children die during early childhood. Since the late 1950s, several repair techniques have been invented and most patients now survive to adulthood (Claessens et al., 2017; Hoffman et al., 2004).

Univentricular hearts

Among the most severe CHDs are heart malformations with univentricular physiology (Figure 2.3 H). Many different types of CHD result in univentricular circulation. The hypoplastic left heart syndrome is the most frequent and most complex variant. Left untreated, only a few patients survive beyond childhood. The so-called Fontan procedure has emerged as an effective palliation for surgical repair. It dramatically improved the exercise capacity, the quality of life and the survival rate. Although most patients survive to adulthood after undergoing the Fontan procedure, these survivors are particularly prone to cardiovascular complications during early adulthood and their long-term survival rate is significantly impaired.

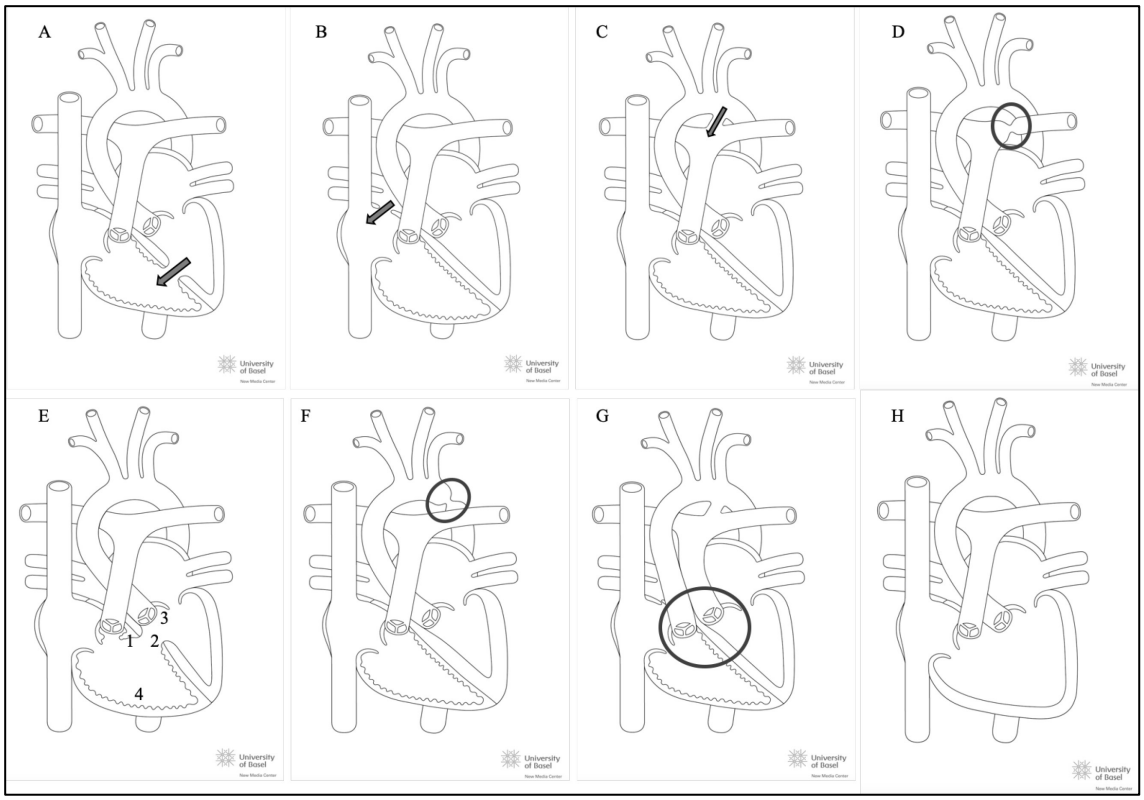

Figure 2.3. Most common subtypes of CHD and their anatomical characteristics. (A) Ventricular septal defect, (B) Atrial septal defect, (C) Persistent ductus arteriosus, (D) Pulmonary stenosis, (E) Tetralogy of Fallot, 1 Pulmonary stenosis, 2 Ventricular septal defect, 3 overriding aorta, 4 right ventricular hypertrophy, (F) Caorctation of the aorta, (G) Transposition of the great arteries, (H) Univentricular heart. Illustrations according to http://www.chd-diagrams.com.

2.3 Brain development and neuroanatomical alterations in congenital heart disease

As mentioned in the chapter 2.2, the fetal circulation is constructed to carry oxygen- and nutrient-rich blood from the placenta to the baby's brain. The brain of a fetus requires up to 50 % of the total oxygen demand (Claessens et al., 2017; Marelli et al., 2016). Even the slightest alterations in this system may lead to severe consequences. For example, researchers were able to demonstrate a direct link between a reduced cerebral oxygen saturation and the impaired brain growth in fetuses with CHD (Sun et al., 2015). In this study, a reduction of only 10 % in arterial oxygen saturation led to a 32 % reduction in cerebral oxygen consumption. Suboptimal prenatal brain development increases the risk of postnatally acquired brain damage (Claessens et al., 2017). As a result of this impaired brain development during gestation, the head circumferences of newborns with CHD are reduced (Matthiesen et al., 2016). Studies showed that significant reductions in the total brain volume, white matter and cortical grey matter, compared to healthy controls, are responsible for this smaller circumferences (Claessens et al., 2017; Sun et al., 2015; von Rhein et al., 2015). A greater deviation in the total brain volume in CHD with advancing gestation could also be shown by Limperopoulos et al. (2010). The same authors also found an association between a reduced blood flow through the systemic ventricle, leading to a lower ventricular cardiac output, and to a smaller total brain volume. This relation is quite evident in transposition of the great arteries. Unsurprisingly, Sun et al. (2015) were able to show that a reduced oxygen supply is also associated with a smaller total brain volume. Reduced volumes of the basal ganglia and the thalami have been shown in univentricular pathologies and transposition of the great arteries in fetuses and neonates compared to healthy controls (Clouchoux et al., 2013). In addition, the cerebellum also shows a smaller postnatal volume in these CHD patients when compared to healthy controls of the same maturity (von Rhein et al., 2015). Prenatal studies on total cortical grey and white matter volume in CHD are rare. However, in fetuses with tetralogy of Fallot, there is evidence that cortical grey and white matter are reduced by at least 10 % by the 30th week of gestation (Schellen et al., 2015). Research suggests that newborns with CHD have a significantly retarded brain maturation (Marelli et al., 2016; Miller et al., 2007). Particularly the third trimester

is considered a critical period in the maturation of the fetal brain, as axons connect, synapses are formed, and cortical networks develop (Marelli et al., 2016). As the cortex shows the greatest relative increase in growth in the later gestation, it may be more affected than other brain structures (Claessens et al., 2017). An important measure of the brain maturation is the degree of cortical folding, known as gyrification, which starts in the later stages of the gestation. Less complex folding (reduced depth or delayed occurrence) has been demonstrated in fetuses with complex CHD, as in hypoplastic left heart syndrome at 30 weeks of gestation (Clouchoux et al., 2013) and in newborns with other univentricular pathologies (Claessens et al., 2016; Clouchoux et al., 2013), compared to heart-healthy fetuses. In contrast, the cortical folding of newborns with transposition of the great arteries seems to be comparable to that of healthy controls (Claessens et al., 2016). A new field of research now aims at developing in utero interventions to prevent brain dysmaturation (Marelli et al., 2016).

In addition to these macrostructural alterations, studies with diffusion tensor imaging also demonstrated modifications at a microstructural level. Several studies showed lower fractional anisotropy values in some CHD (pre neonatal surgery), e.g., in univentricular pathology and transposition of the great arteries, compared to healthy controls throughout the brain (e.g., Hagmann et al., 2016; Miller et al., 2007). In one of the few studies conducted on the impact of microstructural anomalies, an association between low fractional anisotropy values and altered neuronal functional connectivity has been demonstrated by Birca et al., (2016) using electroencephalography, which showed the relevance of unimpaired fetal and neonatal brain development.

Given the fact that fetuses with a CHD show these neuroanatomical abnormalities, it is hardly surprising that these individuals also suffer a wide range of acquired brain injuries. As neonates with brain injuries often do not exhibit clinically evident symptoms, neuroimaging is very important in this young patient group. Frequently acquired brain injuries in newborns with CHD are of ischemic origin. Focal thromboembolic strokes or microhemorrhages are mostly observed after heart surgery (Claessens et al., 2017; Marelli et al., 2016). Therefore, surgeries are often followed by further complications like hypoxia and/or seizures (Keir et al., 2019). Patients with cyanotic CHDs are at the highest risk of experiencing focal infarction (Marelli et al., 2016).

White matter lesions are also reported frequently in neonates with CHD and are associated with lower blood pressure (Claessens et al., 2017; Miller et al., 2007). Some research even suggest that white matter lesions in particular are a characteristic pattern in newborns with CHD (e.g., Marelli et al., 2016). Furthermore, a longer time span between the birth and a heart surgery is associated with a higher risk for acquired brain injuries (Lynch et al., 2014).

There is evidence suggesting that a wide spectrum of acquired structural brain alterations also exist in adolescents and young adults with CHD. In addition, these acquired brain injuries in CHD are reportedly associated with neurodevelopmental outcomes (e.g., von Rhein et al., 2014). These are discussed in more detail in the following chapter.

2.4 Neurocognitive functioning of children, adolescents, and adults with congenital heart disease

Brains of fetuses and newborns with CHD can show structural and functional abnormalities. Such abnormalities can have a strong impact on neurocognitive functioning. But, neurocognitive deficits in CHD are of complex etiology. White matter injuries and smaller postnatal brain volumes are associated with adverse neurodevelopment (Claessens et al., 2018; Owen et al., 2014). Studies have shown that children with CHD have lower intelligence quotients (IQ) compared to the average population (Cassidy et al., 2015; Karsdorp et al., 2006). There is not only a general consensus that children with CHD are at an increased risk of neurocognitive impairments, but that their neurocognitive performance is poorer compared to average population. A domain which is typically affected is motor functioning. As normative data shows, motor skills of CHD patients are worse compared to infants and children at school age without a CHD (Bellinger & Newburger, 2010; Newburger et al., 2012). Furthermore, impairments in visual-spatial skills are common as well, as are difficulties in social cognition. Theory of Mind and complex emotion comprehension seem to be mainly impaired (Bellinger et al., 2011; Calderon et al., 2010; Marelli et al., 2016). In addition, language deficits are reported to be impaired, especially in higher-order language skills, such as narrative or pragmatic speech (Bellinger et al., 2003). Additionally, affected children have a higher risk of suffering from attention-deficit-/hyperactivity-disorders and related symptoms

(Bellinger et al., 2015; Calderon & Bellinger, 2015). In a population of patients with severe CHD, the proportion of patients with diagnosed attention-deficit-/hyperactivity-disorders is reported to be three to four times higher than in the general population (Marelli et al., 2016). However, the most affected area seems to be the domain of executive functions. Many studies have shown lower executive functioning in children with CHD in a wide range of subdomains such as working memory, planning abilities and organizational skills, cognitive flexibility and inhibition, error control, sustained attention and self-regulation (Bellinger et al., 2003; Bellinger et al., 2011; Bellinger et al., 2015; Calderon et al., 2010). These deficits explain the higher need for supportive services such as remedial academic or behavioral coaching in this population (Marelli et al., 2016). For this reason and to tailor interventions and therapies, it is important to know about the backgrounds of neurocognitive dysfunctions in children with CHD.

Although the introduced impairments are well known now and several interventional treatments have been established, only few studies have examined their progression into adulthood. What is known so far is that adolescents with CHD continue to show lower IQs than their peers, although their IQs are mostly in the normal range (Bellinger et al., 2011; Calderon & Bellinger, 2015). This was also confirmed in studies with ACHD patients (Eide et al., 2006; Tyagi et al., 2014; Utens et al., 1998). Also, disabilities in psychomotor skills, attention, and processing speed, as well as executive dysfunctions seem to persist beyond childhood (Klouda et al., 2017; Mills et al., 2018; Tyagi et al., 2014). Working memory, flexibility, inhibition, problem-solving, and action planning are considered to be particularly affected (Bellinger et al., 2011; Calderon & Bellinger, 2015; Daliento et al., 2005; Ilardi et al., 2017; Kasmi et al., 2018; Klouda et al., 2017; Mills et al., 2018). Contrarily, impairments in other domains seem to evolve only with the transposition into adulthood. There is evidence that adolescents and young adults with CHD have learning difficulties and memory problems, whereas impairments in these areas in children are barely described (Keir et al., 2019). As a group, ACHD patients often achieve a lower educational level, have a lower income and are more frequently unemployed (Zomer et al., 2012). In general, patients with a CHD are also at a higher risk for psychiatric comorbidities, especially mood dis-

orders such as depressions and anxieties (Daliento et al., 2005; DeMaso et al., 2014). Additionally, behavior difficulties, attention-deficit-/hyperactivity-disorders, autism spectrum disorders as well as inappropriate risk-taking behaviors are more frequently reported in CHD patients (Bellinger et al., 2011; Calderon & Bellinger, 2015; Claessens et al., 2017; Liamlahi et al., 2014).

Some studies have shown an association between the CHD complexity and the severity of neurocognitive impairments. Accordingly, neurocognitive dysfunctions are more frequent and more pronounced with greater CHD complexity. The most affected patients are patients with a univentricular heart defect such as the hypoplastic left heart syndrome (Bellinger et al., 2015; DeMaso et al., 2014; Ilardi et al., 2017; Kasmi et al., 2018; Klouda et al., 2017; Marelli et al., 2016; Mills et al., 2018).

3 Aims of this thesis

The overriding aim of the present thesis is to contribute to a better understanding of the impact of CHD on neurocognition in young adults. The rationale for this main motive has its foundation in previous research which investigated neurocognition in children and adolescents suffering from a CHD. As this is – owing to medical advantages – a steadily growing and aging population, neurocognitive functioning of affected young adults still show an incomplete and inconsistent image. Neurocognitive well-functioning is essential for being a part of our achievement- and competition-oriented society. Developing a better understanding of the neurocognitive functioning in this population allows to establish new preventive and therapeutic approaches. Examining the neuronal underpinnings of the anatomical structures responsible for neurocognitive functioning in ACHD is therefore essential.

After a review of the existing literature in this research field, some research gaps were identified. Although this field of research has received great attention in recent years, studies investigating the neurocognition in ACHD patients are limited in their scope and many questions remain open. Comprehensive studies are missing. More precisely, to our knowledge, no study examining (1) a full spectrum of neurocognition in (2) a sample with many different types of CHD has ever been performed. Despite executive dysfunctions in (A)CHD having been identified and being known to have devastating effects in a patients' everyday life, studies investigating neurocognitive domains other than executive functions such as memory and attention skills are rare. Moreover, the neuroanatomical pathways of neurocognitive dysfunctions in ACHD are barely described. Finally, the Mental Dice Task (MDT), a test providing information on the human random number generation (RNG) performance and a subtle measure of executive function (Brugger et al., 1996), has never been applied in ACHD patients. Likewise, the neuroanatomical correlates of randomization performance have remained unexplored in this patient population. Based on these research gaps, the following questions arose:

1. Do ACHD patients have a lower IQ and poorer neurocognition compared to healthy control participants, and which neurocognitive domains are particularly affected in ACHD?
2. Are there structural differences in the brain between ACHD patients and healthy control participants? If yes, are these differences associated with general intellectual functioning as reflected by the IQ?
3. Does the randomization performance in ACHD differ from that of healthy control participants? If yes, what are the neuroanatomical correlates of randomization performance?

This thesis, which comprises a cross-sectional cohort study design, includes three studies (described in Chapter 5), tries to give answers to the three research questions mentioned above. The first study investigated differences in the neurocognitive profiles between ACHD patients and healthy controls participants. The second study focused on differences in IQ and (macro)structural brain abnormalities. The third study aimed at evaluating the value of one distinct procedure, RNG, for differentiating ACHD patients and healthy control participants. The neuroanatomical correlations of randomization behavior should also be elucidated.

4 General methods

This chapter presents the methods used in the three studies included in this thesis. While this chapter provides a general overview, more specific methodological steps of the respective studies are discussed in the empirical part of this thesis (Chapter 5).

4.1 Recruitment and participants

All samples of the three studies involve the same individuals. Sixty-eight patients with a diagnosed CHD were recruited at the outpatient cardiac clinic of the University Hospital Zurich. Cardiac diagnoses included different types of CHD and different CHD complexities, the latter ranging from simple (e.g., isolated congenital aortic valve disease) to moderate (e.g., tetralogy of Fallot) and severe (e.g., transposition of the great arteries). One patient was later excluded from further analyses because the definite cardiac diagnose (cardiomyopathy) is not categorized as a CHD. Additionally, 55 age-, gender-, and socio-economic status (SES)-matched healthy control participants without a cardiac history were included. Control participants were recruited as peers of the CHD patients or through personal contacts of the study team and provided information about their physical and mental health status, established by questionnaire. All study participants had to comply to the following requirements: native German speaker, aged between 18 and 32 years, and absence of congenital or acquired neurological disorder or genetic syndrome affecting the intellectual development. The neuropsychological examination took place at the Neuropsychology Unit of the University Hospital Zurich. The brain magnetic resonance imaging (MRI) was performed at the Children's University Hospital Zurich. The examination of one participant took approximately three hours. Control participants received a financial compensation for their participation. Table 4.1 provides an overview of the two groups.

Table 4.1. Characteristics of the CHD and the control group.

	CHD group	Control group	t	χ^2	p
N	67	55			
Age	M = 26.92	M = 26.04	1.364		.175
	SD = 3.68	SD = 3.32			
	Range = 19.16 - 32.67	Range = 19.86 - 32.56			
Sex				.226	.635
female	30 (44.78 %)	27 (49.09 %)			
male	37 (55.22 %)	28 (50.91 %)			
Nationality				.352	.553
Swiss	63 (94.03 %)	53 (94.36 %)			
other	4 (5.97 %)	2 (5.64 %)			
SES	8[a] / (7.75; 10)[b]	9[a] (8; 10)[b]	-1.346		.181

[a] Median. [b] Interquartile range. SES: Socio-economic status, ranges from 2 (lowest) to 12 (highest) and reflects parental education. T-test are two-tailed.

4.2 Neurocognitive assessment

For each participant, neurocognitive performance was examined with an extensive battery of neuropsychological tests, assessing a wide range of domains such as attention and processing speed, memory, executive functions, visuospatial and motor functions, and general intellectual functioning. The test selection was based on test procedures widely used in clinical practice. All tests, apart from the behavioral randomization test (MDT), were standardized and normative data was available. In addition, a published questionnaire was used to survey self-reported executive dysfunctions in an adult's everyday behavior. Table 4.2 gives an overview of the neuropsychological tests and the questionnaire used.

Table 4.2. Neuropsychological tests and the questionnaire applied in the neurocognitive assessment.

