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The Extent, Impact and Stability of Cognitive Functioning in Adult Congenital Heart Disease

Submitted by:
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for the Degree of
Doctor of Philosophy (PhD) in Health Psychology

School of Health Sciences
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DEDICATION

I dedicate this thesis to my inspiration, my father Alok Tyagi. Thank you for teaching me how to dream, believe and achieve everything I do with tenacity and dedication. Your words of encouragement once written to me *"Child always remember a hammer shatters glass but forges steel, and I know you have the steel in you…."* saw me though some of the most trying hours of this endless journey. It is your faith in my abilities and my strength that makes me want to achieve everything in life. Thank you for being my inspiration and for always making your presence felt. Above all thank you for envisioning this dream for me, and I hope I have made you proud.

DECLARATION

I, Manavi Tyagi Maharshi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis. I grant powers of discretion to the University Librarian to allow the thesis to be copied in whole or in part without further reference to the author. This permission covers only single copies made for study purposes, subject to normal conditions of acknowledgement.

ABSTRACT

The aim of this thesis was to establish the extent, impact and stability of cognitive functioning in Adult Congenital Heart Disease (ACHD) patients. A cross-sectional and a follow-up study were conducted to address these objectives. The aims of the cross-sectional study were to i) identify the extent of cognitive impairments ii) compare cognitive performance across structural complexity groups, iii) identify factors associated with cognition in ACHD. The follow-up study aimed to evaluate the stability of cognitive functioning over time and identify predictors of change.

Three hundred and ten ACHD patients from the Heart Hospital, London were recruited. Participants were divided into four structural complexity groups: Tetralogy of Fallot (ToF), Transposition of the Great Arteries (TGA), Single Ventricle (SV) and Simple. Each participant completed a neuropsychological (NP) test battery and psychosocial self-report questionnaires.

The results showed ACHD patients with IQ below the normative mean score. Impairment in executive function, attention and motor function were noted. The TGA group had the worst overall cognitive functioning. The Simple group performed significantly better than the TGA and SV groups on attention. Demographic, clinical and mood factors were associated with cognitive function. No association between cognitive functioning and Quality of Life was found.

In the follow-up study 153 participants were followed-up (over 4 years). The NP test battery was re-administered to assess change over time. Mood, demographic and clinical factors were assessed to identify predictors of change in cognitive functioning.

The results indicated both a decline and an improvement in performance on tests assessing attention, memory, executive functioning and motor functioning. Education and oxygen saturation levels predicted change in memory.

The results of this study address a gap in the literature and highlight the extent of cognitive impairments in ACHD. It also indicates a range of intrinsic and modifiable factors that are associated with and predict change in cognitive outcomes. The clinical implications of the findings are discussed. Recommendations for clinical practice include regular, ongoing assessment of cognition in ACHD patients.

THESIS STRUCTURE

This thesis aims to identify the level of cognitive functioning in ACHD, while also comparing functioning across different types of ACHD, and examining the stability of cognitive functioning over time. The thesis used both a cross sectional and a longitudinal study design to address these objectives. For ease of interpretation, the background and findings of this thesis are presented in two parts: the cross-sectional and the follow-up (longitudinal).

Chapter 1 discusses the nature, prevalence and incidence rates of ACHD and also describes the most common forms of Congenital Heart Disease (CHD), pertinent to this study. A brief description of each condition and its associated treatments and prognosis is presented.

Chapter 2 examines the concept of cognitive functioning, and introduces the domains of cognitive functions assessed in this thesis. It also presents a brief discussion of some of the challenges associated with the measurement of cognitive functioning.

Chapter 3 discusses the relationship between the brain and the heart, and explains how these two organs can impact each other in patients with CHD. It also presents an overview of the existing evidence on cognitive outcomes in children with CHD.

Chapter 4 presents the findings of the systematic review that examines the existing evidence on the extent of cognitive impairment in the ACHD population.

Chapter 5: discusses the association between cognitive functioning and Quality of Life (QoL) in ACHD patients. It presents a brief overview of the literature on QoL in ACHD.

Chapter 6 presents an introduction to the cross-sectional study and details its aims and objectives.

Chapter 7 provides a detailed description of the study design, measures and methodology adopted. It also describes the statistical strategy adopted to answer the research questions and objectives of this study.

Chapter 8 reports the results of the cross-sectional analysis.

Chapter 9 discusses the results of the cross-sectional study pertinent to each of the research aims and objectives in the context of the existing literature. It also makes recommendations for future research and discusses implications of the study findings.

The follow-up study is presented in Chapters 10-14.

Chapter 10 introduces the concept of longitudinal neuropsychological (cognitive) assessment. It discusses the different techniques available in the literature to measure change in cognitive functioning reliably over time. It also presents the available longitudinal evidence on change in cognitive functioning in the ACHD population.

Chapter 11 presents the rationale, aims and objective of the follow-up study.

Chapter 12 details the study design, methodology, and the statistical strategy adopted to address each of the research objectives in the follow-up study.

Chapter 13 reports the results of the follow-up study.