Neurocognitive function	Neuropsychological test	Norm. N =	Reference
	Attentional functions and processing speed		
Divided attention	Tests of Attentional Performance, divided attention	808	Zimmermann & Fimm, 2007
Visual-verbal information processing speed	Delis-Kaplan Executive Function System, color naming condition	1750	Delis et al., 2001
Graphomotor information processing speed	Trail Making Test, number connecting condition	911	Tombaugh, 2004
	Learning and memory		
Verbal learning	Auditory Verbal Learning and Memory Test, total of five learning trials	500	Helmstaedter et al., 2001
Verbal recall	Auditory Verbal Learning and Memory Test, short and long delay recall	500	Helmstaedter et al., 2001
Verbal recognition	Auditory Verbal Learning and Memory Test	500	Helmstaedter et al., 2001
Visual learning	Brief Visuospatial Memory Test-Revised, total of three learning trials	456	Benedict, 1997
Visual recall	Brief Visuospatial Memory Test-Revised, long delay recall	456	Benedict, 1997
Visual recognition	Brief Visuospatial Memory Test-Revised	456	Benedict, 1997
Verbal memory span	Wechsler Adults Intelligence Scale, verbal span forward condition		Tewes et al., 2006
Visual memory span	Wechsler Memory Scale - Revised, visual span forward condition	201	Härting et al., 2000
	Executive functions		
Visual-verbal interference control	Delis-Kaplan Executive Function System, color-word interference condition	1750	Delis et al., 2001
Visual-verbal flexibility	Delis-Kaplan Executive Function System, color-word shifting condition	1750	Delis et al., 2001
Verbal fluency	Regensburger verbal fluency test	634	Aschenbrenner et al., 2000
Design fluency	HAMASCH-5-point test	184	Haid et al., 2000
Graphomotor flexibility	Trail Making Test, number and letter connecting condition	911	Tombaugh, 2004
Verbal working memory	Wechsler Adults Intelligence Scale, verbal span backward condition	1897	Tewes et al., 2006
Visual working memory	Wechsler Memory Scale - Revised, visual span backward condition	201	Härting et al., 2000
Constructive solution behavior	Standardized Link's Probe	220	Metzler, 2000
Response inhibition	Stop-Signal-Task	N/A	Logan, 1994
Randomization performance	Mental Dice Task	N/A	
	Visuoconstructive functions		
Visuospatial & -constructive skills	REY Complex Figure Test, copy condition	601	Meyers & Meyers, 1995
	Motor functions		
Neuromotor skills	Zurich Neuromotor Assessment	662	Largo et al., 2007
	Cognitive reserve		
Crystallized intelligence	Wechsler Adults Intelligence Scale – Fourth Edition, vocabulary subtest	1650	Petermann, 2012
Fluid intelligence	Wechsler Adults Intelligence Scale – Fourth Edition, matrix reasoning subtest	1650	Petermann, 2012
	Questionnaire		
Self-reported executive dysfunction	Behavior Rating Inventory of Executive Function – Adult Version	1136	Roth & Gioia, 2005

4.3 MR Imaging

Supervised by experienced medical technicians, a brain MRI on a 3 Tesla MR scanner (Signa MR750, GE Healthcare, Milwaukee, WI) was performed. The following sequences were scanned: High-resolution T1-weighted 3D spoiled gradient echo (axial SPGR) pulse sequence, T2-weighted sagittal fast spin-echo pulse sequence (sagittal Cube), susceptibility-weighted sequence SWI (axial SWAN), and T2-weighted 3D fast spin-echo sequence (sagittal ASL). An experienced neuroradiologist, who was blinded to the group assignment (CHD patient versus control partici

pants), evaluated the MRI images. To evaluate structural brain abnormalities, MRI data were classified by Nora Kessler, the co-author, into four categories, namely abnormal global brain cerebral atrophy, white matter lesions, focal infarction or focal atrophy, and microhemorrhages. The classification followed the methodology of Bellinger et al. (2011) and Bolduc et al. (2018). The co-author, Nadja Naef, processed the cortical reconstruction and the volumetric segmentation with the Freesurfer image analysis suite version 5.3.0, a freely program available online.

5 Empirical part

This chapter introduces three publications. I figure as first author in the studies 1 (Schlosser et al., 2021) and 3 (Schlosser et al., 2023). In the study 2 (Kessler et al., 2020), I figure as co-author.

Study 1

Neurocognitive functioning in young adults with congenital heart disease: Insights from a case-control study

Study 2

Structural brain abnormalities in adults with congenital heart disease: Prevalence and association with estimated intelligence quotient

Study 3

Counting on random number generation: Uncovering mild executive dysfunction in congenital heart disease

5.1 Study 1

Neurocognitive functioning in young adults with congenital heart disease:

Insights from a case-control study

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Conflicts of interest
None.

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards approved by the ethics committee of the Canton of Zurich and all the participants gave written informed consent prior to participation, in accordance with the Declaration of Helsinki.

5.1.1 Abstract

Background: While there is evidence that cognitive impairment of children with congenital heart disease (CHD) may persist into adolescence, little is known about the spectrum of neurocognitive functioning of young adults with this disorder. The aim of this study was to assess neurocognitive functioning in a population of young adults with different types of CHD.

Methods: Cross-sectional cohort study in young adults with CHD and a group-matched healthy control group. We assessed neurocognitive and general intellectual functioning with a comprehensive battery of standardized neuropsychological tests. In addition to task-based assessments, questionnaire data of executive dysfunctions in everyday life were measured with the Behavior Rating Inventory of Executive Function – Adult Version.

Results: A total of 67 patients (55 % men) with CHD and 55 healthy controls (51 % men) were included for analysis. Mean age at assessment was 26.9 (3.68) and 26.0 (3.32) years, respectively. The CHD group performed poorer in the domains of Executive Functions, Memory, Attention & Speed, and general intellectual functioning. Patients with a CHD of severe complexity were more affected than patients with simple or moderate complexity. Behavior Rating Inventory of Executive Function – Adult Version scores indicated that patients' self-rated deficits in behavior regulation in everyday life was higher compared with healthy controls.

Conclusion: Our findings indicate lower neurocognitive functioning in young adults with a CHD, particularly in those with severe defect complexity. In view of the potentially enhanced risk for cerebrovascular and neurodegenerative disease in this patient group as reported in the literature, systematic longitudinal monitoring of neurocognitive functioning is recommended.

5.1.2 Introduction

Congenital heart disease affects about one percent of all newborns and comprises one third of all congenital anomalies (van der Linde et al., 2011). With the advent of open-heart surgery and contemporary cardiology care, the majority of patients survive to adulthood, leading to rapidly growing cohorts of young adults with CHD (Marelli et al., 2016; Moons et al., 2010). Even with

optimal care, these patients are not cured, but remain at increased risk of elevated morbidity and mortality (Diller et al., 2015; Greutmann et al., 2015).

Studies in infants and children with CHD found an increased risk of altered brain development, perioperative brain injury (Claessens et al., 2017) and neurodevelopment disorders including social interaction difficulties, language disorders, inattentive and impulsive behavior, as well as motor and visual-motor difficulties and cognitive dysfunctions such as problems in executive functioning (Calderon & Bellinger, 2015; Liamlahi et al., 2014; Tyagi et al., 2014). These neuropsychological deficits can restrict educational achievements, employability, and quality of life (Bellinger et al., 2009). Although there are indications that impairments may persist into adolescence (Bellinger & Newburger, 2010; Mills et al., 2018; von Rhein et al., 2011), only few studies have examined whether neurocognitive functioning is also affected in young adults with CHD (Daliento, 2005; Eide et al., 2006; Utens et al., 1998; Utens et al., 1994). A recent meta-analysis (Mills et al., 2018) emphasized general negative effects of a CHD on cognitive outcomes such as executive functioning, processing speed, attention, memory, psychomotor abilities, and literacy and numeracy. In a recent comprehensive review (Keir et al., 2019), the authors concluded that " (…) attention and executive functions are the most commonly affected areas of cognitive performance" (p. 1679).

The current study set out to assess the full spectrum of neurocognitive functioning including general intellectual and executive function, memory, attention, and processing speed in a population of young adults with different types of CHD. Based on previous research, we hypothesize that executive function, attention, and processing speed may be particularly affected. Moreover, we predict that the complexity of CHD is associated with the degree of impairment.

5.1.3 Methods

5.1.3.1 Study design and population

Patients were recruited from previous study cohorts on quality of life in young adults with CHD (Rometsch et al., 2019; von Rhein et al., 2011). Of 191 eligible patients contacted by letter, phone, or E-mail, 68 (36 %) agreed to participate. Non-participants did either not respond to our request (n = 59, 31 %) or refused participation (n = 64, 33 %). All patients were fluent in German language and had no congenital or acquired neurological disorder or a genetic syndrome affecting intellectual development. One patient had to be excluded after being tested because the cardiac diagnosis (cardiomyopathy) did not represent a CHD. Thus, the final sample comprised 67 patients with different types of CHD. See Table 5.4 for a detailed list.

The participants of the control group consisted of healthy peers of the patients (n = 41, 75 %) or were recruited from personal contacts of the study team (n = 14, 25 %). Peers of patients included friends, classmates, and siblings. All healthy controls (n = 55) were group-matched to the CHD group for gender, age, and parental education (i.e., socio-economic status), as carefully as possible. Sample characteristics are reported in Table 5.1.

The recruitment of this cross-sectional cohort study took place between October 2016 and October 2018. All participants underwent a standardized neuropsychological examination. The neuropsychological assessment took place at the Neuropsychology Unit of the University Hospital Zurich. The duration of the whole examination was approximately 3 hours. The study was approved by the Ethical Committee of the Canton of Zurich, Switzerland, and written informed consent was obtained from all study participants.

Table 5.1. Sample characteristics.

Variable	CHD group, n = 67	Control group, n = 55	Group differences (p-value)[a]
Age (years)	26.92 (3.68)	26.04 (3.32)	0.175
Sex (male), n (%)	37 (55.22)	28 (50.91)	0.635
Nationality (Swiss), n (%)	63 (94.03)	53 (96.36)	0.553
Parental SES (median/IQR)	8 / (7.75; 10)[b]	9 / (8; 10)[c]	0.181

[a] P-values are two-tailed. [b] n = 51. [c] n = 51. IQR: Interquartile range. SES: Socioeconomic status range from 2 (lowest) to 12 (highest) and reflects parental education.

5.1.3.2 Neurocognitive assessment

All participants completed a questionnaire collecting data on demographic, socio-economic, and medical conditions. Parental SES was estimated using a six-point scale based on the mean of maternal and paternal education (Largo et al., 1989). Possible SES values ranged from 2 (lowest) to 12 (highest). Educational level of the patients was measured by the number of years of school attendance until completion of an initial education with a higher value representing a higher education. Patients medical data were retrieved from medical records, and CHD complexity was classified into simple, moderate, and severe according to Warnes et al. (2001).

Language-associated, visual, and practical functions were tested with clinical screenings (Schnider, 2004). We tested neuropsychological outcome with a wide range of standardized neuropsychological procedures. IQ was assessed using the short form of the Wechsler Adults Intelligence Scale, Fourth Edition (Petermann, 2012). This short form consists of the vocabulary and the matrix reasoning subtests and has been validated as estimating the full-scale IQ (Daseking et al., 2014). Verbal memory functions were assessed with the German version of the Auditory Verbal Learning and Memory Test (Helmstaedter et al., 2001). We used total words correctly recalled after the first trial, total learning over five repetitions, number of correct short- and long-term recalled words, and corrected recognition as outcome measures. Visual memory was assessed with the Brief Visuospatial Memory Test-Revised (Benedict, 1997). As for verbal memory, we used total learned figures after the first exposure, total learning as well as long-term retrieval and corrected recognition as outcome measures. We tested attention and speed with the divided attention subtest (reaction time to visual and auditory presented stimuli) of the Test of Attentional Performance (Zimmermann & Fimm, 2007) and numbers subtest of the Trail Making Test (Tombaugh, 2004), which provides information on the graphomotor processing speed (completion time connecting numbers). Visual motor and visual perceptive skills were assessed with the Rey Complex Figure Test (Meyers & Meyers, 1995). We used total completion time and the scored points as outcome variables. We evaluated executive functions using verbal (Regensburger Wortflüssigkeits-Test) (Aschenbrenner et al., 2000) and non-verbal (Five-Point-Test) (Haid et al., 2000) fluency tasks, and used correct words or figures produced as outcome measure. The Color-

Word Interference Test from the Delis–Kaplan Executive Function System (Delis et al., 2001) provides information on processing speed, interference, and cognitive flexibility by completion time on each trial. The numbers and letters subtest from the Trail Making Test (Tombaugh, 2004) provides information on graphomotor flexibility (completion time connecting numbers and letters). Furthermore, we applied the digit span task (longest forward and backward span) from the Wechsler Adult Intelligence Scale (Tewes et al., 2006) to assess verbal working memory. Visual working memory was assessed with the Wechsler Memory Scale (Härting et al., 2000) (longest forward and backward span). We used total scored points of the "Standardized Link's Probe" (Metzler, 2000) to asses constructive solution behavior. The global score of the Stop Signal Task (Verbruggen et al., 2008) was used to measure response inhibition. All scores were compared against the normative values of the respective test manuals. The resulting t-scores were used for subsequent analysis, whereby values t = 50 +/− 10 represents normal range.

In addition to these task-based neuropsychological procedures, participants had to complete the German version of the Behavior Rating Inventory of Executive Function – Adult Version (Roth & Gioia, 2005). This is a 75-items clinical questionnaire capturing self-reported executive dysfunctions in adult's everyday behavior. The Behavior Rating Inventory of Executive Function – Adult Version provides a Global Executive Composite and two index scores. The Behavioral Regulation Index (e.g., "I tap my fingers or bounce my legs," "I have angry outburst") reflects the ability to maintain regulatory control of one's behavior and emotional responses and is composed of the Inhibit, Shift, Emotional Control, and Self-Monitor subscales. The Metacognition Index (e.g., "I need to be reminded to begin a task even when I am willing," "I get overwhelmed by large tasks") captures the individual's ability to initiate activity and generate and plan problem-solving ideas, to sustain working memory and to organize the required material and environment. It is composed of the subscales Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials. Behavior Rating Inventory of Executive Function – Adult Version questionnaires of three patients had to be excluded due to incomplete answers. We also excluded data of one control subject because of a strong outlier (> 1 SD of the mean of the control group).

This resulted in a sample of n = 95 completed self-reported Behavior Rating Inventory of Executive Function – Adult Version data (n = 49 CHD group; n = 46 control group).

5.1.3.3 Statistical analyses

To examine differences in demographic variables and individual tests between the CHD and the control group, we applied t-tests for independent samples. Furthermore, we used Pearson Chi-Square to analyze group differences in frequencies. To correct for multiple testing, False Discovery Rate was used to calculate the adjusted p-values (Benjamini–Hochberg Method) (Benjamini & Hochberg, 1995). To describe the extent of the group differences, we calculated effect sizes using Cohen's d. Whereas d = 0.2 reflects small, d = 0.5 reflects moderate, and d = 0.8 reflects strong effects (Cohen, 1988). Effects of d > 0.42 assumed to be as clinical relevant (Ferguson, 2016). The individual tests were summarized into the global scores Executive Function, Memory, and Attention & Speed for further analysis (see Table 5.2). T-scores of all individual tests were averaged across all tasks of each global score. To analyze group differences of the global scores and the Behavior Rating Inventory of Executive Function indices between the CHD and the control group or between the CHD complexities and the control group, analyses of variances with Tukey's post-test were calculated. P-values < 0.05 (two-tailed) were considered significant. We used IBM SPSS 25 statistical software for Windows.

5.1.4 Results

5.1.4.1 Group characteristics

Comparison of baseline characteristics of the participating and non-participating patients revealed no significant difference (see Table 5.5). The final sample consisted of 67 young adults with CHD and 55 gender-, age-, and parental-SES-matched healthy controls (see Table 5.1 for demographic variables). The control group (M = 15.06, SD = 1.89) had more education than the CHD group (Mean = 14.18, SD = 2.07) (t (120) = -2.414, p = 0.017). Eighteen patients (27 %) had a simple, 33 (49 %) a moderate, and 16 (24 %) a severe CHD. Gender was equally distributed between

patients with simple, moderate, and severe complexity, and there was no difference in parental SES between the groups. However, there were significant educational differences between patients with severe CHD (Mean = 12.84; SD = 1.48) and moderate CHD (Mean = 14.67; SD = 2.13) on the one hand, and the control group (Mean = 15.06; SD = 1.89) on the other hand (both $p < 0.05$). Thirty-nine patients (58 %) had undergone at least one surgical repair procedure on cardiopulmonary bypass (heart–lung machine) and nine patients (13 %) two or more cardiopulmonary bypass surgeries.

5.1.4.2 Neurocognitive findings

For all patients, language, language-associated, visual, and practical performance was unaffected. Table 5.2 summarizes the findings of the neuropsychological outcomes. Mean estimated IQ was significantly lower in the CHD than in the control group. Also, the CHD group showed a lower performance in visual memory (total learned figures after the first exposure and after three trials), verbal working memory (forward and backward span), divided attention (auditory reaction time), processing speed (color naming, connecting numbers), and visual-verbal interference inhibition. After correction for multiple testing, effects for visual first encoding, visual learning, and interference control remained significant. Effect sizes were small to medium for most tasks. Although T-scores were in the normal range, the rate of patients who performed more than 1 standard deviation (SD) below the comparison mean (i.e., range for clinically relevant impairments) was higher in the CHD group than in the control group (short-term verbal recall 16.7 % versus 3.6 %, $p = 0.021$; total visual learning 23.9 % versus 3.6 %, $p = 0.002$; long term visual recall 11.9 % versus 1.8 % $p = 0.033$; estimated IQ 12.3 % versus 1.8 %, $p = 0.038$).

Table 5.2. Neuropsychological test performance of the CHD and control group and assignment of all tests to the corresponding global score. If not otherwise stated, mean T-scores and SDs are reported.

			CHD group n = 67	Control group n = 55	Group differences (p-value[a] / adj. p-value after FDR)	Effect size (Cohen's d)
Executive function						
CWIT	interference	completion time	51.48 (8.10)	56.10 (6.78)	0.001** /0 .013*	0.613
	flexibility	completion time	52.72 (7.03)	55.11 (6.91)	0.062 / 0.129	0.343
RWT	S-Words	correct words	46.15 (8.56)	47.82 (4.77)	0.291 / 0.393	0.235
5-point test		correct figures	55.48 (7.50)	57.53 (5.04)	0.075 / 0.134	0.315
TMT	numbers and letters	completion time	49.02 (12.52)	52.78 (9.30)	0.059 / 0.134	0.336
WIE	verbal WM	longest span fw and bw	51.00 (8.99)	54.79 (9.00)	0.022* / 0.110	0.421
WMS-R	visual WM	longest span fw and bw	50.36 (8.13)	50.67 (7.01)	0.822 / 0.856	0.041
SLP		total score	47.79 (14.67)[b]	50.32 (11.73)	0.306 / 0.383	0.189
SST		total score	46.47 (6.22)[b]	45.96 (11.12)	0.753 / 0.856	0.058
Memory						
VLMT	total learning	number of correct items	54.02 (7.63)[b]	55.60 (5.76)	0.196/ 0.288	0.231
	short term recall	number of correct items	49.10 (10.06)[b]	51.42 (7.03)	0.138 / 0.216	0.263
	long term recall	number of correct items	57.24 (8.30)[b]	58.53 (1.48)	0.221 / 0.307	0.208
	recognition	number of correct items	52.47 (9.47)[b]	55.25 (5.77)	0.050 / 0.139	0.347
BVMT-R	total learning	number of correct items	48.34 (12.01)	54.84 (7.45)	0.000** / 0.000**	0.636
	long term recall	number of correct items	47.78 (6.76)	49.51 (3.64)	0.074 / 0.142	0.310
	recognition	number of correct items	48.77 (4.35)	49.02 (4.18)	0.756 / 0.822	0.058
Attention & Speed						
TAP	auditory response	mean reaction time	41.08 (7.52)[b]	44.42 (8.42)	0.023* / 0.096	0.421
	visual response	mean reaction time	47.82 (7.07)[b]	50.40 (7.44)	0.053 / 0.133	0.356
CWIT	color naming	completion time	50.20 (6.73)	52.67 (6.70)	0.045* / 0.141	0.368
TMT	numbers	completion time	50.34 (9.63)	53.87 (7.85)	0.031* / 0.111	0.398
Tests not assigned to a global score						
WAIS-IV	estimated IQ	total score	98.51 (11.21)[c]	104.38 (12.09)	0.007* / 0.044*	0.505
VLMT	first encoding	number of correct items	8.13 (2.17)[d]	8.15 (2.06)[d]	0.977 /0.977	0.009
BVMT-R	first encoding	number of correct items	6.40 (2.45)[d]	7.73 (2.19)[d]	0.002* / 0.017*	0.569
RCFT	copy	total score	44.33 (10.48)	47.10 (7.86)	0.099 / 0.165	0.295
	time	completion time	48.81 (5.65)	48.33 (6.07)	0.659 / 0.785	0.082

[a] P-values are two-tailed. [b] sample size n = 66. [c] sample size n = 65. [d] number of correct words / figures recalled after the first trial, reported are raw scores since no T-scores exist for these variables. Global scores consist of the averaged T-scores. BVMT-R: Brief Visuospatial Memory Test-Revised; CWIT: Color-Word; FDR: False discovery rate; Interference Test; IQ: Intelligence quotient; RCFT: REY Complex Figure Test; RWT: Regensburger Wortflüssigkeits-Test; SLP: Standardized Link's Probe; SST: Stop-Signal-Task; TAP: Test of Attentional Performance; TMT: Trail Making Test; VLMT: Verbal Learning and Memory Test; WIE: Wechsler Intelligenztest für Erwachsene; WM: Working memory (fw: forward, bw: backward); WMS-R: Wechsler Memory Scale. Effect size d = .02 (small), .05 (medium), .8 (strong); d > .42 as cut-off for clinical relevance. * p < .05. ** p < .001

To analyze whether the CHD group differed from the control group in the three global scores and the Behavior Rating Inventory of Executive Function indices, analyses of variance were calculated. Mean T-scores of all global scores and the Behavior Rating Inventory of Executive Function indices are summarized in Table 5.3, and Figures 5.1 and 5.2 present a graphical overview of the data. We found significant group differences for global Executive Function ($F(1) = 5.713$, $p = 0.018$), Memory ($F(1) = 10.569$, $p = 0.001$), and Attention & Speed ($F(1) = 9.945$, $p = 0.002$) between the CHD and the control group. For the Behavior Rating Inventory of Executive Function indices, we found significant group differences only for the Behavior Regulation Index ($F(1) = 5.015$, $p = 0.027$), with the CHD group scoring higher, indicating higher self-reported executive function impairments in this domain of everyday behavior. There were no group differences for Global Executive Composite ($F(1) = 2.873$, $p = 0.093$) and Metacognition Index ($F(1) = 0.898$, $p = 0.346$).