Chapter 14 presents and discusses the outcomes of the follow-up study in the context of the existing literature.

Chapter 15 presents an overall discussion of the thesis. It synthesizes the results of both sets of analyses (cross-sectional and follow-up) and presents a discussion on the contributions of this study to the existing literature. It also highlights the strengths and weaknesses of this thesis along with making suggestions for future research, and recommendations for clinical practice.

LIST OF ABBREVIATIONS

ACE	Angiotensin Converting Enzyme
ACHD	Adult Congenital Heart Defect
AF	Atrial Fibrillation
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AQT	A Quick Test of Cognitive Speed
AR1	Autoregressive model of first order
AS	Aortic Stenosis
ASD	Atrial Septal Defect
AVSD	Atrio Ventricular Septal Defect
CESD-10	Centre for Epidemiological studies Short Depression Scale
CHD	Congenital Heart Defect
CI	Confidence Intervals
CNS	Central Nervous System
CNS - VS	Central Nervous System - Vital Signs
COA	Coarctation of Aorta
COWA	Controlled Oral Word Association Test
CPB	Cardiopulmonary Bypass
CT Scan	Computerised Tomography
DHCA	Deep Hypothermic Circulatory Arrest
DILV	Double-Inlet Left Ventricle
DV	Dependent Variable
ECC	Extra Corporeal Circulation
EF	Ejection Fraction
ES	Effect Size
FSIQ	Full Scale Intelligence Quotient
GIT	Groninger Intelligence Test
GP	Grooved Pegboard
GP-D	Grooved Pegboard - Dominant Hand
GP-ND	Grooved Pegboard - Non-Dominant Hand
GUCH	Grown-Up Congenital Heart
HA	Hypothermic Arrest

HF	Heart Failure
HLHS	Hypoplastic Left Heart Syndrome
HRQoL	Health Related Quality of Life
IBM SPSS	IBM Statistical Package for Social Sciences
ICC	Interclass Correlation
ICD	Implantable Cardiovascular Defibrillator
ICU	Intensive Care Unit
IE	Infective Endocarditis
IPCCC	International Paediatric and Congenital Cardiac Code
IQ	Intelligence Quotient
IQR	Inter-Quartile Range
IV	Independent Variable
LV_NRGA	Left Ventricle Normally Related Great Arteries
LVEF	Left Ventricular Ejection Fraction
LVOTO	Left Ventricular Outflow Track Obstructions
MAPCAS	Major Aortopulmonary Collateral Arteries
MCI	Mild Cognitive Impairment
MCS	Mental Component Summary Score
MESH	Medical Subject Headings
MLM	Multilevel Modelling
MRI	Magnetic Resource Imagining
NA	Negative Affect
NAA	N-Acetyl Aspartate
NHLBI	National Heart, Lung, and Blood Institute
NHS	National Health Services
NP	Neuropsychological
NRES	National Research Ethics Service
NS-SEC	National Statistics Socio-Economic Classification
NYHA	New York Health Assessment
OPA	Out Patient Appointments
PA	Pulmonary Atresia
PA	Positive Affect
PA-IVS	Pulmonary Atresia with Intact Ventricular Septum
PANAS	Positive and Negative Affect Scale
PCS	Physical Component Summary Score
PFO	Patent Foramen Ovale
PH	Pulmonary Hypertension

PIQ	Performance Intelligence Quotient
PMM	Predictive Mean Matching
PRI	Perceptual Reasoning Index
PRISMA	Preferred Reporting Items for Systematic Reviews & Meta Analysis
PS	Pulmonary Stenosis
PSI	Processing Speed Index
PVL	Periventricular Leukomalacia
QoL	Quality of Life
R&D	Research and Development
RAVLT	Rey Auditory Verbal Learning Test
RCI	Reliable Change Index
RCT	Randomized Control Trials
REML	Restricted Estimate Maximum Likelihood
RVEF	Right Ventricular Ejection Fraction
RVOTO	Right Ventricular Outflow Track Obstructions
SAS	Sub-Aortic Stenosis
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SDMT - O	Symbol Digit Modalities Test - Oral
SDMT - W	Symbol Digit Modalities Test - Written
SE	Standard Error
SED	Standard Error of the Difference
SES	Socio-Economic Status
SF-36	Short Form - 36
SNST	Stroop Neuropsychological Screening Test
STAI-6	Spielberger State Anxiety Inventory-6
SV	Single Ventricle
SVAS	Supravalvular Aortic Stenosis
TA	Tricuspid Atresia
TCPC	Total Cavopulmonary Connection
TGA	Transposition of the Great Arteries
TMT	Trail Making Test
TMT-A	Trail Making Test - A
TMT-B	Trail Making Test - B
TOE	Transthoracic / Transesophageal Echocardiography
ToF	Tetralogy of Fallot
TRT	Test Re-test

UCLH	University College London Hospital
UK	United Kingdom
VAS	Valvular Aortic Stenosis
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence Quotient
VSD	Ventricular Septal Defect
WAIS	Wechsler Adult Intelligence Scale
WAIS-III	Wechsler Adult Intelligence Scale - III
WAIS-IV	Wechsler Adult Intelligence Scale - IV
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WCST-64	Wisconsin Card Sorting Test - 64
WCST-CLR	Wisconsin Card Sorting Test - Conceptual Level Response
WCST-FTM	Wisconsin Card Sorting Test - Failure to Maintain set
WCST-TTC	Wisconsin Card Sorting Test - Trials To Complete first category
WMI	White Matter Injury

1 BACKGROUND TO CONGENITAL HEART DISEASE

1.1 Prologue

The aim of this chapter is to present a detailed overview of Congenital Heart Disease (CHD) and its associated treatments. It presents a description of the normal heart and its morphology, followed by a description of CHD and its prevalence, incidence and mortality rates. Lastly, the long-term complications of CHD are also discussed.

1.2 The structure and function of a normal heart

In order to understand the different types of CHD, it is important to first understand the structure and function of a normal heart. The heart is a hollow and cone shaped muscular structure located between the lungs in an area referred to as the thoracic cavity (See Figure 1.1: The thoracic cavity below). By adulthood, it is normally 10cm long, 255-350gms in weight, and roughly the size of its owner's fist; and its main function is to pump blood throughout the body.

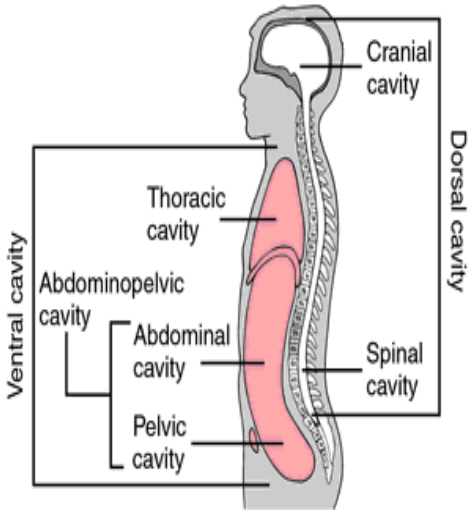

Figure 1.1: The thoracic cavity
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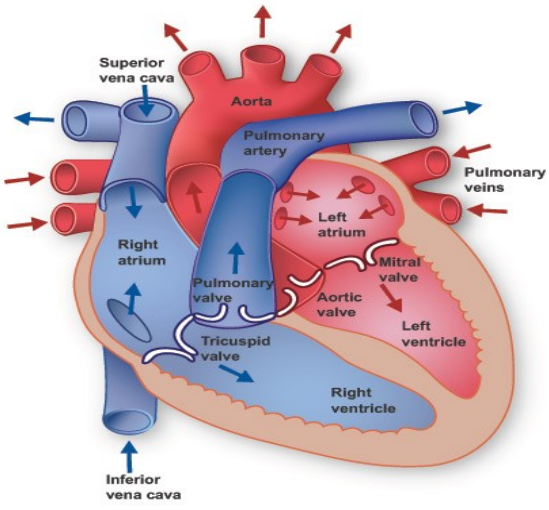

Figure 1.2: The normal heart
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A normal heart consists of four chambers (two left, two right) that are separated by a muscular wall called the septum. The Atria (upper chambers) receive blood; the right atrium receives deoxygenated blood from the superior vena cava, inferior vena cava and the coronary sinus, while the left atrium receives oxygenated blood from the pulmonary veins. The Ventricles (lower chambers) are responsible for pumping blood into the pulmonary and systemic circulation (as seen in Figure 1.2 above) (Katz, 2010).

The flow of blood within the heart is controlled by the opening and closing of four valves, which are in turn controlled by the body's blood pressure (See Figure 1.2 above). The circulatory cycle of the heart consists of deoxygenated blood from the superior and inferior vena cava and the coronary sinus being drained into the right atrium, which then passes through the valve and into the right ventricle (See in Figure 1.1 above). Blood then travels through the pulmonary valve into pulmonary arteries and into the lungs where the oxygen is absorbed and carbon dioxide released. The oxygenated blood then returns to the heart via the pulmonary veins which empty out into the left atrium. The blood then goes through the valve into the left ventricle from where it enters the aorta through the aortic valve and begins its journey of systemic circulation (See Figure 1.2 above) (Katz, 2010). The average heart pumps 5.25 litres of blood per minute (range 4.0–8.0 litres per minute).

1.3 Congenital Heart Disease (CHD)

CHD is a heterogeneous group of conditions that are present from birth and are characterised by structural and functional abnormalities of the heart with varying levels of complexity (Karsdorp et al, 2007). This can vary from a hole in the septum to a more serious condition like the deformity or even the absence of a ventricle or valve.

1.3.1 The Aetiology of CHD

The aetiology of most CHD is unknown, with only 10 % to 20% of cases with an identifiable cause (Buskens et al, 1995). It is thought to be multifactorial in origin with evidence of genetic and environmental factors being responsible. Some evidence suggests the role of genetic factors, with a higher incidence of CHD in cases where the parent (usually the mother) is diagnosed with CHD (Deanfield et al, 2003).