Overall, scores were within the normal range for both groups. However, five patients (2.45 %) and one control participant (0.46 %) reached clinically relevant values of > 65 (Global Executive Composite: two patients versus no control; Behavior Regulation Index: three patients versus no control; Metacognition Index: two patients versus one control).

Table 5.3. Results of the computed global scores and the BRIEF indices in mean T-scores and SD for the CHD group including different complexities and the control group.

	Global scores				BRIEF indices			
	n	Executive Function	Memory	Attention & Speed	n	GEC	BRI	MI
Control group	55	52.43 (4.09)[a]	53.79 (3.16)	50.34 (5.58)	49	46.12 (6.56)	45.53 (6.64)	47.14 (6.95)
CHD group	66	50.26 (5.50)[b]	51.43 (4.54)	47.42 (4.61)	50	48.60 (7.91)	48.86 (8.07)	48.62 (8.45)
simple	18	50.04 (4.30)[c]	50.67 (4.72)	48.24 (3.74)	13	46.77 (7.28)	47.46 (8.55)	46.62 (7.59)
moderate	33	51.47 (5.77)	52.76 (4.40)	47.81 (5.13)	27	49.48 (7.97)	49.52 (7.55)	49.67 (8.67)
severe	15	47.87 (5.63)	49.44 (3.88)	45.58 (4.09)	10	48.60 (8.91)	48.90 (9.40)	48.40 (9.35)

[a] n = 54. [b] n = 65. [c] n = 17. BRI: Behavior Regulation Index. GEC: Global Executive Composite. MI: Metacognition Index. For the BRIEF indices, higher scores correspond to poorer self-reported executive functions.

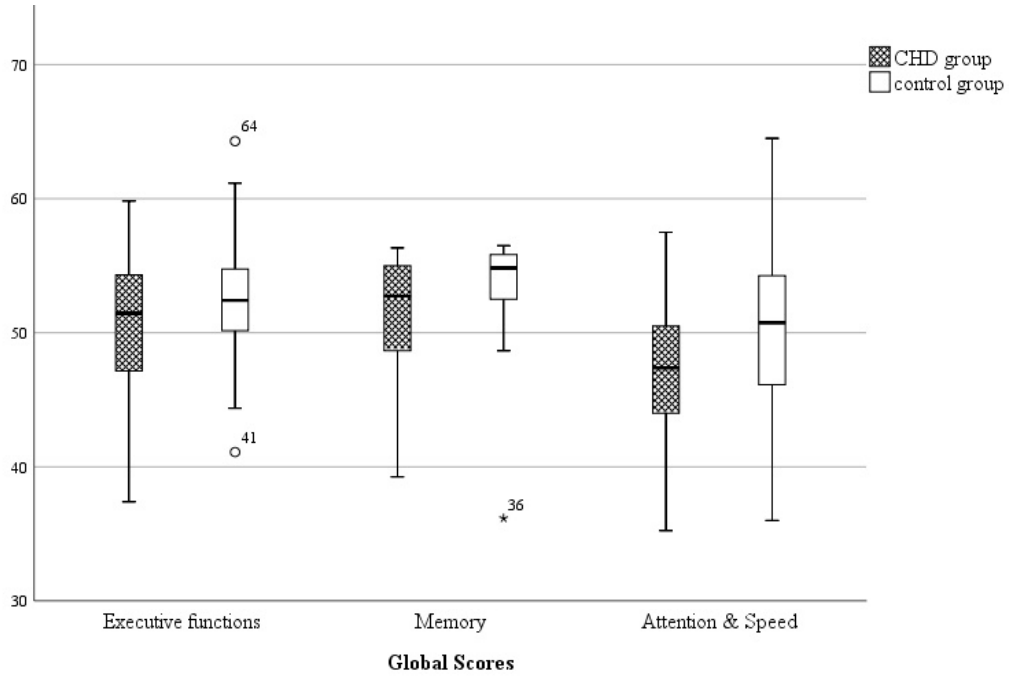

Figure 5.1. Global scores comparison for the CHD and the control group. ° indicates a mild outlier (> 1.5 x IQR), * indicates an extreme outlier (> 3 x IQR). Y-axis represents T-scores (clinical cut-off at –1 SD = 40).

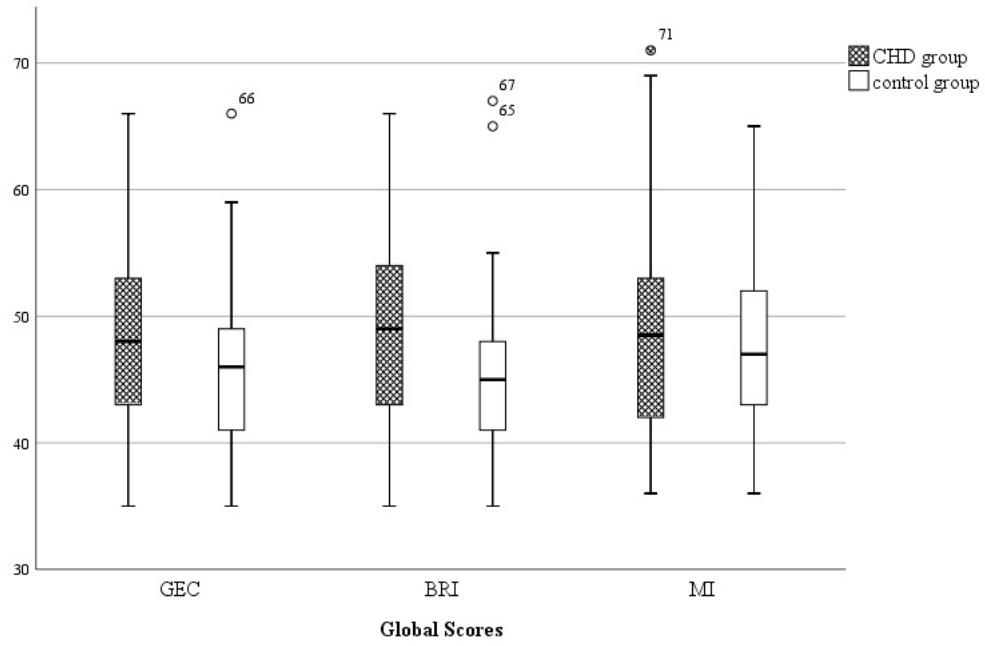

Figure 5.2. Comparison of the dimensions of the BRIEF-A questionnaire for the CHD and the control group. Higher scores correspond to poorer self-reported executive functions. ° indicates a mild outlier (> 1.5 x IQR). Y-axis represents T-scores (clinical cut-off at –1 SD = 40). BRI: Behavior Regulation Index; GEC: Global Executive Composite; MI: Metacognition Index.

5.1.4.3 Impact of the congenital heart disease complexity on neurocognitive functioning

We found significant differences for all global scores: Executive Function ($F(3) = 3.887$, $p = 0.011$), Memory ($F(3) = 6.565$, $p < 0.001$), and Attention & Speed ($F(3) = 4.214$, $p = 0.007$). Figure 5.3 illustrates that the control group performed best and patients with severe CHD complexity performed worst in all three global scores. A Tukey post-hoc test revealed that performance for global Executive Function was statistically significantly lower for patients with severe CHD complexity (47.87 ± 5.63 T-scores, $p = 0.009$) than for the control group (52.43 ± 4.09 T-scores). For the global Memory score, the Tukey post-hoc analyses showed poorer scores for simple (50.67 ± 4.72 T-scores, $p = 0.019$) and severe (49.44 ± 3.88 t-scores, $p = 0.001$) CHD compared with the control group (53.79 ± 3.16 T-scores) on the one hand, and severe (49.44 ± 3.88 T-scores, $p = 0.034$) compared with moderate (52.76 ± 4.40 T-scores) CHD on the other hand. For global Attention & Speed, severe CHD (45.58 ± 4.09 T-scores, $p = 0.009$) differed significantly from the control group (50.34 ± 5.58 T-scores). None of the other groups differed significantly from each other. Nevertheless, even patients with a simple CHD showed also clinically relevant deficits compared with the control group in all global scores (Executive Function: $d = 0.500$; Memory: $d = 0.776$; Attention & Speed: $d = 0.443$) assuming effects of $d > .42$ as clinically relevant (Ferguson, 2016). No group differences were found for the Behavior Rating Inventory of Executive Function – Adult Version indices (Global Executive Composite $F(3) = 1.353$, $p = 0.262$; Behavior Regulation Index $F(3) = 1.872$, $p = 0.140$; Metacognition Index $F(3) = 0.751$, $p = 0.525$).

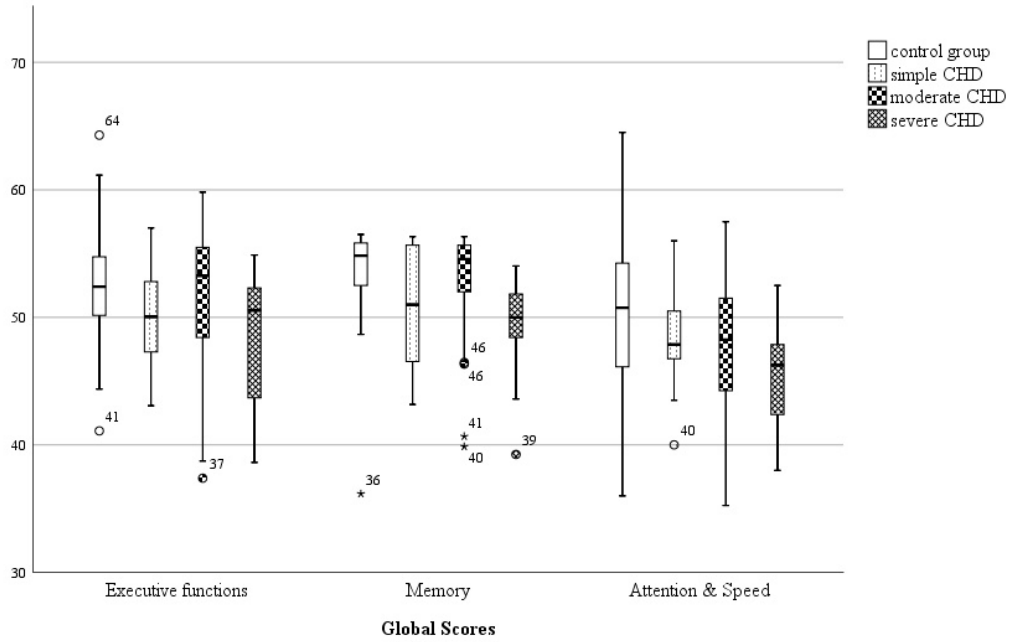

Figure 5.3. Global scores comparison for the CHD complexities and the control group. ° indicates a mild outlier (> 1.5 x IQR), * indicates an extreme outlier (> 3 x IQR). Y-axis represents T-scores (clinical cut-off at –1 SD = 40).

5.1.5 Discussion

In this cross-sectional cohort study, we report lower neurocognitive functioning in multiple domains in young adults with CHD in comparison to gender-, age-, and parental-SES-matched healthy controls. Patients with severe CHD complexity were most affected. For a better understanding of the affected functions, we created global scores for the domains of Executive Functions, Memory, and Attention & Speed. The CHD group scored poorer in all three global scores compared with the control group. Even though the mean test results of the CHD group in our sample were within the normal range, the number of patients scoring above the cut-off for clinically relevant impairments was larger than that of the control group. Our findings expand results from existing studies on young adults with CHD by three important aspects. First, previous studies reported impairments in executive functioning, problems with memory or attention in cohorts with either smaller sample sizes or secondly, in patients with specific types of CHD. For example, Daliento et al. (2005) included only patients with tetralogy of Fallot, and Kasmi et al. (2018) assessed neurocognitive outcomes in adults with transposition of the great arteries. Other investigators studied either only male patients (Eide et al., 2006) or included a large proportion of

patients with a neurological comorbidity (Ilardi et al., 2017). Third, our findings are more specific than those of previous studies using only intelligence scales as neurocognitive assessment (Eide et al., 2006; Utens et al., 1998; Utens et al., 1994) or questionnaire data of the Behavior Rating Inventory of Executive Function – Adult Version to assess executive functioning (Løvstad et al., 2016). The association we found between the CHD complexity and the degree of impairment in neurocognitive functioning confirms findings by other researchers examining adults with CHD (Ilardi et al., 2017; Klouda et al., 2017). Importantly, however, patients with a simple CHD also showed difficulties in the three neurocognitive domains, even if their performance was not statistically different from that of the control group.

When looking at the results in more detail, we identified lower performances in visual memory, verbal working memory, divided attention, processing speed, interference control, and estimated IQ. Although effect sizes were small to medium, they suggest probability of clinical relevance. Even though it is difficult to draw a precise comparison between studies in children and adults with CHD (e.g., for methodological reasons), it is apparent that certain functional deficits persist into adolescence and adulthood (Mills et al., 2018). The most notable indication of such a persistence can be found in the executive functions (Calderon & Bellinger, 2015). Apart from these findings, our results also provide indication of deficits that become only apparent with increasing age, particularly memory impairments. There is little evidence of memory deficits in children with a CHD (Tyagi et al., 2014). As the demands of different life stages change, the associated neurocognitive deficits also tend to emerge at different developmental stages. Whereas executive dysfunctions and attention deficits seem to appear already during childhood, memory problems may only become evident in early adulthood (Keir et al., 2019).

Beside group differences in objective neuropsychological performance, the CHD group differed from the control group also in the self-reported executive function abilities in everyday life. The CHD group reached higher scores compared with the control group in the Behavior Regulation Index, indicating higher self-reported executive functional impairments in this domain. We also note that only five patients (2.50 %) and one control participant (0.46 %) reached

clinically relevant scores. This finding indicates that our study sample has a relatively high self-perceived executive function level in everyday life.

Overall, the CHD group performed worse in the neuropsychological testing, but the differences we found were not clinically relevant for most patients. This may be due to the fact that this study population is a high functioning population. This assumption is supported by a relatively high educational level among the CHD group. Furthermore, the examined population was relatively young and still at the height of their cognitive capacities.

A recent publication (Bagge et al., 2018) showed that the CHD population might be at increased risk for early-onset dementia, in particular those patients with CHD of severe complexity. Whether neurocognitive (dys-)functioning in young adults with CHD is associated with the onset of early dementia requires long-term follow-up. Reportedly, patients with a CHD have also an increased risk for vascular cerebral injuries which become more prevalent with ageing (Marelli et al., 2016). Whether subclinical neurocognitive disability at young adult age predicts a greater susceptibility of adverse outcomes in case of later cerebrovascular events requires long-term follow-up studies of cohorts as presented in our study.

In conclusion, young adults with CHD, particularly those with severe CHD complexity, may require special attention by health care professionals, as impaired neuropsychological functions can restrict educational achievement and employability. More specifically, executive deficits may impact patients' ability to set targets, plan actions and self-control as impulse control and emotion regulation. Memory problems can restrict academic achievements, and attention deficits can influence the ability to maintain efficiently a full working day. To identify, monitor, and treat potential difficulties in neurocognitive functioning with aging, one may consider neuropsychological assessment a routine clinical procedure.

5.1.5.1 Limitations

It must be considered that the response rate of 36 % of the eligible patients is rather low. A reason for this low rate could be that the current study required a much more intensive examination including three hours of neuropsychological testing than the previous studies. For example, the one by Rometsch et al. (2019), was a questionnaire study only. However, participating and non-participating patients did not differ in sample characteristics like sex and CHD complexity. The studied samples of patients with CHD and healthy controls were highly educated with 14 and 15 years of schooling, respectively. Note that, according to the Swiss educational system, regular schooling encompasses a period of 12 years. On average, patients with a severe CHD complexity attended this obligatory school period only. Therefore, generalizability to the population at large is limited, and the high neurocognitive performance may not reflect the actual neurocognitive performance of all young adults with a CHD. We included patients with different types of CHD, which increases heterogeneity of the study group and may have impacted statistical power. Accordingly, sample sizes were too small for subgroup analyses of specific CHD types (e.g., transposition of the great arteries). Finally, our study was a single center study and, strictly speaking, the validity of the findings is restricted to a regional cohort.

5.1.6 Conclusion

The findings of this study indicate lower neurocognitive functioning in young adults with CHD, particularly for patients with a CHD of severe complexity. Importantly, the measurable neurocognitive impairments are not clinically relevant for the majority of the CHD group. Whether subclinical neurocognitive dysfunction, as found in this study, translates into adverse long-term outcomes or predisposes to early-onset neurodegenerative decline requires careful prospective longitudinal follow-up studies.

5.1.7 Supplementary material

Table 5.4. CHD diagnoses and classification into simple, moderate, and severe complexity.

Simple CHD, n (%)	18 (26.9 %)
Isolated congenital aortic valve disease	7 (10.4 %)
Repaired ventricular septal defect	3 (4.5 %)
Isolated congenital mitral valve disease	3 (4.5 %)
Previously ligated or occluded ductus arteriosus	1 (1.5 %)
Small atrial septal defect	1 (1.5 %)
Mild pulmonary stenosis	1 (1.5 %)
Other simple CHD[a]	2 (3.0 %)
Moderate CHD, n (%)	33 (49.3 %)
Coarctation of the aorta	8 (11.9 %)
Tetralogy of Fallot	8 (11.9 %)
Ventricular septal defect with coarctation of the aorta	4 (6.0 %)
Ventricular septal defect with right ventricular outflow tract obstruction	3 (4.5 %)
Ventricular septal defect with mitral valve disease	2 (3.0 %)
Ebstein's anomaly	2 (3.0 %)
Pulmonary valve stenosis	2 (3.0 %)
Supravalvar aortic stenosis	1 (1.5 %)
Atrioventricular canal defects	1 (1.5 %)
Anomalous pulmonary venous drainage	1 (1.5 %)
Other moderate CHD[b]	1 (1.5 %)
Severe CHD, n (%)	16 (23.9 %)
Transposition of the great arteries	11 (16.4 %)
Fontan procedure	3 (4.5 %)
Pulmonary atresia	1 (1.5 %)
Double-outlet ventricle	1 (1.5 %)

[a] Ventricular septal defect with tricuspid valve disease, n = 1; Congenital mitral valve disease and small atrial septal defect, n = 1. [b] Ventricular septal defect and abnormal origin of the left pulmonary artery from descending thoracic aorta, n = 1.

Table 5.5. Comparison of the participating and non-participating patients with CHD.

Variable	Participants n = 67	Non-participants n = 115	Group differences (p-value)
Age (years), mean (SD)[a]	26.9 (3.7)	24.3 (3.7)	<0.0001[†]
Sex			
Male, n (%)	37 (55.2)	67 (58.3)	0.690[‡]
Female, n (%)	30 (44.8)	48 (41.7)	
Complexity of CHD			
Simple, n (%)	18 (26.9)	37 (32.2)	0.150[‡]
Moderate, n (%)	33 (49.3)	40 (34.8)	
Severe, n (%)	16 (23.9)	38 (33.0)	

[a] Age of participating patients was measured at present assessment, age of non-participating patients at previous assessments. [†]t-test for independent samples. [‡]Pearson Chi^2 test.

5.2 Study 2

Structural brain abnormalities in adults with congenital heart disease: Prevalence and association with estimated intelligence quotient

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Conflicts of interest
None.

Ethical standards
The authors assert that all procedures contributing to this work comply with the ethical standards approved by the ethics committee of the Canton of Zurich and all the participants gave written informed consent prior to participation, in accordance with the Declaration of Helsinki.

5.2.1 Abstract

Background: Little is known about the prevalence of structural brain abnormalities and neurocognitive functioning in the growing population of patients with adult congenital heart disease (ACHD). Thus, our aim was to assess structural abnormalities on brain magnetic resonance imaging (MRI) and their association with intelligence quotient (IQ) in ACHD patients.

Methods: Cross-sectional study in ACHD patients and healthy controls as comparison group. Brain MRI was performed on a 3 TMR scanner, and inspection of structural abnormalities was performed blinded to ACHD or control status. IQ was estimated using the vocabulary and matrix reasoning subtests from the Wechsler Adult Intelligence Scale, Fourth Edition.

Results: A total number of 67 (55 % males) ACHD patients and 55 (51 % males) controls were included (mean age 26.9 and 26.0 years respectively). Abnormalities on brain MRI were detected in 29 of 46 (63 %) ACHD patients and in none of the controls. Abnormalities consisted of focal infarction or atrophy, white matter lesions, microhemorrhages, and global atrophy. Mean estimated IQ was significantly lower in ACHD patients than in controls (98.51 versus 104.38; 95 % CI: -10.09 to -1.66; P value = 0.007). Comparison between patients with and without cerebral abnormalities revealed no significant difference in estimated IQ.

Conclusion: Our findings indicate a high prevalence and wide spectrum of structural brain abnormalities in ACHD patients. Furthermore, this population is at a higher risk of impaired intellectual functioning than healthy controls. However, the present study could not establish a statistically significant association between MRI findings and estimated IQ.

5.2.2 Introduction

Congenital heart disease is a heterogeneous group of heart defects with great variability in complexity, severity, and symptoms (Tyagi et al., 2014). Due to major advancements in the treatment of CHD patients in recent decades, survival rate and life expectancy have increased significantly (Mandalenakis et al., 2016; Moons et al., 2010). Nowadays, the majority of these patients reach adulthood, resulting in a growing population of patients with ACHD (Klouda et al., 2017; Marelli et al., 2016; Tyagi et al., 2014; van der Linde et al., 2011).

A high prevalence and wide spectrum of structural brain abnormalities such as cerebral white matter hyperintensities, microhemorrhages, and strokes has been detected in adolescents and young adults with CHD (Bolduc et al., 2018). Furthermore, register based studies revealed an increased absolute and relative risk for clinically evident ischemic and hemorrhagic strokes in the ACHD population (Giang et al., 2018; Lanz et al., 2015; Mandalenakis et al., 2016). There is evidence that these structural findings correlate with functional performance in adolescents (Bellinger et al., 2015; von Rhein et al., 2014). Neurocognitive and executive function impairments have been described in childhood and adolescence and may persist into early adulthood (Bellinger et al., 2011; Bolduc et al., 2018; Karsdorp et al., 2006). This is clinically relevant, as even mild cognitive impairments can limit the academic attainments and societal contributions of this growing patient population (Marelli et al., 2016).

Whereas the neurocognitive profiles of school-age children and adolescents with CHD are well described, few studies have evaluated neurocognitive functioning in the ACHD population (Ilardi et al., 2017; Kasmi et al., 2018; Klouda et al., 2017). The scarce findings available suggest impairments in visuospatial function, working memory, and executive function (Ilardi et al., 2017; Kasmi et al., 2018). However, little is known about the prevalence of structural brain abnormalities and their association with functional outcome in the population of ACHD. The association of structural findings with neurocognitive functioning has only been investigated in one study in adult patients with tetralogy of Fallot with a wide age range (20 - 69 years) (Sluman et al., 2017). To our best knowledge, no studies have been published on either the prevalence and range of subclinical cerebral abnormalities across a wide spectrum of CHD diagnoses and their impact on neurocognitive functioning in the ACHD population during early adulthood (< 33 years).

Therefore, we aimed to address this gap by assessing the prevalence of structural brain abnormalities on magnetic resonance imaging (MRI) in a mixed cohort of ACHD patients and by investigating the association of such abnormalities with intellectual functioning. We hypothesize that structural brain abnormalities will occur more frequently in ACHD patients than in controls; structural brain abnormalities and complexity of CHD diagnoses will correlate with intellectual

functioning; and intellectual functioning in ACHD patients is impaired compared to healthy controls.

5.2.3 Methods

5.2.3.1 Study design and population

In this cross-sectional study, adults with different types of CHD between 18 and 32 years of age were recruited from two previously examined cohorts (Rometsch et al., 2019; von Rhein et al., 2011) at the University Hospital Zurich between October 2016 and October 2018. Exclusion criteria were comorbidities affecting neurocognitive outcome, such as chromosomal aberrations, genetic syndromes, severe psychiatric diseases, and severe neurological impairments. Testing for a genetic disorder was only performed when clinically indicated. Participants were also excluded if they did not have sufficient command of the German language. Healthy controls were recruited as peers or as age-, sex-, and parental-SES-matched controls from the general population. The study was approved by the Ethical Committee of the University of Zurich, and written informed consent was obtained from all study participants prior to study participation.

All study participants completed a questionnaire that gathered demographic, socioeconomic, and medical background information. Educational level was measured with reference to the Swiss education system using a scale ranging from 1 to 6, with higher scores indicating higher educational levels. Parental SES was estimated based on paternal and maternal educational levels, leading to a scale ranging from 2 (lowest SES) to 12 (highest SES). In addition to the self-reported medical variables, the following information was retrieved from electronic patient charts at the University Hospital Zurich: type of CHD, maximum oxygen consumption (relative VO2max), ventricular ejection fraction, number of cardiopulmonary bypass surgeries, and extracorporeal bypass time. Type of CHD was classified as simple, moderate, or severe heart defect according to Warnes et al. (2001). Physical exercise capacity was classified as severely reduced exercise capacity (< 60 %), reduced exercise capacity (60 - 85 %), or normal capacity (> 85 %). Systemic ventricular ejection fraction was determined by echocardiography or by cardiac MRI and was classified into three groups: no ventricular dysfunction (ejection fraction > 52 %), mild ventricular

dysfunction (ejection fraction 40 - 52 %), and moderate to severe ventricular dysfunction (ejection fraction < 40 %).

5.2.3.2 Cerebral MRI

Brain MRI was performed as part of the study protocol on a 3 T MR scanner (Signa MR750, GE) at the Children's University Hospital Zurich. Hearing protection was provided with earplugs and headsets. The following sequences were scanned and assessed for structural abnormalities: T2-weighted sagittal fast spin-echo sequence (repetition time (TR) = 10,000 ms, echo time (TE) = 95 ms, field of view (FOV) = 260 mm, matrix = 512 × 512 mm, slice thickness (ST) = 3 mm), T2-weighted 3D fast spin-echo sequence (TR = 2800 ms, TE = 95 ms, FOV = 256 mm, matrix = 256 × 256 mm, ST = 1 mm), T1-weighted 3D spoiled gradient echo pulse sequence (SPGR) (TR = 11 ms, TE = 5 ms, inversion time = 600 ms, FOV = 256 mm, matrix = 256 × 192 mm, ST = 1 mm, flip-angle = 8°), susceptibility-weighted sequence (SWI) (TR = 53 ms, TE = 31 ms, FOV = 240 mm, matrix = 512 × 512 mm, ST = 3 mm), and diffusion tensor imaging (DTI) (TR = 6500ms, TE = 85 ms, FOV = 280 mm, matrix 256 × 256 mm, ST = 3.6 mm). MR images were assessed by an experienced neuroradiologist (R.K.) blinded to group status (ACHD versus controls). Findings were classified according to Bellinger et al. (2011) and Bolduc et al. (2018), into focal infarction or atrophy, white matter lesions, microhemorrhages, global cerebral atrophy (mild or significant), and incidental findings, which were considered to be unrelated to the CHD diagnosis. Brain MRI was classified as abnormal if any of the following findings were present: focal infarction or atrophy, white matter lesion, microhemorrhages, and significant global cerebral atrophy. No study participant had a clinical indication to undergo brain MRI.

5.2.3.3 Neurocognitive assessment

Intellectual functioning was assessed as part of a comprehensive neuropsychological test battery. The administration of the test took about two hours and was performed by two experienced neuropsychologists (L.S., S.R.) at the University Hospital Zurich. The IQ was assessed using a short form of the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Petermann, 2012),

which has been validated as estimating the full-scale IQ (Daseking et al., 2014). The IQ was measured on a standardized scale with a mean value of 100 and SD of ± 15. The short form consists of the vocabulary and matrix reasoning subtests. Crystallized intelligence is measured by the vocabulary subtest and describes the ability to solve tasks using acquired knowledge and experience. Fluid intelligence is measured by the matrix reasoning subtest and describes the ability to solve new tasks, or to adapt to new situations without resorting to acquired knowledge (Daseking et al., 2014).

5.2.3.4 Statistical analyses

Normally distributed variables are reported as mean and SD, whereas non-normally distributed variables are reported as median and interquartile range (IQR). Comparisons of continuous demographic and socioeconomic variables were made using a t-test for independent samples for normally distributed data, and a Mann-Whitney U test for non-normally distributed data. A Pearson Chi^2 test was used for comparison of categorical variables. A Pearson Chi^2 test was also used to evaluate differences in the prevalence of structural findings on brain MRI among ACHD subjects and healthy controls. Estimated IQ comparison between the groups was made using a t-test for independent samples, and analysis of variance with Tukey's post-test was used to compare estimated IQ in different subgroups of CHD complexity. All statistical analyses were performed in SPSS statistical package version 25 and R Version 3.6.1. P values < 0.05 were considered statistically significant.

5.2.4 Results

5.2.4.1 Group characteristics

Patients were recruited from the cohort of a study examining quality of life in young adults with CHD (Rometsch et al., 2019). Of that original sample of 188 ACHD patients, seven subjects were excluded due to Marfan syndrome. In addition, we also approached ten eligible patients from

another study examining neurocognitive outcome in adolescence (von Rhein et al., 2014). Therefore, a total number of 191 ACHD subjects were eligible for the study, among whom 64 refused participation and 59 could not be invited to participate the study due to invalid contact information. The data of one patient had to be excluded for further analysis after tasting, because the medical condition (cardiomyopathy) was not a CHD. Thus, the final sample enrolled in the study comprised 67 ACHD patients (response rate 35.6 %), with a mean age of 26.9 (SD 3.7) years. Comparison of baseline characteristics of the participating and non-participating patients revealed no difference in sex, complexity of CHD, or physical exercise capacity. There was a difference in systemic ventricular ejection function, with the participating patients less likely to suffer from systemic ventricular dysfunction than the non-participating patients (Table 5.8). We recruited 55 healthy control subjects who had a mean age of 26.0 (SD 3.3) years. There was no significant difference between the ACHD and the control subjects with respect to age at assessment, sex, nationality, or parental SES. Demographic and cardiac characteristics of the enrolled ACHD patients and the controls are presented in Table 5.6. Of the 67 patients, 18 (26.9 %) had a simple heart defect, 33 (49.3 %) a moderate, and 16 (23.9 %) a severe one. A total of 24 (35.8 %) patients were born with a cyanotic CHD, and 49 (73.1 %) had at least one cardiopulmonary bypass surgery. Detailed information on underlying CHD diagnoses are outlined in the Table 5.9.

Table 5.6. Characteristics of the CHD and the control group.

Variable	CHD group, n = 67	Control group, n = 55	p-values
Age (years), mean (SD)	26.92 (3.68)	26.04 (3.32)	0.175[a]
Sex (male), n (%)	37 (55.22)	28 (50.91)	0.635[b]
Nationality (Swiss), n (%)	63 (94.03)	53 (96.36)	0.553[b]
Socioeconomic status[c], median (IQR)	8 (7.75; 10)	9 (8; 10)	0.181[d]
Years of schooling (years), median (IQR)	14 (12; 16)	15 (14; 17)	0.013[d]
Complexity of CHD			
simple, n (%)	18 (26.9)		
moderate, n (%)	33 (49.3)		
severe, n (%)	16 (23.9)		
Cardiopulmonary bypass surgeries			
none, n (%)	19 (28.4)		
one, n (%)	30 (44.8)		
two or three, n (%)	18 (26.9)		
Cyanotic CHD at birth, n (%)	24 (35.8)		

[a] t-test for independent samples. [b] Pearson Chi^2 test. [c] Socioeconomic status range from 2 (lowest) to 12 (highest). [d] Mann-Whitney U test. CHD: Congenital heart disease; IQR: Interquartile range.

5.2.4.2 Cerebral MRI findings

Brain MRI was obtained in 46 ACHD subjects. Reasons for missing MRI were MR-incompatible implants (e.g., pacemaker or coils, n = 12) or other medical circumstances (claustrophobia n = 2, obesity n = 1, pregnancy n = 1). Five patients refused to participate in the neuroimaging part. Among the 55 healthy controls, brain MRI was obtained in all but one, who refused to undergo MRI. Structural brain abnormalities were detected in 29 of the 46 (63.0 %) ACHD individuals and in none of the controls ($Chi^2(1) = 47.95$; p-value < 0.0001; n = 100). Most of the findings were focal or multifocal structural abnormalities. Among these findings, the most common abnormalities were microhemorrhages. These were found in 25 (54.3 %) ACHD subjects. Details on structural findings on brain MRI are depicted in Table 5.7. Representative examples of the structural abnormalities are displayed in Figure 5.4. One patient had multifocal white matter lesions, potentially indicating an underlying vasculopathy. Furthermore, this patient showed significant atrophy with enlarged extra-axial cerebrospinal fluid spaces, which could be related either to the CHD diagnosis or the suspected vasculopathy. The detected brain MRI findings were clinically silent. The need for one or more cardiopulmonary bypass surgeries was found to be a risk factor for structural abnormalities on brain MRI: Structural brain abnormalities were detected in 27 of 33 (81.8 %) ACHD patients who had undergone at least one cardiopulmonary bypass surgery and in only 2 of 13 (15.4 %) ACHD patients who had no history of cardiopulmonary bypass surgery ($Chi^2(1) = 17.66$; p-value < 0.0001; n = 46). Furthermore, microhemorrhages were only detected in patients who had undergone cardiopulmonary bypass surgery ($Chi^2(1) = 21.57$; p-value < 0.0001; n = 46).

Table 5.7. Structural brain abnormalities in the CHD and the control group.

Variable	CHD group, n = 46		Control group, n = 54	p values
	No CPB surgery, n = 13	CPB surgery, n = 33		
Overall structural abnormalities[a], n (%)	2 (15.4)	27 (81.8)[b]	0 (0.0)	<0.0001
Focal and multifocal abnormalities, n (%)	2 (15.4)	27 (81.8)	0 (0.0)	<0.0001
Focal infarction or atrophy, n (%)	1 (7.7)	5 (15.2)	0 (0.0)	0.008
White-matter lesions, n (%)	1 (7.7)	2 (6.1)	0 (0.0)	0.094
Microhemorrhages, n (%)	0 (0.0)	25 (75.8)	0 (0.0)	<0.0001
Global abnormalities, n (%)	4 (30.8)	7 (21.2)	3 (5.6)	0.010
Significant cerebral atrophy[c], n (%)	0 (0.0)	3 (9.1)	0 (0.0)	0.094
Mild cerebral atrophy[c], n (%)	4 (30.8)	4 (12.1)	3 (5.6)	0.110
Incidental findings[d], n (%)	0 (0.0)	3 (9.1)	6 (11.1)	0.500

[a] Presence of any or multiple of the following findings: focal infarction or atrophy, white-matter lesions, microhemorrhages, and significant cerebral atrophy. [b] 8 (24.2 %) when excluding microhemorrhages. [c] Consisting of enlarged extra-axial cerebrospinal fluid spaces and/or enlarged ventricles. [d] In the CHD group, the incidental findings were arachnoid cyst (n = 2), and clivus cyst (n = 1). In the control group, the incidental findings were arachnoid cyst (n = 1), neuroglial cyst (n = 1), capillary telangiectasia (n = 2), and developmental venous anomaly (n = 2). CHD: Congenital heart disease; CPB: Cardiopulmonary bypass surgery.

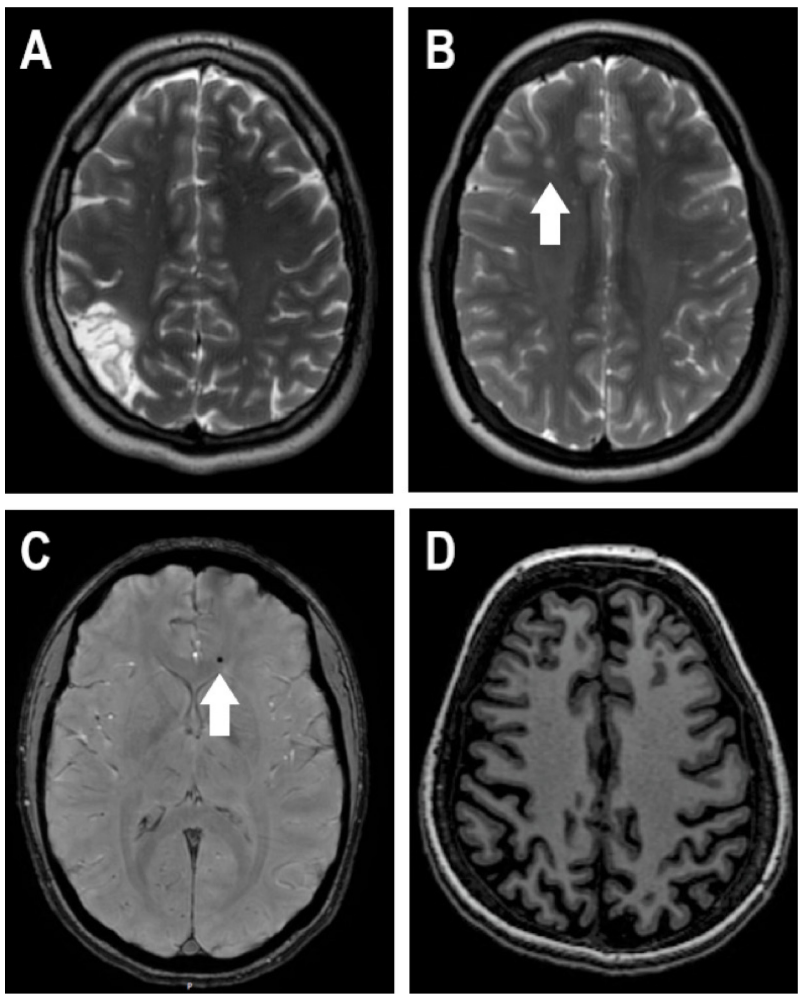

Figure 5.4. Examples of structural brain abnormalities. (A) Right parietal post-ischemic defect on a T2-weighted image of a 29-year-old male with transposition of the great arteries. (B) T2-hyperintense frontal white matter lesion on a T2-weighted image of a 24-year old female with transposition of the great arteries. (C) Multiple microhemorrhages on SWI image of a 25-year-old female with isolated congenital mitral valve disease. (D) Global parenchymal volume reduction with enlarged cerebrospinal fluid spaces on a T1-weighted image of a 22-year-old male with repaired ventricular septal defect.

5.2.4.3 Neurocognitive findings

Neurocognitive assessment was performed in all 67 ACHD patients and the 55 control subjects. In two ACHD individuals, the short form of the WAIS-IV was not completed due to missing subtests as a result of errors in test administration.

Mean estimated IQ in ACHD subjects was found to be significantly lower than in healthy controls (98.51, SD 11.21 versus 104.38, SD 12.09; 95 % CI: -10.09 to -1.66; p = 0.007) but within the normal range. The proportion of subjects with an estimated IQ below 85 (-1 SD) was higher in ACHD patients than in healthy controls (10.8 % versus 1.8 %; p = 0.069). For the analysis of estimated IQ in ACHD complexity subgroups, patients with simple and moderate CHD were combined in one group. Greater complexity of CHD was associated with lower estimated IQ (F(2, 62) = 9.19, p-value < 0.0001). Post-hoc analysis with Tukey's test revealed that patients with severe CHD had lower mean estimated IQ (89.60, SD 9.44) than patients with simple/moderate CHD (101.18, SD 10.34, p = 0.0016) and controls (p < 0.001) respectively. No difference in estimated IQ was found between simple/moderate CHD and controls (p = 0.31) (Figure 5.5).

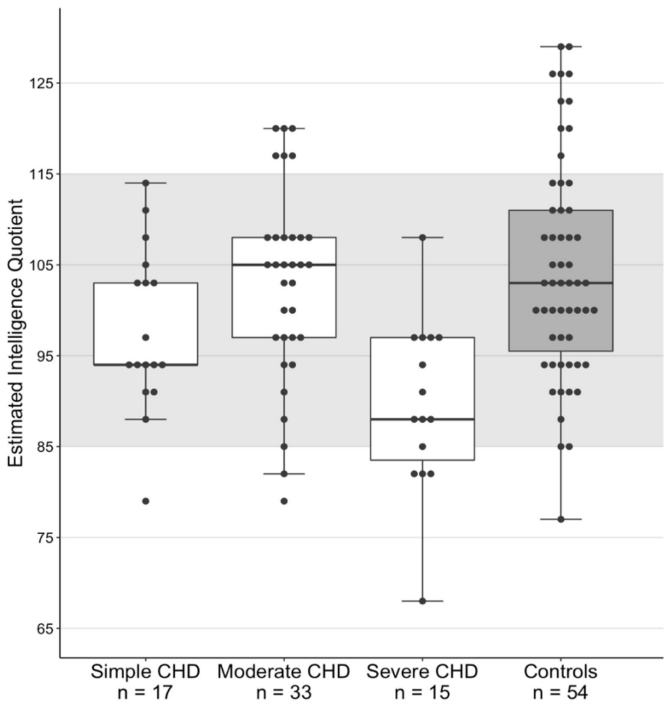

Figure 5.5. Boxplots comparing median estimated IQ among the CHD complexities and the healthy controls. CHD complexities correspond to classification by Warnes et al. (2001). Simple and moderate CHD subtypes were combined. Normal IQ range, i.e. 100, SD ± 15, is highlighted in gray. Significant difference in estimated IQ between severe CHD and controls, and severe CHD and simple/moderate CHD.