With regards to environmental and external factors, it is reported that the presence of certain maternal diseases including German measles, maternal diabetes, and autoimmune conditions like Systemic Lupus Erythromatous can predispose an offspring to CHD (Nass and Frank, 2010). Along with maternal diseases, other factors such as smoking or excessive alcohol intake during pregnancy are also thought to contribute to CHD (Nass and Frank, 2010). Furthermore, there is evidence of an association between CHD and chromosomal abnormalities, for instance higher rates of CHD are reported in patients with chromosomal abnormalities such as Down's syndrome (Vis el al, 2009). However, there is a paucity of evidence on the interacting and cumulative effects of these factors in causing CHD, which prevents firm conclusions from being drawn about the aetiology of CHD.

1.3.2 Symptoms and diagnosis of CHD

There are usually no outwardly observable signs and symptoms in most forms of CHD. However, some commonly found characteristics include: shortness of breath, dizziness, fainting, arrhythmias (irregular heart beat), cyanosis (present in cyanotic conditions, characterised by lack of oxygen in the blood leading to blueness of skin), palpitations (heartbeat abnormalities) and fatigue (Harrox, 2002). The characteristic symptomology and the structural malformations of different forms of CHD are discussed below in more detail.

CHD can be diagnosed as early as the antenatal period, using ultrasound (foetal echocardiography) during early pregnancy (Brown and Sullivan, 2014). Initial physical

examination and diagnostic tests such as chest radiography, magnetic resonance imagining (MRI), computerised tomography (CT scan) and transthoracic or transesophageal echocardiography (TOE) are used for the purpose of diagnosis (Popelova et al, 2008).

1.3.3 Incidence and Prevalence

Estimating the incidence and prevalence rates of CHD is challenging, due to the large variation in the classifications used by authors to define different forms of CHD (Garne et al, 2012). As a result, the prevalence and incidence rates of CHD vary greatly across the existing literature.

1.3.3.1 Incidence of CHD

Defining the incidence rates of CHD is complex, given that the conventional meaning of incidence: "the occurrence of a new case of a certain disease" does not apply to CHD due to its congenital nature (Van Der Bom et al, 2011). In CHD the number of new cases is generally stated as the number of cases per 1000 births. This term is referred to as the 'birth prevalence', which technically differs from the concept of incidence (Van Der Bom et al, 2011). The ambiguity in defining the nature and types of CHD leads to a wide range of birth prevalence estimates in the literature ranging from 4 to 50 per 1000 births (Hoffman, and Kaplan 2002; Bernier et al, 2010). The UK birth prevalence is reported as 6.4 per 1000 births for all forms of CHD, and 1 per 1000 births for severe forms of CHD (Wren, Reinhardt and Khawaja, 2008).

A systematic review and meta-analysis of the literature on the worldwide birth prevalence of CHD reported that the overall total CHD birth prevalence has increased substantially from 0.6 per 1,000 births in 1930-1934, to 9.1 per 1,000 births in 1997-2011 (See Van Der Linde et al, 2011 for more details). One potential reason for the increase in the birth prevalence rates could be the improvements in the diagnostic techniques over time, which enables identification of new cases. This review and meta-analysis also reported significant geographical differences in the birth prevalence rates, with Asia having the highest (9.3 per 1000 births), followed by Europe

(8.2 per 1000 births), and the lowest birth prevalence being reported in Africa (1.9 per 1000 births) (Van Der Linde et al, 2011).

1.3.3.2 Prevalence of CHD

Prevalence rate is defined as the number of people living with the condition at a particular point in time. The prevalence rate of CHD is calculated by deriving the difference between the number of people born with CHD and those that are deceased or have had a spontaneous closure (i.e. when the heart defect spontaneously corrects itself without the need for surgical intervention) (Van Der Bom et al, 2011). Similar to the estimation of birth prevalence, calculating the prevalence rate of CHD is difficult with different studies using different figures and rationale for estimating prevalence.

In a systematic review of the literature, the overall prevalence rate of CHD was reported as being 3,000 per million adults (Van Der Bom et al, 2011). The prevalence of Adult Congenital Heart Disease (ACHD) patients is rapidly increasing, with more recent reports suggesting an increase in numbers by a 2:1 ratio (Avila et al, 2014). This increase in the prevalence rates of ACHD could be attributed to the improvement in the treatment techniques that have led to an increasing number of children with CHD surviving into adulthood.

1.3.4 Mortality and trends of survival

The survival rate of CHD patients has increased over time. The median age of patients with severe CHD has increased from 11 years (in 1985) to 17 years (in 2000); similarly their median age at death has increased from 37 years (in 2002) to 57 years (in 2007) (Boneva, 2001; Van Der Bom et al, 2011). A 50-70% decline (from 1980-2005) in the mortality rate among patients with CHD has been reported, depending on the diagnosis (Pillutla, Shetty and Foster, 2009). This has led to a 70% increase in adult survivors since the 1950's, leading to a larger ACHD population in comparison to the paediatric population (Van Der Bom et al, 2011).