5.2.4.4 Association of MRI findings with general intellectual functioning

No difference in estimated IQ was found between ACHD patients with or without abnormalities on brain MRI (mean (SD) estimated IQ 96.71 (11.97) versus 99.82 (8.84); 95 % CI: -3.66 to 9.88; p = 0.36). When microhemorrhages were excluded from the definition of abnormal MRI as a post hoc sensitivity analysis, no difference in mean estimated IQ was evident between patients with or without MRI abnormality. Furthermore, there was no difference in mean estimated IQ between patients with cyanotic CHD and acyanotic CHD at birth (mean (SD) estimated IQ 95.87 (13.31) versus 99.95 (9.74); 95 % CI: -1.68 to 9.85; p = 0.16).

5.2.5 Discussion

In this cross-sectional study of young adults with CHD, we report a high prevalence and wide spectrum of structural brain abnormalities. These were strongly associated with previous cardio-pulmonary bypass surgeries. Furthermore, we found that estimated IQ was significantly lower in ACHD patients than in healthy controls and was associated with complexity of CHD diagnosis. Although the majority of ACHD patients scored within the normal range, the proportion of subjects with an estimated IQ below the normal range was higher in ACHD patients than in healthy controls. However, we could not establish a significant correlation between structural brain abnormalities and estimated IQ in ACHD patients.

This is one of the largest studies reporting on structural brain abnormalities in adults with repaired CHD. Over 60 % of patients in our cohort were found to have focal or multifocal or global structural brain abnormalities (21.7 % when excluding microhemorrhages). This is in line with previous reports of structural brain abnormalities in ACHD patients occurring in 47–70 % (Codari et al., 2018; Cordina et al., 2014; Jensen et al., 2015; Sluman et al., 2017). The agreement with previous studies is noteworthy, given the heterogeneity of ACHD patients included in our cohort. Whereas previous studies included only patients with unrepaired cyanotic CHD (Cordina et al., 2014; Horigome et al., 2006; Jensen et al., 2015) or patients with tetralogy of Fallot (Chai et al., 2018; Codari et al., 2018; Sluman et al., 2017), our cohort represents a heterogeneous, predominantly well-functioning sample of mild, moderate, and severe CHD types. A recently

published study in young adults with CHD reported structural brain abnormalities in 24 % (Fontes et al., 2019). Although demographically comparable, comparison is difficult, as that study used a different classification of structural brain abnormalities. Furthermore, our findings are consistent with the reported frequency of structural brain abnormalities in 21 - 66 % in adolescents with CHD (Bellinger et al., 2011; Bellinger et al., 2015; von Rhein et al., 2014). Importantly, all MRI abnormalities in our study were clinically silent and patients had no clinical indication to undergo neuroimaging, as opposed to the incidents included in previous register-based analyses of the risk for ischemic and hemorrhagic strokes in ACHD patients (Giang et al., 2018; Lanz et al., 2015; Mandalenakis et al., 2016).

The most frequently observed structural abnormalities in this study were multifocal microhemorrhages. Although these small perivascular iron deposits have been described previously with a similar prevalence in adolescents with CHD (Bellinger et al., 2011; Bellinger et al., 2015), the underlying pathophysiological mechanisms and their impact on cerebral microstructural integrity remain unknown. Microhemorrhages have been suggested to be biomarkers of cerebral small vessel disease, to increase with age, and to be risk factors for cognitive decline in dementia in the general population (Poels et al., 2011). In the pediatric CHD population, they have been linked to cardiopulmonary bypass surgery (Kim et al., 2017), but they might also be a surrogate marker of vascular damage, blood brain barrier leakiness, and brain aging in ACHD patients (Codari et al., 2018). Further studies are warranted to elucidate the mechanisms of microhemorrhages in ACHD patients and their impact on neurocognitive functioning. Therefore, long-term follow-up studies in the aging population of ACHD patients are necessary to assess the trajectory of brain aging and the associated cognitive decline across the life span. This seems of particular importance, as a recent register-based study suggested the risk for dementia might be increased in ACHD patients compared to the general population (Bagge et al., 2018).

In this study, we report that ACHD patients had a significantly lower estimated IQ than healthy controls but still scored within the normal range. However, in 10.8 % of the ACHD patients the estimated IQ was below the normal range (i.e., < 85). This contrasts with 1.8 % in healthy controls, indicating an increased risk for neurocognitive impairment in this population.

We could not find a significant difference in estimated IQ between ACHD patients with and without structural brain abnormalities, neither when microhemorrhages were excluded. These findings are in line with a recent study in adults with tetralogy of Fallot, which reported normal IQs and no difference among patients stratified by MRI abnormalities (Sluman et al., 2017). More advanced neuroimaging analyses of volumetric and microstructural changes may better capture the consequences of brain abnormalities and injury, and could be associated with neurocognitive functioning.

Finally, we found that estimated IQ was associated with CHD diagnosis subtypes. Patients with the most severe forms of CHD scored worse on IQ testing than did simple/moderate CHD subtypes when classified according to the consensus of the 28th Bethesda Conference on ACHD (Warnes et al., 2001). No difference in estimated IQ was detected between simple/moderate CHD and controls, highlighting that the majority of ACHD patients are neurocognitively well-functioning. Yet, neurocognitive and potentially neuroimaging follow-up of ACHD patients across the lifespan, in particular in most severe subtypes, is warranted to detect those that deviate from this overall positive trajectory.

5.2.5.1 Limitations

Our study should be viewed in the context of its limitations. Firstly, our study was a single-center study. As the treatment of patients with CHD can differ among centers, our findings may not be generalizable to other ACHD populations. Secondly, our patient cohort covers a wide spectrum of CHD diagnoses. We performed a subgroup analysis for different CHD complexity types; however, the statistical power of these analyses might have been limited by the relatively small sample size. Thus, the opportunity for further subdivision of our cohort to make inferences for specific types of CHD was limited. Thirdly, a limited amount of time was available for IQ assessment as part of a comprehensive neuropsychological testing, so we used a short form of the WAIS-IV to measure cognitive performance. Short forms allow the full-scale IQ to be estimated in a time-efficient way but do not provide the same degree of test accuracy as the complete assessment. Thus, our results need to be confirmed by testing the full-scale IQ in the ACHD population. In

addition, we here report only the results of the IQ assessment; executive function outcomes will be reported separately.

Finally, the majority of our cohort had middle to high SES, which might have led to a more favorable cognitive outcome than in the general ACHD population. This is important as SES has previously been described as a strong predictor of intellectual outcome in the CHD population (Naef et al., 2017). However, there was no significant difference in SES between ACHD patients and controls.

5.2.6 Conclusion

The findings of this study indicate a high prevalence and wide spectrum of structural brain abnormalities in ACHD subjects. Furthermore, ACHD patients are at a higher risk of impaired general intellectual functioning than healthy controls. We could not establish a statistically significant association between structural MRI findings and estimated IQ. More longitudinal studies with focus on sequential neuroimaging and neurocognitive outcome assessment are needed to further understand the significance of these cerebral abnormalities for brain ageing and neurocognitive functioning in the ACHD population. Overall, it seems important to monitor brain health by neurocognitive assessment and if indicated, with neuroimaging in patients with CHD across the lifespan.

5.2.7 Supplementary material

Table 5.8. Comparison of the participating and non-participating patients with CHD.

Variable	Participants, n = 67	Non-participants, n = 115	p-values
Age (years), mean (SD)[a]	26.9 (3.7)	24.3 (3.7)	<0.0001[b]
Sex (male), n (%)			0.69[c]
Male, n (%)	37 (55.2)	67 (58.3)	
Female, n (%)	30 (44.8)	48 (41.7	
Severity of CHD			0.15[c]
simple, n (%)	18 (26.9)	37 (32.2)	
moderate, n (%)	33 (49.3)	40 (34.8)	
severe, n (%)	16 (23.9)	38 (33.0)	
VO_{2max} predicted, mean (SD)[d]	00.77 (20.45)	94.35 (22.24)	0.060[b]
Normal exercise capacity, n (%)	52 (81.3)	75 (68.2)	
Reduced exercise capacity, n (%)	9 (14.1)	31 (28.2)	
Severely reduced exercise capacity, n (%)	3 (4.7)	4 (3.6)	
Systemic ventricular dysfunction[e]			
No ventricular dysfunction, n (%)	60 (90.9)	92 (80.0)	0.034[c]
Mild ventricular dysfunction, n (%)	4 (6.1)	22 (19.1)	
Moderate or severe ventricular dysfunction, n (%)	2 (3.0)	1 (0.9)	

[a] Age of participating patients was measured at assessment of this study, whereas age of non-participating patients refers to assessment at time point of previous cohorts. [b] t-test for independent samples. [c] Pearson Chi^2 test. [d] Maximum physical exercise capacity. Participants n = 64; nonparticipants n = 110. [e] Participants n = 66; nonparticipants n = 115. CHD: Congenital heart disease.

Table 5.9. CHD diagnoses classified into simple, moderate, and severe complexity.

Simple CHD, n (%)	18 (26.9
Isolated congenital aortic valve disease	7 (10.4)
Repaired ventricular septal defect	3 (4.5)
Isolated congenital mitral valve disease	3 (4.5)
Previously ligated or occluded ductus arteriosus	1 (1.5)
Small atrial septal defect	1 (1.5)
Mild pulmonary stenosis	1 (1.5)
Other simple CHD[a]	2 (3.0)
Moderate CHD, n (%)	33 (49.3)
Coarctation of the aorta	8 (11.9)
Tetralogy of Fallot	8 (11.9)
Ventricular septal defect with coarctation of the aorta	4 (6.0)
Ventricular septal defect with right ventricular outflow tract obstruction	3 (4.5)
Ventricular septal defect with mitral valve disease	2 (3.0)
Ebstein's anomaly	2 (3.0)
Pulmonary valve stenosis	2 (3.0)
Supravalvar aortic stenosis	1 (1.5)
Atrioventricular canal defects	1 (1.5)
Anomalous pulmonary venous drainage	1 (1.5)
Other moderate CHD[b]	1 (1.5)
Severe CHD, n (%)	4 (6.1)
Transposition of the great arteries	16 (23.9)
Fontan procedure	11 (16.4)
Pulmonary atresia	3 (4.5)
Double-outlet ventricle	1 (1.5)

[a] Ventricular septal defect with tricuspid valve disease, n = 1; Congenital mitral valve disease and small atrial septal defect, n = 1. [b] Ventricular septal defect and abnormal origin of the left pulmonary artery from descending thoracic aorta, n = 1. CHD: Congenital heart disease.

5.3 Study 3

Counting on random number generation: Uncovering mild executive dysfunction in congenital heart disease

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Conflicts of interest
None.

5.3.1 Abstract

Background: Congenital heart disease (CHD) is associated with various neurocognitive deficits, particularly targeting executive functions, of which random number generation (RNG) is one indicator. RNG has, however, never been investigated in CHD.

Methods: We administered the Mental Dice Task (MDT) to 67 young adults with CHD and 55 healthy controls. This 1-minute-task requires the generation of the numbers 1 to 6 in a random sequence. RNG performance was correlated with a global executive function score. Participants underwent MRI to examine structural-volumetric correlates of RNG.

Results: Compared to the controls, the CHD patients showed increased backward counting, reflecting deficient inhibition of automatized behavior. They also lacked a small-number bias (higher frequency of small relative to large numbers). RNG performance was associated with a global executive function score in both groups. In the CHD patients, MRI revealed an inverse association of the counting bias with most of the volumetric measurements and the amount of small numbers was positively associated with corpus callosum volume, suggesting callosal involvement in the "pseudoneglect in number space".

Conclusion: We found an impaired RNG performance in CHD patients, which is associated with brain volumetric measures. RNG, reportedly resistant to learning effects, may be an ideal task for the longitudinal assessment of executive functions in patients with CHD.

5.3.2 Introduction

Human cognition allows us to deal with an enormously broad range of problems we encounter in our environment. It has evolved, and continues to evolve, in an adaptive way to the requirements of an increasingly complex day-to-day life. Neurocognitive operations govern thoughts and actions in an orderly way. In fact, the primary role of neurocognition is to rule, regulate, control and order. Could this be the reason for humans' systematic and miserable failure in one specific task - the generation of a random sequence of responses? A sequence is random if it lacks any order. This is equivalent to saying that it does not carry any information. Number sequences generated by human subjects under the instruction to produce no order are, without exception, too orderly

(Gauvrit et al., 2017; Oomens et al., 2021, for reviews on such RNG experiments). The information they contain can be quantified (traditionally with Evan's RNG index (Evans, 1978), but see section Discussion for alternatives), and the type of deviation from randomness can be qualitatively described. Two of the most prominent sequential biases are an excess of counting forward or backward in steps of 1, and a relative lack of repeats of the same number on consecutive trials.

In various RNG experiments with neuropsychological patient groups, counting bias has been identified as the sequential parameter to differentiate the patients most easily from their respective control group (Table 5.10 for an overview). It was argued that counting would reflect a relative inability to avoid rule-governed behavior and suppress the highly overlearned and automatized algorithm to name numbers according to their natural order. For long, RNG tasks have thus been proposed to constitute an ideal means to monitor frontal executive functions (Brugger et al., 1996; Miyake et al., 2000). Application of repetitive transcranial magnetic stimulation in healthy volunteers (Jahanshahi et al., 1998; Knoch et al., 2005) has indeed revealed that disruption of specifically left dorsolateral prefrontal cortex functions enhanced counting instead of randomizing. Functional neuroimaging (Daniels et al., 2003; Jahanshahi et al., 2000) and electrophysiological studies (Joppich et al., 2004) have also pointed to the crucial role of the *left* dorsolateral prefrontal cortex in mediating the inhibition of prepotent responses during RNG. In stark contrast to the wealth of behavioral and functional imaging studies of RNG is the relative lack of structural brain correlates of the randomization behavior. Geisseler et al. (2016) employed high-resolution structural MRI in patients with multiple sclerosis and healthy controls. All subjects were also administered the MDT which requires the randomization of digits from 1 to 6. While patients showed an enhanced counting bias compared to the controls (cf. also Table 5.10), the neural correlates of this exaggerated non-random behavior were rather unspecific. A higher cortical lesion load in the patient group did correlate with the tendency to count, but there was no consistent association between specific frontal cortex regions and any of the biases investigated.

The other prominent sequential bias in RNG is the avoidance of repetitions of a response on consecutive trials. One could expect that also in this case prefrontal functions are key, as the control of repetitive or perseverative behavior is traditionally associated with the frontal lobes

(Jahanshahi et al., 2000). However, in the context of randomization behavior, neither functional nor structural imaging studies have ever revealed a consistent pattern of correlation between this type of sequential non-randomness and a specific region of the brain. In a gambling context, repetition avoidance was found to be disrupted by lesions to the insular cortex, but not by focal lesions of other cortical regions, including the prefrontal cortex (Clark et al., 2014). Also, a voxel-based morphometry study found repetition avoidance in a computerized card game related to gray matter volumes in the medial temporal and orbitofrontal lobes, in the striatum and the anterior cingulate cortex (Huang et al., 2019).

The purpose of the present study is to extend the existing knowledge of RNG in a patient population with well-known neurocognitive impairments, especially in executive functions. We refer to patients suffering from a CHD. CHD comprises a heterogeneous group of diseases characterized by a structural heart abnormality or a combination thereof at the time of birth (Karsdorp et al., 2006). They constitute around one third of all major congenital anomalies (van der Linde et al., 2011) and affect up to two percent of all newborns (Giang et al., 2022). With the advent of the open-heart surgery and improvements in medical care, currently, around 97 % of the affected children can be expected to survive into adulthood, resulting in a steadily growing population of adult patients with CHD (Mandalenakis et al., 2020; Marelli et al., 2016; Moons et al., 2010). Regardless of this high survival rate, CHD survivors are at an increased risk for various comorbidities such as neuroanatomical alterations and brain injuries (e.g., Claessens et al., 2017). There is also evidence that they are at higher risk for neurodevelopmental disorders including neurocognitive dysfunctions like language, motor function, attention and executive function disorders (Calderon & Bellinger, 2015; Claessens et al., 2017; Tyagi et al., 2014). In a recent meta-analysis, Mills et al. (2018) found a consistent negative effect of a CHD on neurocognitive outcomes. In children and adolescents, neurocognitive impairments have been linked to lower brain volumes and white matter alterations (Ehrler et al., 2020; Latal et al., 2016; Semmel et al., 2018; von Rhein et al., 2014). However, despite the considerable evidence of neurocognitive dysfunctions and their neural underpinnings in children and adolescents with CHD, only few studies examined the spectrum of neurocognitive functioning in grown-up patients (e.g., Ilardi et al., 2017). Specifically,

we described poorer performance in the domains of executive functions, memory and attention and processing speed in a population of young adults with CHD compared to healthy control participants (Schlosser et al., 2021). We developed what we dubbed a "Global Executive Function Score", i.e., a composite measure based on interference control, flexibility, response inhibition, problem solving, working memory and fluency performance. Structural brain correlates of executive functions as measured with this composite score were recently described with an overlapping cohort (Naef et al., 2021). It could be demonstrated that poorer executive functions were associated with smaller brain volumes. Brain volume has been numerously shown to be impaired and related to neurocognition in the CHD population (Bolduc et al., 2018; Marelli et al., 2016). Against this background, it seems conceivable that patients with a CHD exhibit impaired performance in RNG and that the observed impairments may be associated with volumetric cerebral alterations.

The present study pursued two aims. First, we set out to examine the impact of a CHD on randomization performance, specifically as assessed with the MDT. This task has easy instructions and a response range within a healthy person's attention span (Gottselig et al., 2006). We hypothesized an impaired randomization performance by CHD patients, in particular an enhanced counting bias (traditionally interpreted as an executive function deficit in RNG; e.g., Brugger et al., 1996). We also explored associations between specified variables of the MDT and the global executive function score (GEF), as described above. Second, we explored for the first time structural brain correlates of RNG in young adults diagnosed with CHD, albeit with a focus on the gross level of volumetric analysis (data reported in Naef et al., 2021).

Table 5.10. Systematic overview of RNG studies reporting counting bias in neuropsychological patient groups (chronological order). Only studies which analyzed counting forward and/or backward in steps of 1 (+1 or -1; e.g. 7,8; 4,3) and/or in steps of 2 (+2 or -2; e.g. 1,3; 8,6) are included.

Study	Patients and healthy control participants (HCP)	Characteristics of RNG task	Main findings
Thomas (1962)	10 patients with brain damage (unspecified lesion localization) and 10 HCP	Writing down numbers from 0 to 9 at a self-paced response rate. Variable sequence length	Patients show enhanced counting (+1, -1, +2, -2; not differentiated)
Kuroki et al. (1976), cited in Brugger et al. (1996)	52 patients with a seizure disorder and 43 HCP	Saying numbers from 1 to 10 at a 1Hz response rate. Sequence length 100	Patients show enhanced counting (not differentiated)
Rosenberg et al. (1990)	20 patients with schizophrenia, 23 with alcohol dependency and 45 HCP	Saying numbers from 1 to 10 at a self-paced rate. Sequence length 100	Patients with alcohol dependency show enhanced counting (not differentiated) over HCP, but not over patients with schizophrenia
Spatt & Goldenberg (1993), Exp.2	35 patients with frontal lobe lesions and 20 HCP**	Saying numbers from 1 to 9 at 1 Hz and 0.2 Hz response rates. Sequence length 81	Patients show enhanced counting (not differentiated); both groups show enhanced counting at faster rate
Spatt & Goldenberg (1993), Exp.3	26 patients with PD and 20 HCP**	Saying numbers from 1 to 9 at 1 Hz and 0.2 Hz response rates. Sequence length 81	Patients show enhanced counting (not differentiated); both groups show enhanced counting at faster rate
Azouvi et al. (1996)	18 patients with closed head injury and 18 HCP**	Saying numbers from 1 to 9 at a self-paced rate. Sequence length 40. RNG task once in single, once in dual task condition	No group difference in counting (+1), but groups count significantly more under dual compared to single task conditions
Brugger et al. (1996)	30 patients with probable AD and 30 HCP**	MDT	Patients show enhanced counting (+1)
Brown et al. (1998)	16 patients with PD and 8 HCP*	Saying numbers from 1 to 9 at a self-paced rate. Sequence length 100	Patients and controls show enhanced counting (+1 reps. +2)
Williams et al. (2002)	14 patients with autism (low-functioning) and 14 HCP* (included one more control group)	Typing keys from 1 to 9 at a self-paced rate. Sequence length 100	No group differences in counting (+1)
Jahanshahi et al. (2003)	10 patients with primary dystonia and 12 HCP***	Saying numbers from 1 to 9 at 0.5 Hz response rate. Sequence length 100	Patients only tendentially more counting (+1 and +2)
Ho et al. (2004)	30 patients with HD (19 symptomatic, 11 asymptomatic) and 20 HCP**	Saying numbers from 1 to 9 at a 1.2 Hz response rate. Sequence length 100	Symptomatic patients show enhanced counting (+1) than asymptomatic und HCP
Dirnberger et al. (2005)	6 patients with PD and 6 HCP*	Saying numbers from 1 to 9 at three different rates (1, 0.5, 0.33 Hz). Sequence length 150, 75 and 50 resp.	Patients show enhanced counting (composite of +1, -1), counting bias increased from lower to higher rate
Matsukawa et al. (2006)	48 patients with SLE and 39 HCP (included one more comparison group with schizophrenia in remission)	Saying numbers from 1 to 9 at a self-paced rate. Sequence length 100	Patients show enhanced counting (composite of +1, +2, -1, -2)
Rinehart et al. (2006)	12 patients with autism (high-functioning), 12 with Asperger's disorder and 12 HCP***	Saying numbers from 1 to 10 first at a 1 Hz response rate, then at a self-paced rate. Sequence length 100	Asperger patients count more than HCP (+1). HCP show more and Asperger patient less counting under 1Hz rate. High-functioning patients not different from HCP, no effect of pacing

Study	Patients and healthy control participants (HCP)	Characteristics of RNG task	Main findings
Salamé & Danion (2007)	23 patients with schizophrenia and 24 HCP**	Saying numbers from 1 to 10 at three different rates (1, 0.5, 0.25 Hz). Sequence length 100	Patients show enhanced counting (+1 and -1); both forward and backward counting increases from lower to higher response rates
Thobois et al. (2007)	6 patients with PD, off medication and bilateral DBS in the STN on vs. off, no HCP	Saying numbers from 1 to 9 at 1 Hz response rate. Sequence length 100	No difference in counting (composite of +1, -1)
Peters et al. (2007), Study 4	26 patients with schizophrenia and 40 mid-age and 299 young HCP	Saying numbers from 1 to 10 at 1 Hz response rate. Sequence length 100	Patients show enhanced counting (for both overall count score (+1, +2, -1, -2) and for steps of +1, separately)
Proios et al. (2008)	20 patients with aphasia, 101 HCP**	MDT (non-compliance with 1 Hz rate was tolerated)	Patients show enhanced counting (+1, -1; not differentiated)
Loetscher & Brugger (2009)	19 patients with neglect after right hemisphere damage and 29 HCP**	MDT	No group difference in counting (neither +1, +2, -1 or -2)
Obeso et al. (2011)	18 non-demented patients with PD and 29 HCP*	Saying numbers from 1 to 9 at 1 Hz response rate. Sequence length 100	Patients show enhanced counting in steps of 1 (+1, -1; not differentiated), but not in steps of 2 (+2, -2; not differentiated),
Chan et al. (2011)	44 patients with schizophrenia and 48 HCP*	Writing down numbers from 0 to 9 at a self-paced response rate. Sequence length 500	No group difference in counting (+1)
Dirnberger et al. (2014)	6 patients with schizophrenia and 6 HCP***	Saying numbers from 1 to 9 at three different response rates (1, 0.5, 0.33 Hz). Sequence length 100	No group difference in counting (+1, -1; not differentiated)
Naim-Feil et al. (2014)	24 alcohol-dependent patients and 23 HCP*	Saying numbers from 1 to 9 at 1 Hz response rate. Sequence length 100	No difference in overall count score (+1, +2, -1, -2), but patients tend to count more (+1; p=0.05)
Münte et al. (2015)	12 patients with PD and 12 HCP*	Pressing number keys on a computer keyboard at 0.55 Hz response rate. Sequence length not specified	Patients show enhanced counting (+1, -1; not differentiated)
Williams et al. (2015)	15 patients with PD with bilateral DBS in the STN on vs. off	Saying numbers from 1 to 9 at three different response rate (1, 0.5, 0.33 Hz). Sequence length 100	Enhanced counting (+1, -1; not differentiated) at faster rate with DBS on
Geisseler et al. (2016)	44 patients with multiple sclerosis and 39 HCP**	MDT	Patients show enhanced counting (+1)
Sheppard et al. (2016)	74 HIV-seropositive patients and 54 HCP**	Saying numbers from 1 to 10 at 1 Hz response rate. Sequence length 100	Patients show enhanced counting (+1, -1, +2, -2; not differentiated)
Shinba (2017)	14 patients with depressive disorder, 11 with anxiety disorder and 41 HCP*	Saying numbers from 0 to 9 at 1 Hz response rate. Sequence length 100	No group difference in counting (+1, -1; not differentiated)
Williams et al. (2020)	23 patients with PD on and off dopaminergic medication, no HCP	Saying numbers from 1 to 9 at 1 or 0.5 Hz response rate. Sequence length 100	Enhanced counting (+1, -1; not differentiated) at faster rate; no effect of medication

AD: Alzheimer's Disease; DBS: deep brain stimulation; HCP: matched healthy control participants; HD: Huntington's disease; MDT: Mental Dice Task (saying numbers from 1 to 6 at 1Hz response rate, sequence length 66); PD: Parkinson's Disease; RNG: Random number generation; SLE: systemic lupus erythematosus; STN: subthalamatic nucleus. * = age matched; ** = age and education matched; *** = age and IQ matched

5.3.3 Methods

5.3.3.1 Study design and population

For the present cross-sectional cohort study, young adults between 18 and 32 years with a CHD were identified from two previous studies (Rometsch et al., 2019; von Rhein et al., 2011) and recruited between October 2016 and October 2018 from the outpatient clinic of cardiology at the University Hospital Zurich (see Schlosser et al., 2021 and Naef et al., 2021). All participants were native German speakers (95.1 % Swiss, 2.46 % German and 2.46 % citizens of Liechtenstein). Exclusion criteria were comorbidities affecting neurocognitive functioning, such as neurological impairments or genetic syndromes. Cardiological data was taken from the in-clinic medical records of the patients. CHD complexities were defined as simple, moderate and severe according to Warnes et al. (2001). Most patients with CHD are routinely screened for 22q11.2 microdeletion syndrome during childhood, and all participants are followed by dedicated ACHD-specialists. Therefore, it is very unlikely that patients with previously unrecognized genetic syndromes affecting neurocognitive functioning were enrolled in this study, although not all participants underwent formal genetic testing. Age-, gender- and parental-SES-matched healthy controls were recruited. SES was estimated based on the sum of maternal and paternal educational levels (each ranging from 1 to 6), resulting in a 12-point scale ranging from 2 (lowest) to 12 (highest). Educational level was based on the actual number of years of schooling until completion of an initial education. The Ethical Committee of the Canton of Zurich, Switzerland approved this study and a written informed consent was obtained from all participants, in accordance with the Declaration of Helsinki.

5.3.3.2 Neurocognitive assessment

Random number generation

The MTD was administered as part of an extensive neuropsychological test battery (Schlosser et al., 2021) in its standardized form (Brugger et al., 1996). Participants were asked to name the numbers from 1 to 6 in a random order by imagining throwing a die over and over again, each

time naming the face that would show up. They were instructed to respond synchronously with an auditory stimulus, which was a metronome at the speed of 1Hz. A total of 66 valid numbers were recorded. If a participant named an invalid number, e.g. “7”, (s)he was corrected and the task continued until 66 valid digits were collected.

Towse & Neil (1998) developed a freely available computer software that allows the calculation of a number of different indicators of sequential (non)randomness. Detailed information on these calculations, including theoretical explanations, is described elsewhere (Towse & Neil, 1998). Before data collection, we had selected several of these measures for the present investigation. First, as a global measure of randomness, we calculated Evans’ RNG index (Evans, 1978) and the redundancy score. These measures are not statistically independent, but were selected because most previous work on RNG had relied on one or the other. Both reflect the observed frequencies of digrams compared to the number in a true random sequence. Specifically, redundancy represents the deviation from mathematical randomness, a redundancy score of 0 % indicating equiprobability of response alternatives, and a redundancy score of 100 % indicating complete redundancy (Towse & Neil, 1998). Under the assumption of an enhanced response stereotypy in the CHD group, we predicted higher scores in both measures for the CHD patients. We also computed the distribution of the first-order difference (FOD), which is based on the arithmetic difference between each response and its preceding one (Brugger et al., 1996). We calculated all possible eleven FODs (from -5 to +5, including 0) for the sake of illustration; meaningful group differences were only expected for the three most frequent FODs, i.e., -1 (backward counting), 0 (repetition) and +1 (forward counting). Figure 5.6 shows all possible pair combinations and the theoretical distribution of the resulting FODs. We predicted a distinctive forward counting bias in the CHD group, on the assumption of an impaired inhibition control of automatized counting. A further special case reflects the FODs of 0, which corresponds to response repetitions. Although we did not expect group differences in this variable (see section Discussion, Chapter 5.3.5), we expected to elucidate behavioral and neural correlates of the pervasive tendency to avoid direct repetitions in RNG experiments.

In addition to these measurements of (non-)randomness, three more variables were considered. The first was the sum of small digits (i.e., 1, 2 and 3). Previous research with healthy volunteers identified a "small-number bias" in the MDT, i.e., digits 1, 2 and 3 occurred more frequently than digits 4, 5 and 6 (Loetscher & Brugger, 2007). Motivated by Schmidt et al. (2021), who reported on this spatial measure of RNG in two patient groups, we included it here in an exploratory way. Two more non-sequential measures were collected: the number of rule breaks (numbers not shown on a die, e.g., 7) and the total number of skipped metronome beats. We predicted a higher number of rule breaks and skipped beats in the CHD group on grounds of an impaired inhibition ability. Both, number of rule breaks and skipped beats, have been proved as useful monitoring of executive function in RNG (e.g., Gottselig et al., 2006).

Global executive functioning

T-scores for each participant of the following executive function tasks were averaged and combined to a GEF. *Interference control* was assessed by the third condition of the Color-Word Interference Test from the Delis–Kaplan Executive Function System (Delis et al., 2001). *Flexibility* was examined with the Color-Word Interference Test (fourth condition) and the numbers and letters subtest of the Trail Making Test (Tombaugh, 2004). *Response inhibition* was measured by the Stop Signal Task (Verbruggen et al., 2008) and to assess *problem solving* the Standardized Link's Probe (Metzler, 2000) was applied. *Fluency* performance was assessed by a verbal (Aschenbrenner et al., 2000) and non-verbal (Haid et al., 2000) fluency task. Finally, verbal (Petermann, 2012) and visual (Härting et al., 2000) digit span (longest forward and backward span) was used to examine *working memory.* We predicted correlations between the GEF and the following executive function dependent MDT variables: counting (especially forward counting), RNG index, redundancy, and repetitions.

5.3.3.3 Cerebral MRI

MRI scanning was performed within one month after neuropsychological examination. A 3T GE MR750 scanner at the Children's University Hospital Zurich was used for MRI data acquisition.

For participants' safety, hearing protection was provided by earplugs and headsets. To estimate brain volumes three-dimensional T1 high-resolution weighted images were acquired (scan parameters: repetition time/echo time = 11/5 ms; inversion time = 600 ms; flip angle = 8°; acquisition matrix = 256 × 192, reconstruction matrix: 256x256; field of view = 256 cm). An experienced medical researcher (N. N.) conducted cortical reconstruction and volumetric segmentation with the Freesurfer image analysis suite version 5.3.0, which is documented and freely available for download online. For a detailed description of the MRI postprocessing, see Naef et al. (2021). Due to insufficient imaging quality, MRI data of two CHD patients and one control participant had to be rejected for further volumetric analyses.

5.3.3.4 Statistical analyses

Statistical analyses of the demographic and cognitive data were performed with SPSS. P-values below 0.05 were considered significant. Group comparisons were based on parametric tests (ttest for independent samples, Chi-Square). To analyze group differences between the CHD complexities, analyses of variances with Tukey's post-test were calculated. If not stated otherwise, False Discovery Rate was used to correct for multiple testing according to the Benjamin-Hochberg-Method (Benjamini & Hochberg, 1995). Association between MDT variables with GEF were calculated using univariate linear regression models including MDT as dependent variables and group, GEF and an interaction of group with GEF as independent variables. Association between MDT variables with brain volumes (as reported in Naef et al., 2021) were calculated using univariate linear regression models including MDT as dependent variables and group, brain volumes and an interaction of group with brain as independent variables.

5.3.4 Results

5.3.4.1 Group characteristics

A total of 191 patients with CHD were identified from two previous studies (Rometsch et al., 2019; von Rhein et al., 2011). From these, 123 could either not be reached (n = 59, 31 %) or

refused participation (n = 64, 33 %). There was no difference in sex (p = 0.69) and CHD complexity (p = 0.15) between participants and non-participants. However, participants were older (26.9 vs. 24.3 years, p < 0.001). Thus, the final sample consisted of 67 CHD patients (response rate 35 %) (Table 5.11 provides information on medical parameters). All performed on the MDT and the executive tasks. MRI was performed in 46 participants; in twelve MRI safety could not be ensured (e.g., due to implants) and for nine participants MRI was not possible for various other reasons (refused imaging n = 5; claustrophobia n = 2; obesity n = 1; pregnancy n = 1).

A total of 55 healthy control participants served as comparison group. They were recruited as peers of the CHD patients (n = 41, 75 %) or personal contacts of the study team (n = 14, 25 %). Peers included siblings, friends and classmates. Control participants provided information about their physical and mental health by questionnaire and were matched to the CHD group for gender, age and parental-SES as carefully as possible. All were tested with the MDT, the executive function tests and underwent MRI acquisition. One control participant refused neuroimaging for personal reasons.

Demographic variables are reported in Table 5.12. The CHD and the control group did not differ in age (CHD: 26.9 (SD 3.86) vs. controls: 26.0 (SD 3.32) years, p = 0.175), gender (CHD: 37 (55 %) vs. controls: 28 (51 %) males, p = 0.635) and parental-SES (CHD: 8 (IQR 7.75; 10) vs. controls: 9 (IQR 8; 10), p = 0.181). The CHD participants showed 0.88 years less schooling than the control participants (t(120) = -2.414, p = 0.017; CHD: 14.18 (SD 2.07) vs. controls: 15.06 (SD 1.89)). However, compared to the Swiss educational system with a regular schooling period of twelve years, both groups had a relatively high level of education. Of the CHD group, 18 (27 %) individuals had a simple, 33 (49 %) a moderate and 16 (24 %) a severe CHD complexity (Warnes et al., 2001). Gender was equally distributed and no differences were found in age and parental-SES between simple, moderate and severe CHD complexity (all p > 0.050).

Table 5.11. Characteristics of the CHD group with CHD diagnosis classified into defect complexity simple, moderate and severe according to Warnes et al. (2001).

Heart defect complexity, n (%)	
Simple	18 (26.9)
Isolated congenital aortic valve disease	7 (10.4)
Repaired ventricular septal defect	3 (4.5)
Isolated congenital mitral valve disease	3 (4.5)
Previously ligated or occluded ductus arteriosus	1 (1.5)
Small atrial septal defect	1 (1.5)
Mild pulmonary stenosis	1 (1.5)
Other simple CHD[a]	2 (3.0)
Moderate	33 (49.3)
Coarctation of the aorta	8 (11.9)
Tetralogy of Fallot	8 (11.9)
Ventricular septal defect with coarctation of the aorta	4 (6.0)
Ventricular septal defect with right ventricular outflow tract obstruction	3 (4.5)
Ventricular septal defect with mitral valve disease	2 (3.0)
Ebstein's anomaly	2 (3.0)
Pulmonary valve stenosis	2 (3.0)
Supravalvar aortic stenosis	1 (1.5)
Atrioventricular canal defects	1 (1.5)
Anomalous pulmonary venous drainage	1 (1.5)
Other moderate CHD[b]	1 (1.5)
Severe	16 (23.9)
Transposition of the great arteries[c]	11 (16.4)
Fontan procedure	3 (4.5)
Pulmonary atresia	1 (1.5)
Double-outlet ventricle	1 (1.5)
Cyanotic heart defect, n (%)	24 (35.8)
Device, n (%)	
Pacemaker	3 (4.5)
Number of CBP surgeries, n (%)	
0[d]	19 (28.4)
1[e]	30 (44.8)
2[f]	9 (13.4)
3[g]	9 (13.4)
Age in years at first CBP surgery, Median (IQR)[h]	0.88 (0.17; 5.22)
ECC time in minutes, Median (IQR)[i]	143 (69; 208)
NYHA classification, n (%)	
I	63 (94.0)
II	4 (0.6)
Cardiac medication[j]	14 (20.9)
ACE-Inhibitors / Angiotensin II receptor antagonists	10 (14.9)
Beta blockers	3 (4.5)
Calcium channel blockers	2 (2.9)
Anticoagulation with vitamin K antagonists	3 (4.5)

[a] Ventricular septal defect with tricuspid valve disease, n = 1; Congenital mitral valve disease and small atrial septal defect, n = 1; [b] Ventricular septal defect and abnormal origin of the left pulmonary artery from descending thoracic aorta, n = 1. [c] 1 with congenitally corrected transposition of the great arteries with moderate sized ventricular septal defect and severe pulmonary stenosis (unrepaired), 7 with complete transposition after atrial switch repair and three with complete transposition and arterial switch operation. [d] 8 with simple, 10 with moderate, and 1 with severe CHD; [e] 7 with simple, 11 with moderate, and 12 with severe CHD; [f] 1 with simple, 7 with moderate, and 1 with severe CHD; [g] 2 with simple, 5 with moderate, and 2 with severe CHD; [h] 4 missing values; [i] 21 missing values; [j] some of the patients had multiple medications; CBP: Cardiopulmonary bypass; ECC: Extracorporal circulation.

Table 5.12. Characteristics and test performance of the CHD and the control group.

Variable	Patients, n = 67	Controls, n = 55	p-value	adj. p-value (after FDR correction)
Sample characteristics				
Age (years)	26.92 (3.68)	26.04 (3.32)	0.175	0.350
Sex (male), n (%)	37 (55.22)	28 (50.91)	0.635	0.635
SES (median / IQR)	8 / (7.75; 10)[a]	9 / (8; 10)[b]	0.181	0.241
Years of school	14.18 (2.07)	15.06 (1.89)	0.017	0.068
Sequential MDT measures, mean (SD)				
RNG index	0.417 (0.045)	0.407 (0.033)	0.180	0.450
R	1.343 (2.908)	1.021 (0.845)	0.429	0.429
FOD 1 fw counting	12.239 (4.000)	12.964 (4.611)	0.354	0.443
FOD 0 direct repetitions	4.851 (4.859)	5.800 (4.318)	0.261	0.435
FOD -1 bw counting	14.164 (4.195)	12.382 (3.582)	0.014	0.049
Non-sequential MDT measures, mean (SD)				
Small numbers	32.328 (4.117)	34.291 (2.522)	0.002	0.012
Rule breaks	0.448 (.744)	0.527 (1.034)	0.623	0.623
Skipped beats	3.910 (6.746)	2.855 (4.809)	0.332	0.398
GEF in T-Scores	50.125 (5.775)[c]	52.353 (4.094)[d]	0.016	0.032

[a] n = 62; [b] n = 51; [c] n = 65; [d] n = 54; FOD: First order difference; GEF: Global executive function; IQR: Interquartile range; MDT: Mental Dice Task; R: Redundancy; RNG: Random number generation; SES: Socio economic status, range from 2 (lowest) to 12 (highest). P-values are two tailed.