1.4 Nomenclature and classification of CHD

Given the inherent diversity of CHD, several ways of categorizing the different CHD conditions into groups have been developed. A comprehensive system of nomenclature called the International Paediatric and Congenital Cardiac Code (IPCCC) has been developed by the Society for Nomenclature of Paediatrics and Congenital Heart Disease (Franklin et al, 2008). Specialists in the field of cardiology created the IPCCC in order to name and classify the different forms of paediatric and congenital heart disease and their treatments, for the purpose of improving patient outcomes, risk stratification and comparing outcomes internationally between different specialist centres. This classification is increasingly being used in clinical practice by cardiologists but its value in research is yet to be established.

A common categorization often used in the field of research is that of cyanotic and acyanotic forms of CHD; cyanotic conditions are those characterised by poor blood oxygen saturation levels while acyanotic conditions have normal oxygen saturation levels. However, such a broad classification fails to take into account the range of complexity of the different conditions included within these two groups. For instance, one could classify a range of conditions as "cyanotic" however the prognosis, incidence rates and long-term outcomes of different cyanotic conditions may vary considerably. This variation is overlooked when assessing these distinct conditions as a group. Given the large amount of variability in the different forms of CHD and their associated treatments and prognosis, the outcomes of each condition could be expected to vary. Therefore, merging together a range of conditions does not allow a clear understanding of the impact of the different conditions on long-term outcomes such as quality of life, prognosis and recovery over time.

Alternatively, a potentially useful way to classify and evaluate the wide range of conditions in CHD could be based on the varying levels of structural complexity of these different conditions. Such a classification takes into account the variability in the anatomy, prognosis, treatments and symptomologies of the different forms of CHD and allows the assessment of different long-term

outcomes (e.g. quality of life, cognitive functioning) in patient groups with different levels of structural complexity. Furthermore, it enables both independent and comparative analysis of the different conditions.

The patient group categorization adopted within this thesis was based on the idea of assessing different levels of structural complexity both independently and among themselves, and is presented within Chapter 7 (Section 7.2.1.2). For the purposes of this thesis some of the most common forms of CHD were divided, based on the level of the anatomical complexity of the structural heart defect, into four groups i) "Simple" group, ii) Tetralogy of Fallot (ToF), iii) Single Ventricle (SV), and iv) Transposition of the Great Arteries (TGA). A detailed description of each of these groups is presented later in the chapter (see Table 1.1 for a summary of the complexity classification used within this thesis).

The label used to describe and differentiate these four groups is "structural complexity groups". Although TGA and SV groups are structurally different they are considered 'complex' in their level of anatomical complexity. The ToF group, while considered complex can also be referred to as 'moderately complex' in the absence of cyanosis when compared to SV and TGA. The 'Simple' group is the least anatomically complex group of conditions in comparison to the other three groups and hence labelled 'Simple'.

Within the thesis, the term 'structural complexity groups' is used when referring to the four independent groups collectively. When making comparisons between SV, TGA and ToF groups with the 'Simple' group, these three conditions will collectively be referred to as 'more structurally complex' conditions and the Simple group as 'Simple'/ 'less structurally complex' conditions, unless individual complexity groups are specified (i.e. labelled as TGA, ToF, SV). When making comparisons between SV and TGA group with the ToF group these conditions will be referred to as 'more structurally complex' conditions and ToF as a 'moderately complex' condition. Evidence presented within this thesis is discussed using this classification

and terminology irrespective of the classification adopted by the authors in the existing literature. This is done to maintain consistency of terminology across the thesis, and to enable comparison of existing evidence in the context of the classification used in this study.

1.4.1 "Simple" group

1.4.1.1 Atrial Septal Defect (ASD)

ASD is defined as one or more communications or openings across the atrial septum that allows the flow of blood between the left and right atria of the heart (See Figure 1.3 below) (Geva, Martin and Wald, 2014). There are different forms of ASD based on the specific location of the defect along the septum, for an overview of the different type see Geva, Martin and Wald, (2014). ASD accounts for approximately 9-11% of all CHD in childhood and about 22-30% in adulthood, and is more common in females than males (2:1) (Harrox, 2002).

ASD is generally asymptomatic in childhood and is usually diagnosed well into adulthood (Baumgartner et al, 2010). Although smaller ASDs do not cause many symptoms, larger ASDs may lead to some symptomology including palpitations (heart beats faster and becomes more noticeable), shortness of breath, arrhythmias and heart failure later in life when the patients are in their forties (Silversides et al, 2010).

Operative treatment for CHD can be classified as palliative or total/complete surgical repair or correction, depending on the objective of the treatment. Palliative procedures do not correct the defect, they help manage the symptoms and improve an abnormal heart function, while the total/complete repair refers to procedures that are aimed at correcting the defect and obtaining normal heart function (Yuan and Jing, 2009).

Treatment for ASD can involve palliative procedures such as transcatheter closures and/or surgical correction. Transcatheter closure involves inserting a closure device through a catheter (tube) that is usually inserted through the groin up to the heart where the device is placed in

order to close the opening (ASD). The use of a transcatheter closure is considered safe and less invasive than surgical correction for most forms of ASD (Shen, Zhou and Gao, 2003), and is considered to provide similar results to those obtained by surgery (Silversides et al, 2010). However, open-heart surgery (complete repair) involving sewing a patch over the opening may be required in some cases depending on the size of the ASD. Repair surgery has a low mortality rate (1%) and patients have good long-term outcomes (Baumgartner et al, 2010). The morphology of the defect is an important factor in determining which procedure is appropriate.

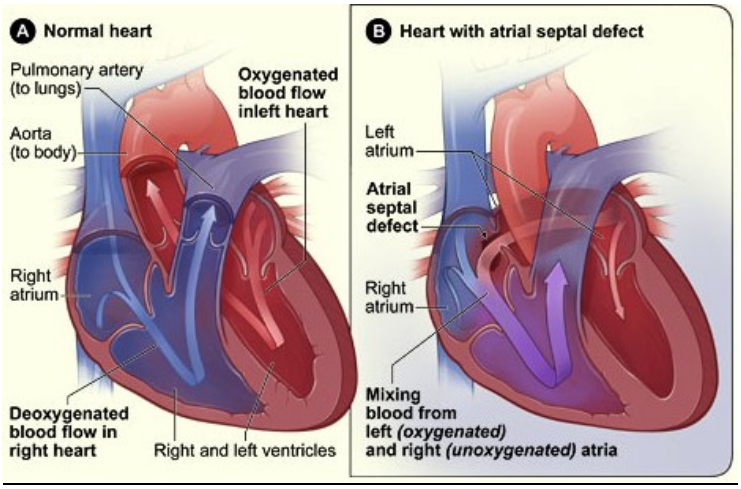

Figure 1.3 Normal heart and heart with ASD
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Most patients that undergo an ASD closure in the first two decades of life lead regular lives with excellent outlooks and normal survival (Gatzoulis, Webb, and Daubeney, 2010). However older age at repair has been reported as a risk factor for long-term complications (Attie et al, 2001). Most patients that have undergone correction for ASD do not require frequent follow-up, unless patients who have undergone late repair experience additional complications such as progressive pulmonary vascular disease, which warrants regular follow-up (Gatzoulis, Webb, and Daubeney, 2010)

Table 1.1 Details of the structural complexity group classification used in the present study

The Groups	Anatomical complexity of the heart defect	Cyanosis	Specific diagnosis and surgical procedures included in each structural complexity group within this study				Need for repeated surgical interventions
"Simple" group	Less complex (Simple)	×	Atrial Septal Defect (ASD) (surgical or percutaneous)	Ventricular Septal Defect (VSD)	Coarctation of the Aorta (early/late repair, re-COA)	Pulmonary stenosis, Valvular Aortic Stenosis	×
"ToF" group	Complex to Moderately complex	✓	Tetralogy of Fallot (TOF)	Pulmonary atresia (PA)	Major Aortopulmonary collateral arteries (MAPCAS)	Pulmonary valve replacement	✓
"SV" group	Complex	✓	Fontan operation	Total Cavopulmonary Connection (TCPC)	Cyanotic patients under single ventricle diagnosis		✓
"TGA" group	Complex	✓	Mustard procedure	Senning procedure	Senning patients (including pacemakers & Implantable Cardioverter Defibrillators)		✓

1.4.1.2 Ventricular Septal Defect (VSD)

VSD is the presence of one or more communications or openings along the ventricular septum, leading to an increased blood flow to the lungs (See Figure 1.4 below). It can occur in several places along the ventricular septum and may vary in size; it may also present as a secondary defect to other conditions such as ToF and atrioventricular septal defect (King and de Moor, 1999). VSD is one of the most common forms of CHD accounting for approximately 33% of all CHD (Harrox, 2002). VSD is the most common heart defect in childhood and is present in 3-3.5 per 1000 births, while in adults it is estimated to be much lower (0.3 per 1000 births) due to the high incidence of spontaneous closures (Hoffman and Kaplan, 2002; Warnes et al, 2001).

Symptom presentation in VSD is determined by the size of the defect; small VSD usually present no symptoms but they may be at an increased risk of endocarditis (infection of the inner lining of the heart) and paradoxical embolism (blockage of a systemic artery by a blood clot) (Findlow and Doyle, 1997).

Patients with medium VSD may present symptoms like heart failure, chest infections, and normal or moderately high blood pressure in the pulmonary artery; while those with large VSD may present with congestive cardiac failure, chest infections and failure to thrive (King and de Moor, 1999). Spontaneous closure of the VSD may occur in about 35%-40% of patients mostly in the first 2 years of their lives with a 10% chance of closure in adolescence and adulthood (Neumayer, Stone and Somerville, 1998).