5.3.4.2 Neurocognitive findings

Results of the MDT and the GEF are reported in Table 5.12. The two groups did not differ in the RNG index and the redundancy score (p-values > 0.050). The distribution of the FODs is shown in Figure 5.6. FODs were compared to reference values for both groups separately. For FOD -1 (backward counting), FOD 0 (repetitions) and FOD +1 (forward counting), both groups differed significantly from the expected mathematical values of a real die (CHD: FOD -1, $t(66) = 9.746$, $p = 0.000$; FOD 0, $t(66) = -10.358$, $p = 0.000$; FOD +1, $t(66) = 6.279$, $p = 0.000$; Controls: FOD -1, $t(54) = 6.649$, $p = 0.000$; FOD 0, $t(54) = -8.931$, $p = 0.000$; FOD +1, $t(54) = 6.102$, $p = 0.000$). The CHD group showed a significantly more pronounced backward counting than the control group ($t(120) = 2.492$, $p = 0.014$, adj. $p = 0.049$). No corresponding difference was found for forward counting ($t(120) = -0.930$, $p = 0.354$, adj. $p = 0.443$) and repetitions ($t(120) = -1.128$, $p = 0.261$, adj. $p = 0.453$).

With respect to the non-sequential measures of the MDT, the CHD group produced significantly less small numbers than the control group ($t(120) = -3.090$, $p = 0.002$, adj. $p = 0.012$). More precisely, while 65.5 % (n = 36) of the control participants showed a small-number bias,

only 40.3 % (n = 27) of CHD patients did so ($Chi^2(2) = 10.809$, p = 0.004). No group differences were found in the number of rule breaks or skipped beats (p-values > 0.050).

Within the CHD group, we found a significant difference for the RNG index between the CHD complexities (F(2) = 3.587, p = 0.033). A Tukey post-hoc test revealed that performance for RNG index was significantly lower for patients with a moderate CHD complexity (0.407 ± 0.337) than for those with simple CHD complexity (0.440 ± 0.003). No group differences were found for the other examined variables of the MDT (redundancy: F(2) = 1.256, p = 0.292; FOD +1: F(2) = 1-209, p = 0.305; FOD 0: F(2) = 0.169, p = 0.845; FOD -1: F(2) 2.481, p = 0.092; small numbers: F(2) 0.948, p = 0.393; rule breaks: F(2) = 0.694, p = 0.503; skipped beats: F(2) = 0.328, p = 0.721).

Compared to the control group, the CHD group performed poorer on the GEF (t(114.3) = -2.455, p = 0.016, adj. p = 0.032). The GEF was associated with the RNG index (F(3, 115) = 6.670, p < 0.001, adj. p = 0.001, B = -0.004, 95% CI: -0.006; -0.001, β = -0.500, p = 0.003), forward counting (F(3, 115) = 2.872, p = 0.039, adj. p = 0.062, B = -0.379, 95% CI: -0.656; -0.102, β = -0.460, p = 0.008) and repetitions (F(3, 115) = 3.701, p = 0.014, adj. p = 0.037, B = 0.360, 95% CI: 0.061; 0.660, β = 0.401, p = 0.019). There was no interaction of group with the GEF on the MDT variables (for all interaction p-values > 0.050).

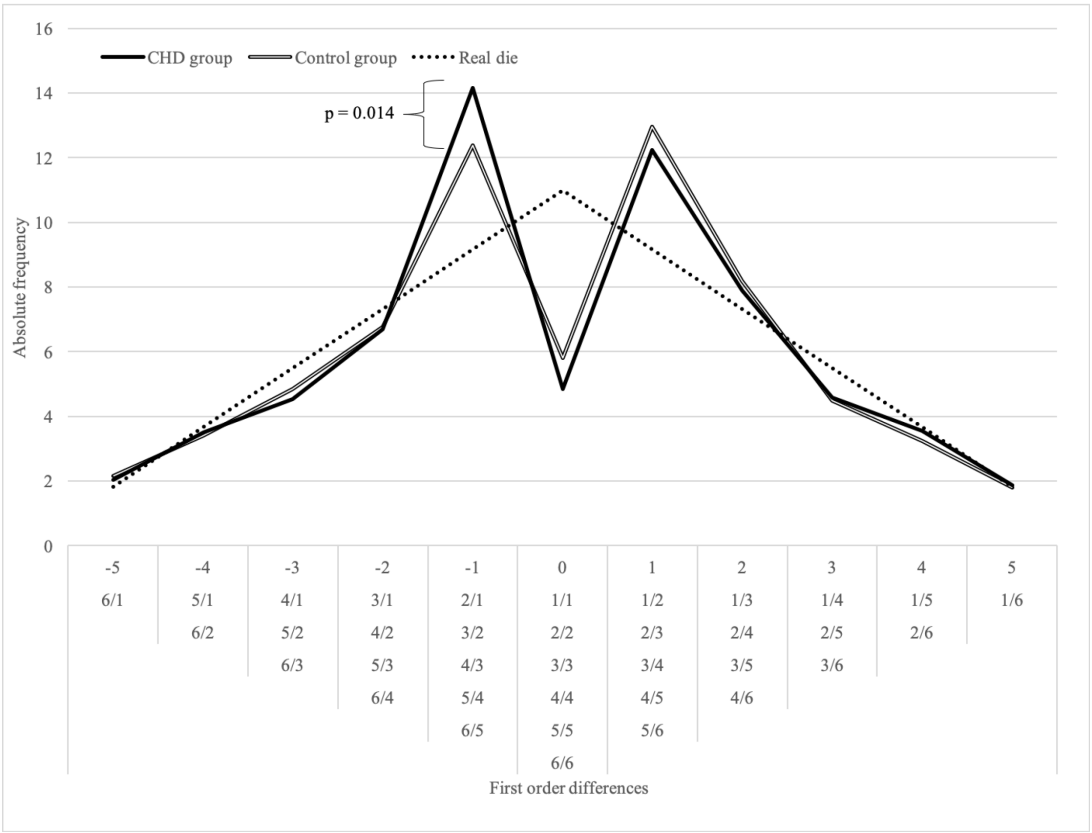

Figure 5.6. Distribution of the first order differences (FODs). Backward counting is demonstrated at point -1 on the x-axis, aversion of direct repetitions at point 0, and forward counting at point 1.

5.3.4.3 Cerebral MRI findings

As reported previously (Naef et al., 2021), relative to the control group, the CHD group had a significantly reduced total brain volume, white matter and corpus callosum volume. There were no group differences for grey matter and cerebellar volume (see Table 5.13). After adjusted for total brain volume, only corpus callosum volume proved to be significantly different between the two groups.

Multiple regression models with the MDT variables as dependent, brain volumetric data as independent variables and an interaction term of group and brain volumes, showed significant associations only on backward counting (FOD -1) and small numbers. In a model with group and an interaction of group with all measured brain volumes on backward counting (FOD -1), there were no main effects of any brain volumetric data over all subjects (all p-values > 0.05). However, there were significant interactions of group with all measured brain volumes on backward counting (total brain volume: $F(3, 93) = 10.015$, $p < 0.001$, adj. $p < 0.001$, $B = 0.007$, 95% CI: -0.013;

0.007, β = -2.526, p = 0.008; white matter: F(3, 93) = 7.527, p < 0.001, adj. p < 0.001, B = -0.030, 95% CI: -0.056; -0.004, β = -1.675, p = 0.025; grey matter: F(3, 93) = 10.897, p <0.001, adj. p < 0.001, B = -0.037, 95% CI: -0.062; -0.012, β = -2.865, p = 0.005; corpus callosum: F(3, 93) = 4.588, p = 0.005, adj. p = 0.006, B = -3.429, 95% CI: -6.559; -0.300, β = -1.285, p = 0.032) except for the cerebellar volume (F(3, 93) = 3.745, p = 0.014, adj. p =0.014, B = -0.098, 95% CI: -0.223; 0.026, β = -1.506, p = 0.119). An interaction model of group and brain volumetric data on small numbers showed a significant interaction of the group with corpus callosum volume (F(3, 93) = 5.488, p = 0.002, adj. p = 0.010, B = 3.407, 95% CI: 0.415; 6.398, β = 1.319, p = 0.026).

When calculating the effect of brain volumes on backward counting for the groups separately, there were significant associations only within the CHD group, in particular for the total brain volume (F(1, 42) = 25.434, p < 0.001, adj. p = 0.000, B = -0.021, 95% CI: -0.030; -0.013, β = -0.614), the white matter (F(1, 42) = 15.500, p < 0.001, adj. p = 0.000, B = -0.034, 95% CI: -0.051; -0.017, β = -0.519), the grey matter (F(1, 42) = 29.394, p < 0.001, adj. p = 0.000, B = -0.042, 95% CI: -0.058; -0.027, β = -0.642), and the corpus callosum (F(1, 42) = 5.094, p = 0.029, adj. p = 0.036, B = -2.442, 95% CI: -4.625; -0.258, β = -0.329). The same analyses for corpus callosum on small numbers revealed only a significant association within the CHD group (F(1, 42) = 5.392, p = 0.025, adj. p = 0.058, B = 3.000, 95% CI: 0.393; 5.607, β = 0.337).

Table 5.13. Brain volumes in cm^3 of the CHD and the control group, mean (SD).

Brain volumes	CHD group, n = 44	Control group, n = 53	p-value
Total brain volume	1067.256 (113.526)	1113.039 (97.878)	0.006
Total white matter volume	432.623 (59.815)	461.755 (52.630)	0.001
Total grey matter volume	608.705 (59.305)	622.790 (52.577)	0.084
Total cerebellar volume	118.759 (12.588)	120.175 (12.221)	0.632
Corpus callosum volume	2.855 (0.527)	3.171 (0.449)	< 0.001

Group comparison calculated with univariate analysis of covariance with age and sex as covariates, total and regional brain volumes as dependent and group as fixed factors. P-values are two-tailed. Bonferroni correction for multiple testing was applied. Data from Naef et al. (2021).

5.3.5 Discussion

We set out to investigate the ability of young adults with CHD to repeatedly name a number between 1 and 6, in a sequence as random as possible. Structural MRI was obtained for each participant to explore potential neural correlates of the randomization performance in patients with CHD and in healthy controls.

We could not find a generally poorer RNG performance in our patient group. Participants with CHD did not perform significantly different from control group participants in the two global measures of information content, i.e., the RNG Index and the redundancy score. This is in line with previous findings with the MDT, according to which a healthy brain's internal random generator deviates substantially from a real die, that group differences in overall randomness will only be evident in the presence of marked neurological impairment (e.g., Brugger et al., 1996). In neuropsychological patient groups with only relatively mild cognitive deficits, no enhanced redundancy was found in comparison to healthy control persons (e.g., Brown et al., 1998 and Geisseler et al., 2016). However, with regards to the different complexities of CHD, we found that patients with simple CHD scored worse on the RNG Index than patients with moderate CHD. This finding is counterintuitive and probably accountable to the relatively small number of patients in the single subgroups. Nevertheless, overall randomness in the present study was significantly associated with a compound measure of executive functioning (Schlosser et al., 2021) in both groups. This finding adds to previous numerous observations that human subjects' ability to mimic a randomization device depends on frontal executive functions.

Counting and backward counting bias

With respect to more specific performance measures, both studies mentioned above (Brown et al., 1998; Geisseler et al., 2016), which did not find group differences in overall randomness, did uncover group differences in a single variable, the individual's tendency to count. "Counting bias" is certainly the most prominent RNG measure to consistently demonstrate differences between neuropsychological patient groups and their respective controls (Table 5.10 for a comprehensive overview). While we had predicted that patients with a CHD would display enhanced *forward*

counting in steps of 1 (the canonical way of arranging numbers in everyday life), we found them to diverge from controls only in *backward counting*. We interpret this finding as pointing to the relatively mild executive function deficits in the CHD group; any excessive counting must have been detected during the task and "compensated" for by a less salient way of seriation, i.e., the arrangement of the digits in a *de*scending order. This interpretation is supported by findings reported by Brown et al. (1998) (see Table 5.10). These authors tested non-demented patients with Parkinson's disease and a control group with an RNG task either performed singly or simultaneously with an additional task (manual tracking). While in a single RNG task, only patients showed an increased number of counting steps of 1, healthy participants "compensated" with an excess of a less obvious counting in steps of 2. This compensation mechanism broke down, however, in the dual task situation, which arguably strained executive resources; now also the healthy participants counted in steps of 1 (and patients' counting bias was exaggerated).

The usual interpretation of counting bias as mostly related to the inability to inhibit overlearned routines (e.g., Knoch et al., 2005; Miyake et al., 2000) is supported by the association between this bias (forward in steps of 1) and a composite measure of executive functioning (on which the CHD patients scored lower than controls; cf. Schlosser et al. (2021)). The worse the executive functions, the further a participant's number sequence would diverge from true randomness. The fact that counting bias was *negatively* associated with the quality of executive functioning, but the number of repetitions showed a positive correlation, demonstrates that these two biases should be treated separately from one another (and not lumped together to form one global randomization index).

Repetition behavior

Not surprisingly, the number of immediate repetitions in the MDT did not differ between the two participant groups. Even in patient populations with marked neurocognitive deficits the avoidance of repetitive responses is usually as prominent as it is in healthy participants. This has been interpreted as a floor effect by Peters et al. (2007), p. 632: "in attempts to produce responses at random, repetitions are generally so strongly avoided that group differences would not likely be observed,

nor would correlations with other neuropsychological performance measures show up". In fact, the only two studies listed in Table 5.10, which report differences in the number of repetitions, are Williams et al. (2002) and Rinehart et al. (2006). In both, RNG performance of low-functioning (Williams et al., 2002) and high-functioning (Rinehart et al., 2006) autistic patients respectively, was characterized by a larger number of direct repetitions. In a motor random generation task, this finding of increased repetitive responding was recently replicated (Weiss et al., 2017). Autism may be unique in that perseveration tendencies in RNG do not involve the continuation of a rule (i.e., counting, as evident in most other patient groups) but target the repetition of an identical element (a single digit, in the case of RNG). We recommend Frith (1996) and Kiep and Spek (2017) for a discussion of perseveration and repetition types in the framework of autism spectrum disorders and Tan et al. (2020) on a three-fold prevalence of autism in CHD.

Small number bias

With respect to the non-sequential measures of the MDT, participants with CHD named fewer small numbers (1, 2 and 3) than the control group. They actually showed a 60 %-preference for high numbers, which is contrary to that of the control participants, who showed a 65 %-preponderance for naming 1, 2, or 3. Loetscher and Brugger (2007) demonstrated a "small number bias" across a set of 16 independent experiments and interpreted it as a pseudoneglect in number space. Pseudoneglect refers to the tendency of healthy individuals and animals (Diekamp et al., 2005), to show an orientation bias toward the left side of space and reflects the right hemisphere's dominance for spatial exploration. Later experimentation has supported the spatial interpretation of the small number bias in RNG (Badets et al., 2015; Di Bono & Zorzi, 2013; Loetscher et al., 2010) and pointed out its association with hemispheric differences in frontal lobe mediated cognitive functions (Bachmann et al., 2010). The biological basis of a bias for small numbers (the left side of number space) is also elucidated by experiments with nonhuman species (Rugani et al., 2020). Studies with young children showed that the bias to prefer small over high numbers in RNG develops over time, actually for children below the age of eleven it is reversed (Towse et al., 2014). The lack of a small number bias in young adults with CHD was unexpected. We had

simply included this measure with the intention to explore its possible structural cerebral correlate for the first time. We will further comment on our unexpected finding when discussing the MRI results (see below).

Two other measures not related to the sequential properties of a generated random sequence are the number of rule breaks (naming a digit outside of the response class) and of skipped beats of the metronome. Previous research has described neuropsychological patient groups impaired in one or the other measure (e.g., Geisseler et al., 2016; Gottselig et al., 2006). In the present study, no group differences were found in either measures.

Brain volumetric analyses

Turning now to the data obtained in the structural neuroimaging part of the study. Compared to the control group, the CHD group had generally smaller brain volumes, significantly so for the total brain and separately for the total white matter (Naef et al., 2021). In accordance with previous findings (Fontes et al., 2019), grey matter volumes were not different between the two groups. Cerebellar volume did also not differ between the two groups, but corpus callosum volume did. In fact, as reported in Latal et al. (2016) and in von Rhein et al. (2014), after adjusting for total brain volume, corpus callosum volume was the only volumetric measure that significantly differentiated between the CHD and the control group. This may not surprise as the largest white matter bundle in the human brain, the corpus callosum, is among the structures most affected by a CHD, already in neonates (Hagmann et al., 2016; Pérez-Cruz et al., 2022).

The only measure of sequential randomness which differentiated between the CHD and the control group was backward counting. In the patients group it was inversely associated with all volumetric measures except the volume of the cerebellum. This underscores the importance of counting bias in studies on RNG in neurological patient groups as illustrated in Table 5.10. We could not find any significant association between repetition behavior and brain volumetric data. This mirrors a previous finding in patients with multiple sclerosis (Geisseler et al., 2016).

As noted above, the CHD group did not display the small number bias usually found in healthy individuals, which was also present in our healthy control group. But, exclusively in the

CHD group, the amount of produced small numbers was associated with corpus callosum volume; the smaller this bias, the smaller the volume of the corpus callosum. Pseudoneglect in physical space has repeatedly served as an indicator of the corpus callosum maturation (e.g., Hausmann et al., 2003). In line bisection studies, prepubescent children usually place the subjective mid-point ipsilateral to the bisecting hand. Yet from around puberty a consistent left-sided shift (i.e. pseudoneglect) can be noticed for both hands. This shift is interpreted as an indication of maturation of the corpus callosum, which would gradually allow the transfer of attention-based visuomotor functions across both hands. In a line bisection study with 46 healthy children ages 8 to 18 years, Pulsipher et al. (2009) described a linear relationship between corpus callosum volume and age. However, the authors did not find the hypothesized age-dependent relationship between corpus callosum volume and bisection bias. On this ground, they questioned the validity of the line bisection test for monitoring corpus callosum functions. Asymmetries in number space could be a more suitable measure as they do not involve a lateralized motor output and might assess lateral asymmetries of attention in a more direct way. The herein established lack of a small number bias in association with a structurally compromised interhemispheric connection is compatible with observations regarding a pseudoneglect in physical space after a corpus callosum stroke (Wolk & Coslett, 2004).

No structural cerebral correlate of the number of rule breaks and skipped beats could be identified. A low number of such naming and pacing errors and a low variance across participants may be responsible for the absence of relationships between brain structure and behavior.

Clinical implications

With medical advances, surviving a CHD is no longer an exception, but rather the norm. This has resulted in a steadily growing and aging population with CHD. Nonetheless, with increasing age, this population is not cured, but remains confronted with other comorbidities, for example neurocognitive impairments. We could demonstrate poorer executive functioning in young adults with CHD compared to healthy controls; measured with a specific randomization task and with

an executive function score. If these executive dysfunctions are associated with pronounced cognitive decline needs further research. However, there is a growing consensus that patients with CHD are at higher risk for dementia (e.g., Bagge et al., 2018; Kovacs & Bellinger, 2021; Marelli et al., 2016). The risk of dementia has lately been estimated to be about 61 % higher for patients with CHD compared to the general population (Bagge et al., 2018). A recent study demonstrated that even patients with a simple CHD face a higher risk for early brain degeneration (Downing et al., 2022). Therefore, episodic neuropsychological examination, for example with the MDT, ought to be reputable as a routine clinical screening instrument.

5.3.5.1 Limitations

Several limitations of this study should be mentioned. First, the response rate of the eligible patients of 36 % was relatively low. The more extensive scope of this present examination with additional requirements that included neuropsychological examination and cerebral imaging compared to the original questionnaire study is a likely factor. Second, although CHD patients and control participants did not differ in age, sex, and parental-SES, the control group attendant school for almost one year longer (CHD 14.18 vs. controls 15.06 years). However, it must be noted that RNG has repeatedly been shown to be uncontaminated by education (e.g., Gauvrit et al., 2017). Third, despite the large number of research on RNG (see Table 5.10, which only lists work specifically investigating counting bias), there are still no available normative data for the MDT. It would seem desirable to compare the RNG performance of young adults with CHD with normative data based in a larger population. Also, in recent literature on RNG performance alternative measures of sequential non-randomness have been proposed (see especially Gauvrit et al., 2017; Oomens et al., 2021; Schulz et al., 2021) and should be considered in future research. Finally, our study was a single center study, and the validity of the results is thus limited to a regional cohort.

5.3.6 Conclusion

In conclusion, considering that randomization tasks are largely unaffected by education and repeated administration, the MDT may be suitable for longitudinal assessments of the neurocognitive functioning in patients with CHD. Instructions are easy to grasp even by children and patients with mild form of dementia.