Patients with a small VSD tend to remain asymptomatic and do not require treatment, however those with a larger VSD require timely closure of the defect as they are at an increased risk of developing congestive heart failure and irreversible pulmonary vascular disease (a condition affecting blood vessels that connect the heart and lungs) (Gatzoulis, Webb, and Daubeney, 2010). The aim of surgery is to correct the defect by closing the hole using a patch under open-

heart surgery (Harrox, 2002). Transcatheter closure may be performed as an alternative to surgery for those who cannot undergo surgery or those who have undergone previous surgical interventions (Aleem et al, 2006).

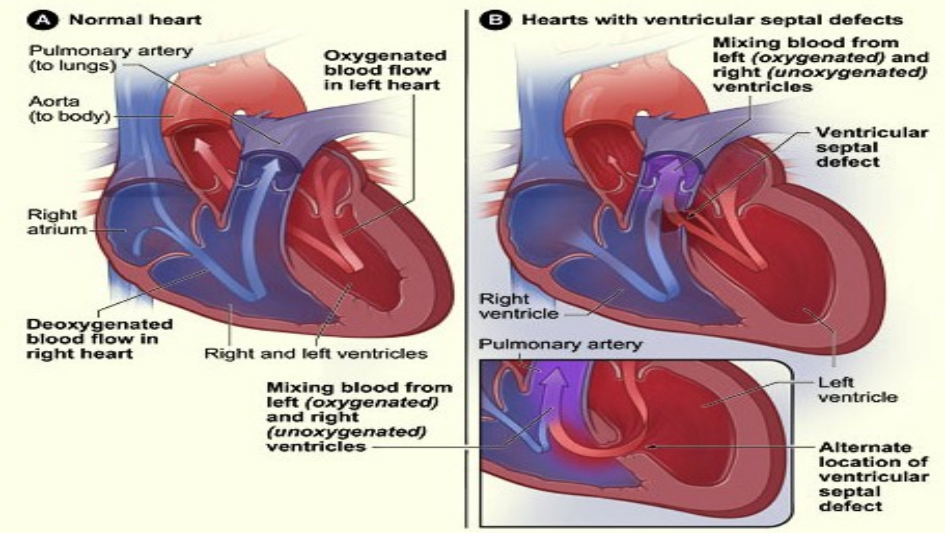

Figure 1.4: Normal heart and heart with VSD
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Surgical repair greatly improves the long-term morbidity and mortality outcomes of VSD patients (Meijboom et al, 1994; Roos-Hesselink et al, 2004). The operative mortality rate for surgical repair is quite low (1%-2%) and offers good long-term outcomes (Baumgartner et al, 2010). The prognosis for VSD patients is good, with no restriction in activity necessary unless there are complications from surgery (Gatzoulis, Webb, and Daubeney, 2010).

1.4.1.3 Left Ventricular Outflow Track Obstructions (LVOTO)

LVOTO are a group of conditions that are characterized by an obstruction or blockage in the blood flow through the left ventricle. A number of conditions can be classified as LVOTO; the common forms include Coarctation of the Aorta (CoA) and Valvular Aortic Stenosis (VAS).

Coarctation of the aorta (CoA)

CoA is characterized by the constriction (narrowing) of the aorta, which is the main artery leading out of the heart (See Figure 1.5 below). CoA constitutes about 5%-8% of all CHD and is more common in males than in females (2:1) (Park, 1997; Gatzoulis, Webb, and Daubeney, 2010). CoA may occur as an isolated defect (simple CoA) or in conjunction with other cardiac defects (complex CoA) mainly bicuspid aortic valve (up to 85%), VSD, and mitral valve abnormalities; the prevalence of isolated CoA is approximately 0.33 per 1000 births (Gatzoulis, Webb, and Daubeney, 2010).

The symptoms of CoA can be present in several systems including the respiratory, gastrointestinal and renal; some of the signs and symptoms include congestive heart failure usually seen in patients with a coexisting VSD, shortness of breath, nosebleeds, dizziness, hypertension and headaches (Harrox, 2002; Gatzoulis, Webb, and Daubeney, 2010). Depending on the severity of the condition some patients may remain asymptomatic and only be diagnosed upon examination in adulthood.

Treatment for CoA can include transcatheter and/or surgical correction, dependent on the time of diagnosis, degree of constriction and the presence of other associated cardiac defects. The use of transcatheter interventions in CoA is less common, and surgery is generally conducted at the time of diagnosis, in order to prevent later morbidity and mortality (Gatzoulis, Webb, and Daubeney, 2010). The primary aim of surgery is to relieve the constriction and reduce the strain to the aorta, before hypertension causes irreversible consequences (Harrox, 2002).

There are several surgical techniques that are used to treat CoA, such as subclavian flap repair (the Subclavian artery is opened and used to widen the aorta), end-to-end anastomosis (involves removal of the narrowing and sewing the two ends together), and interposition graft (involving the use of synthetic material to bypass or remove the narrowing) (See Gatzoulis, Webb, and Daubeney, 2010 for more details on the surgical procedures). Long-term complications are

associated with all forms of treatment; some of the main complications may include aneurysm (excessive swelling) of the aorta and/or site of intervention and recoarctation (reoccurrence of the constriction after correction) (Gatzoulis, Webb, and Daubeney, 2010).