6 General discussion

The present thesis aims to contribute to a better understanding of the impact of a CHD on the neurocognition of affected young adults and to uncover the relationship between the impairment of neurocognitive functions and neuroanatomical alterations. In this last part of the thesis, the findings generated by the empirical studies are summarized and discussed by answering to the research questions presented in Chapter 3. Furthermore, strengths and limitations of the three studies are discussed and, finally, clinical implications and suggestions for future research are presented.

6.1 Neurocognitive functioning in young adults with congenital heart disease

There is a broad consensus that children with a CHD experience neurocognitive impairments, particularly affecting the IQ as a general measure of the neurocognitive performance. Various more specific neurocognitive domains such as motor functions, visual-spatial skills, the social cognition, language skills, attention functions, and especially executive functions have also been shown to be affected (Bellinger et al., 2003; Bellinger & Newburger, 2010; Calderon et al., 2010; Marelli et al., 2016). As improvements in medicine led to a steadily increasing population of grown-up patients with CHD, the neurocognitive performance of affected young adults is brought into focus.

With the first study, we sought to identify the full spectrum of neurocognitive functioning including an estimated IQ. The hypotheses were phrased that patients with a CHD, compared to healthy control participants, would show poorer neurocognitive functioning and a lower IQ in general, and that executive functions, the attention and the processing speed may be particularly affected.

The findings of the first two studies provide support for these two hypotheses. First, we found that the estimated IQ with respect to the general intellectual functioning, was significantly lower in CHD patients compared to the healthy control group. Although the CHD patients on average achieved scores in the normal range, the proportion of participants with an IQ below the

clinical cut-off was notably higher in the CHD group versus the control group (10.8 % vs. 1.8 %). This finding is consistent with the results of previous studies that identified a lower IQ in ACHD patients (e.g., Tyagi et al., 2014 for a brief overview). When looking at the results of the two studies conducted for this analysis in more detail, we can even conclude that 1.5 % (one participant) of the CHD patients displayed an IQ which formally corresponds to an intelligence retardation (IQ range from 50 to 69) and 9 % (six participants) an IQ that classifies as a learning disability (IQ range from 70 to 84) according to the World Health Organization (2015). Compared to this, no participant of the control group displayed an intelligence retardation and only 1.8 % (one subject) formally exhibited a learning disability.

Second, apart from the IQ as a general measurement for the intellectual functioning, poorer performance in three global cognitive domains (1) executive functions, (2) memory, and (3) attention and processing speed could be reported in the CHD cohort compared to the healthy control group. Within the executive functions, evidence for impaired verbal working memory and interference control were found. Consistent with these objective neurocognitive data, CHD patients also reported higher executive function disabilities in everyday life according to the Behavior Regulation Index, reflecting a relatively well self-perceived executive (dys)function level. In the domain of attention and processing speed, especially the ability of divided attention proved to be affected. As predicted, these findings were in line with existing literature (e.g., Calderon & Bellinger, 2015; Mills et al., 2018), supporting the assumption that these deficits which already appear in affected children and adolescents persist into young adulthood. Interestingly, we also discovered poorer memory functions, specifically poorer visual memory functions. This is a cognitive domain with little evidence for relevant impairments in children with CHD (Tyagi et al., 2014). To the best of our knowledge, memory problems have never been reported in ACHD patients so far. This leads to the conclusion that there are not only neurocognitive deficits that persist from childhood, but also deficits that appear only with the transition into early adulthood.

Third, we were able to confirm that the complexity of the heart defect has an impact on neurocognitive functioning as well (Bellinger et al., 2015; DeMaso et al., 2014; Ilardi et al., 2017;

Kasmi et al., 2018; Klouda et al., 2017; Marelli et al., 2016; Mills et al., 2018); the more complex the defect, the more evident the neurocognitive impairment.

To conclude, we showed that the neurocognitive functioning of young adults with CHD is typically poorer than that of healthy control participants. Moreover, the first study highlights the benefits of an extensive neuropsychological examination over the sole assessment of the IQ or questionnaire data. Hence, the first research question can be answered in the affirmative (see Chapter 3); yes, young adults suffering from a CHD show a generally lower neurocognitive functioning (including IQ) compared to healthy control participants. The domains of executive functions, memory, and attention and processing speed are particularly affected. This can be explained by the fact that these domains are part of the key domains of the neurocognitive function (Sachdev et al., 2014). CHD can thus be considered a condition characterized by an adverse neurocognitive development.

6.2 Cerebral brain alterations and their association with neurocognitive performance

Studies on brain imaging of grown up CHD patients are rare, while structural brain anomalies and acquired brain injuries in neonates such as thromboembolic strokes, microhemorrhages and white matter lesions are well explored (Claessens et al., 2017; Marelli et al., 2016; Miller et al., 2007). Based on this research gap, questions about the prevalence of structural brain alterations in ACHD patients and the association of such alterations with neurocognitive functioning emerged (see Chapter 3, second research question). With the second and third studies, we tried to answer these questions by conducting two analyses. On the one hand, we applied the classification of structural brain anomalies according to Bellinger et al. (2011) and Bolduc et al. (2018), to focal infarction or atrophy, white matter lesion, microhemorrhages, and significant global cerebral atrophy. On the other hand, we compared brain volumes between the CHD patients and the healthy control participants. For this analysis we were kindly allowed to have access to the data published by Naef et al. (2021). However, the comparison of brain volumes was not the primary focus of this study. We principally used the brain volume data for the RNG analyses (see Chapter 6.3). We

refer to the work of Naef et al. (2021) for detailed information on brain volume alterations in CHD.

The results of the second study revealed two important findings. First, structural brain anomalies were detected in more than half of the CHD patients (63.0 %), but in none of the healthy control participants. This finding confirms previous reports of structural brain anomalies in ACHD patients (Cordina et al., 2014; Jensen et al., 2015; Sluman et al., 2017), which stated a prevalence of 47 - 70 %. The majority of brain anomalies in our sample were microhemorrhages, present in 25 CHD patients (54.4 %). To date, the underlying pathology of these microhemorrhages is still not fully explained, but cardiopulmonary bypass surgery is considered a potential cause. It is suggested that during a cardiopulmonary bypass surgery gaseous mircoemboli are created (Kim et al., 2017). These microembolic sources can enter the cerebral circulation and lead to hypoxia, ischemia, or even necrosis by obstructing blood vessels in the brain. Microhemorrhages are not only considered a marker of vascular damage, but also of leakiness of the blood brain barrier and of brain aging. Additionally, we detected smaller brain volumes in the CHD patient group compared to the group of healthy control participants. Significant differences were found in the total brain volume, the white matter and the corpus callosum volume. Though after adjusting for the total brain volume, only the corpus callosum volume proved to be smaller in the CHD group. Thus, the first part of this research question can be answered in the affirmative; yes, there are structural differences in the brains of ACHD patients and healthy control participants.

Second, we found no association between structural brain anomalies and the estimated IQ. This finding was unexpected under the assumption previously drawn in literature by Bellinger et al. (2015) and von Rhein et al. (2014) that structural brain anomalies directly influence the neurocognitive performance. Nevertheless, the result is in line with the findings of Sluman et al. (2017), who reported no differences in IQ among patients with tetralogy of Fallot stratified by structural abnormalities. Given these contrasting results, it remains unclear whether the estimated IQ is a methodologically unsuitable measure to analyze the associations with structural brain anomalies in patients with CHD, or whether advanced imaging analyses (e.g., volumetric or mi-

crostructural analyzes) are more effective in revealing correlations with general intellectual functioning. The latter part of the second research question could therefore not be confirmed; we found no association between general intellectual functioning and structural brain anomalies. Associations between the randomization performance and brain volumes are covered in the next section. For volumetric correlates of specifically executive functioning and brain volumes, see Naef et al. (2021).

6.3 Randomization performance and its neural correlates

Random number generation has been suggested as an effective tool to assess the executive functioning in a broad range of neuropsychological patient groups. The behavioral pattern found in studies about RNG is predominantly consistent, showing that human-generated sequences deviate substantially from mathematical randomness. Despite an increasing number of neuropsychologically motivated studies on RNG, this paradigm has never been investigated in a group of patients suffering from a CHD against a healthy control group. Moreover, the neuroanatomical underpinnings of RNG remain almost unexplored. Therefore, our third study pursued three aims. First, we set out to examine the impact of CHD on randomization performance, which was assessed with the MDT. Based on existing literature, we expected an impaired randomization performance, in particular an enhanced counting bias, by CHD patients relative to the healthy control subjects. Second, we explored the connection between the RNG performance and the global executive functioning and expected a positive correlation. Third, we analyzed structural brain correlates of RNG on the gross level of volumetric brain analysis and expected associations between RNG and volumetric measurements.

The findings of the study support these three assumptions. We could show that sequences of RNG produced by CHD patients were more stereotypical than those of the healthy control participants. Specifically, an enhanced *backward* counting tendency was detected. This result is not fully in line with our predictions. In fact, based on previous literature, pronounced *forward* counting would have been anticipated (e.g., Brown et al., 1998; Brugger et al., 1996; Geisseler et

al., 2016). We interpreted this result in the context of the relatively mild executive function deficits in the CHD group and suspect that predominant forward counting was compensated with a less salient digit arrangement. Accordingly, poorer executive functioning was positively associated with a poorer RNG performance. MRI analyses revealed an inverse association with the total brain, white and grey matter, and corpus callosum volume in the CHD group, as s potential neuroanatomical correlate of this backward counting bias. This highlights the importance of both counting biases (forward and backward) in the research of RNG in neuropsychological patient groups to identify executive function deficits and altered brain volumes.

Beside this sequential non-randomness, CHD patients lacked the "small-number bias" which featured in the control group. In line with previous literature (Loetscher & Brugger, 2007), we concluded that the preference for small numbers (1, 2 and 3) of the healthy control subjects can be considered a "pseudoneglect in number space". The absence of this bias in young adults with CHD was unexpected and indicates possible modifications in frontal lobe mediated neurocognitive functions in these individuals. Interestingly, the volumetric brain data revealed a positive association between the amount of small numbers in RNG and the corpus callosum volume in the CHD group, suggesting callosal involvement in the pseudoneglect in number space.

In summary, the randomization performance of young adults with CHD does indeed differs from that of the healthy control participants. However, anatomical correlates of the observed deficits in the RNG performance are weak and could only be revealed in terms of smaller brain volumes and exclusively in the CHD patients group.

6.4 Strengths and limitations

Besides the study-specific strengths and limitations highlighted in the description of the respective studies (see Chapter 5.1.5, Chapter 5.2.5, and Chapter 5.3.5), some general remarks should be mentioned here.

This thesis examined neurocognitive impairments in young adults with CHD, which is an increasingly growing but scarcely studied group of patients with enormous clinical relevance. Many studies investigating neurocognitive impairments in CHD are limited to a specific heart

defect or a relatively small sample size. To overcome these deficits and to grasp the heterogeneity of this medical condition, the presented studies include a large sample with a wide range of different types of CHD. Furthermore, whereas previous studies relied on a limited set of neuropsychological tests and/or did not include MRI, the first study of this thesis especially demonstrates the advantages of a comprehensive neuropsychological assessment over the sole examination of the IQ or a specific neurocognitive domain. As established in the second and third study, combining behavioral with imaging data when studying the consequences of a CHD, has also proven to be an advantage.

However, the chosen approach has had its limitations too. First, there was a disparity in the educational level between the two groups, with CHD patients having a lower level of education compared to the control participants. A similar inequality in the educational level has previously been reported for adults with CHD (e.g., Kovacs & Bellinger, 2021; Keir et al., 2019). These differences in the educational levels may influence neurocognitive outcomes. However, including the educational level as a covariate should not be recommended. We assumed that the level of education is a *consequence* of CHD and therefore a result of the medical condition. Consequently, when comparing both groups, the level of education should not be viewed as a predictor or confounder, but rather as an outcome. We consequently decided not to include the education level as a covariate in the statistical analyses. According to the Swiss educational system however, both groups were relatively highly educated. This may have resulted in an overrepresentation of well-educated participants in the studies relative to the general population. This overrepresentation of highly educated participants may have influenced the neurocognitive performance of the study sample and reduced the representativeness of the cohort for CHD patients on a global scale.

Second, as mentioned above, many different types of CHD were included in the studies, taking into account the diversity of this disease. However, this also leads to methodological difficulties. On the one hand, it may have limited the statistical power. On the other hand, the subgroups of specific CHD types were too small to allow further analyses. Therefore, the conclusions drawn may not be generalizable to all examined diagnoses of CHD at their individual levels.

Third, we attempted to find a link between the neurocognitive performance and the imaging data in several ways. However, no differences could be identified between patients with and without structural brain anomalies and the IQ, while a recently published review demonstrated such relationships (Aleksonis and King, 2022). Brain volumes proved to be a more sensitive measurement in our studies than brain anomalies. We were able to show that patients with smaller brain volumes performed poorer on RNG. This result is in line with the findings of Naef et al. (2021), who demonstrated correlations between brain volumes and a self-conducted global executive function score. Nevertheless, the suitability of identifying links between structural brain measures at a gross level and behavioral data in patients with a CHD must be questioned, as this approach seems not to be very sensitive. Further studies should for instance focus on sequential neuroimaging techniques or specific brain structures, for example in the context of diffusion tensor imaging rather than volumetric analyses. Promising results on the relationship between the white matter microstructure and the neurocognition in ACHD patients were recently published by Ehrler et al. (2021).

6.5 Clinical implications

This thesis demonstrates that neurocognitive impairments resulting from a CHD not only occur in childhood and adolescence, but persist into young adulthood. In addition, we found evidence that yet other impairments only become apparent after patients transition into young adulthood. It is therefore of considerable relevance that affected children are cared for at an early age and receive support in various aspects (cognitive, social, educational, etc.) to reduce the risk of lagging behind in education, suffering from mental illnesses and a higher probability of unemployment. To date, there is still only limited research available on the long-term impact of CHD on the neurocognitive functioning. Looking at the general population, there is growing evidence that cardiovascular-related brain damages precedes the neurocognitive decline and increases the risk of Alzheimer's Disease (e.g., Moore & Jefferson, 2021). Risk factors for neurocognitive impairments such as cardiovascular diseases and/or related risk factors, including cardiac arrhythmias, heart failure, hypertension, and other cardiovascular conditions such as strokes, are elevated in

adults with CHD compared to the general population (Miller et al., 2007). These comorbidities increase the risk of reduced cerebral blood flow, reduced brain volume and early forms of dementia (Kovacs & Bellinger, 2021; Marelli et al., 2016). Marelli et al. (2016) therefore phrased the hypothesis that individuals with CHD may develop neurocognitive impairments earlier than the general population, as they are more likely to suffer from cardiovascular comorbidities. A Danish study evaluated the hazard ratio of dementia in ACHD patients compared to the general population (Bagge et al., 2018). The resulting hazard ratio of the CHD group was 1.61, adjusted for risk factors such as age, gender, and education, meaning that the risk of dementia is about 61 % higher for an ACHD patient than for a reference individual. The hazard ratio increased with greater CHD complexity, with the hazard ratio rising to 1.96 for patients with severe CHD compared to the general population. In addition, the hazard ratio for early-onset dementia (< 65 years) in the CHD group increased to 2.59 (compared to 1.32 at ≥ 65 years). In addition to confirming the results of Bagge et al. (2018), Downing et al. (2022) also demonstrated that not only patients with a severe CHD, but also patients with milder defects are at an elevated risk for early brain degradation. A recently published study found ACHD patients to have significantly lower scores in the Mini Mental State Exam, a well-known dementia screening tool. In this study, 5 % of the ACHD patients even reached the cut-off for mild cognitive impairment (Rodriguez et al., 2021).

Given the steadily growing population of ACHD patients, it must be assumed that the number of patients with pathogenic brain aging processes or any form of dementia associated with a CHD is also increasing. Developing a more profound understanding of the risk of (early-onset) dementia in the CHD population should consequently be a focus in the treatment of CHD patients. Therefore, early and periodically repeated neuropsychological examinations should be established as a routine clinical procedure in these patients.

6.6 Implications for future research

This thesis confirms and extends previous research on neurocognitive impairments in the ACHD population. The clinical manifestation of CHD-related neurocognitive impairments in young adults is not sufficiently described by the traditional and widespread study approach which mainly

analyses the executive functions. Capturing the neurocognitive profile of patients with CHD with an extensive neuropsychological examination is therefore recommended. However, to overcome the limitations of the studies included in this thesis, large datasets which include comprehensive neurocognitive testing are needed. This could be feasible through the establishment of a standardized neuropsychological test battery for this specific patient group. The test battery should focus on executive, attentional and memory function areas. Given that CHD is a widespread medical condition, it seems reasonable to develop such a prototype battery rather than examining specific neurocognitive domains or even specific parameters. This approach could facilitate both illness prognosis and treatment recommendations.

There is a great interest for further research on neuroanatomical correlates. While literature concerning neurocognitive outcomes in CHD is growing, much less is known about the underlining cerebral alterations. To date, very few brain markers have been identified as cerebral predictors for neurocognitive impairments. Thus, it is required for the future research, that additional imaging parameters, especially ones that could be assessed in the early stages of the disease are implemented. Therefore, imaging methods may provide crucial information on the progressing of the disease and the development of neurocognitive impairments. By aligning longitudinal study designs with large study samples, future research including extensive neuropsychological and multiparametric MRI assessments are crucial to provide new insights of the pathogenic underpinnings of neurocognitive impairments in CHD.

6.7 Conclusion

The clinical and scientific understanding of CHD has expanded substantially over the past decades. In addition to the notion that affected children suffer from neurocognitive deficits, especially with respect to executive functions, it becomes increasingly evident that these deficits persist into adulthood and affect multiple neurocognitive domains. Neuropsychological studies have revealed that even patients with a non-severe CHD exhibit poorer neurocognitive performance and carry a greater risk of early-onset dementia compared to those without a CHD. Due to the broad understanding of the importance of neurocognitive (dys-)functioning in CHD, both researchers and

clinicians bear the responsibility to develop a more profound understanding of the neurocognitive deficits involved.

In a nutshell, this thesis discovered three main findings. First, that lower intellectual functioning in general, and impairments in executive and attentional functioning in particular, persist into young adulthood, whereas memory deficits may emerge only with maturation. Second, CHD patients have a high prevalence of structural brain anomalies and smaller brain volumes. Whereas the former is barely associated with cognition, brain volume appears to be a predictor for neurocognitive performance. Finally, we revealed poorer performance on RNG in CHD patients. By the very first application of the MTD in CHD, we offer a simple and practical screening procedure with potential to be useful for clinical and research purpose.

This thesis contributes to the emerging field of research in the neurocognitive sequelae of CHD. It highlights the importance of an extensive neuropsychological examination and focuses on different aspects of neurocognitive functioning in ACHD and provides information about the underlying neural correlates.

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PROFESSIONAL EXPERIENCE

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08/2020 – 08/2021:	University Hospital Zurich, Department of Neurology, Neuropsychologist
02/2019 – 07/2020:	University Hospital Zurich, Department of Neurology, Assistant neuropsychologist
10/2017 – 01/2019:	Children's Hospital Zurich, Department of Developmental Pediatrics, Study coordinator
03/2017 – 08/2017:	University Hospital Zurich, Department of Neurology Psychology intern
10/2014 – 02/2017:	Dr. Acél & Partner AG, Zurich, International consultancy for logistics management, Executive assistant / Deputy office manager
03/2013 – 07/2013:	Zurich Cantonal Bank, Customer advisor private customers

EDUCATION

since 08/2019:	University of Zurich, Doctorate (PhD) in Psychology, Faculty of Philosophy
since 02/2019:	Postgraduate education to become a specialist in neuropsychology
09/2016 – 02/2019:	University of Zurich, Master of Science in Psychology (insigni cum laude)
09/2013 – 07/2016:	University of Zurich, Bachelor of Science in Psychology (magna cum laude)
09/2011 – 07/2013:	Zurich Cantonal Bank, Bankeinstieg für Mittelschulabsolventen
08/2005 – 07/2011:	Kantonsschule Zürcheroberland, Economics and Law

MEMBERSHIPS

Föderation der Schweizer Psychologinnen und Psychologen (FSP)

Schweizerische Vereinigung der Neuropsychologinnen und Neuropsychologen (SVNP)

VARIOUS

Speaker on "Oncologic-associated cognitive impairment" at the Oncology Care Switzerland

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PUBLICATIONS

El-Garci, A., Zindel-Geisseler, O., Dannecker, N., Rothacher, Y., Schlosser, L., Zeitlberger, A., ... & Stienen, M. N. (2023). Successful weaning versus permanent cerebrospinal fluid diversion after aneurysmal subarachnoid hemorrhage: post hoc analysis of a Swiss multicenter study. *Neurosurgical Focus*, *54*(4), E3.

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