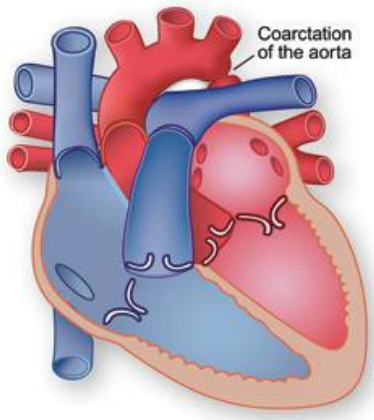

Figure 1.5: Image of a heart with CoA
© Texas Heart Institute [www.texasheart.org]

Depending on the degree of constriction, 90% of untreated complex CoA patients can die in the first year of their lives; those that survive into adulthood without treatment usually only experience mild CoA, often delaying diagnosis until later in life (Gatzoulis, Webb, and Daubeney, 2010). The prognosis for CoA is better if surgery is performed in childhood; survival rates of 24 and 44 years after surgery are reported as 81% and 73% respectively (Popelova et al, 2008). However, some complex forms of CoA may not necessarily be cured by surgical intervention; while surgical treatment can improve symptomology, the long-term survival is reportedly lower than that of the general population, making life-long follow-up of COA patients important (Gatzoulis, Webb, and Daubeney, 2010).

Valvular Aortic Stenosis (AS)

Valvular Aortic Stenosis (AS) is one of the most common forms of LVOTO, accounting for approximately 8% of all CHD (Gatzoulis, Webb, and Daubeney, 2010; Popelova et al, 2008). AS is the narrowing of the aortic valve opening, causing a restriction in the blood flow from the left ventricle to the aorta (See Figure 1.6 below).

AS can be classified as Sub-Aortic (SAS) or Supravalvular (SVAS) depending on the exact location of the narrowing (stenosis) (Aboulhosn & Child, 2006). Symptoms of AS develop gradually over a period of 10 to 20 years, and can include chest pains, syncope (temporary loss of consciousness) and heart failure (Brickner, Hillis and Lange, 2000)

Treatment for AS is determined by the severity of the defect and the symptoms. Patients may undergo transcatheter interventions as a palliative procedure to manage symptomology. However in order to correct the defect, the definitive treatment for AS involves undergoing an aortic valve replacement, whereby an artificial heart valve replaces the patient's aortic valve, by means of surgery (Brickner, Hillis and Lange, 2000).

The 25-year mortality rate of AS patients is reported as 25% (Hoffman, Kaplan and Liberthson, 2004). Patients that remain asymptomatic have a normal life expectancy; however for those that develop symptoms in adulthood the life expectancy is considered low (Brickner, Hillis and Lange, 2000). The median survival rate after experiencing chest pain, syncope and heart failure is reported as five, three and two years respectively (Brickner, Hillis and Lange, 2000). Given the progressive nature of AS, regular follow-up is recommended for both symptomatic and asymptomatic patients alike (Gatzoulis, Webb, and Daubeney, 2010).

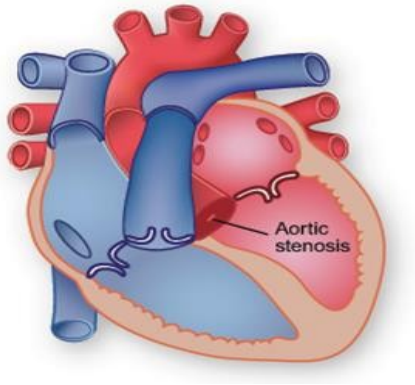

Figure 1.6: Image of a heart with AS
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1.4.1.4 Right Ventricular Outflow Track Obstructions (RVOTO)

RVOTO are a group of conditions that are characterized by an obstruction or blockage in the blood flow through the right ventricle. The most common form is Valvular Pulmonary Stenosis (PS) occurring in 80%-90% of all cases (Popelova et al, 2008).

PS is the narrowing of the pulmonary valve leading to an obstruction in the ejection of blood from the right ventricle into the lungs (Gatzoulis, Webb, and Daubeney, 2010) (See Figure 1.7 below). PS can occur both as an isolated defect and associated with other forms of CHD including ASD, VSD and ToF. As an isolated defect PS occurs in 6%-10% of all CHD, with an equal male to female ratio (Popelova et al, 2008).

Symptoms of PS depend on the severity of the stenosis; some children may remain asymptomatic and only be diagnosed upon physical examination, not requiring treatment until adulthood (Popelova et al, 2008; Gatzoulis, Webb, and Daubeney, 2010). Some of the common symptoms in more severe forms of PS may include fatigue, syncope, chest pains and palpitations (Popelova et al, 2008).

Treatment for PS generally involves the use of transcatheter interventions, which involves relieving the obstruction by dilating the pulmonary valve (Gatzoulis, Webb, and Daubeney, 2010). Surgical treatment may be required in cases where the use of transcatheter intervention is not possible, and there is a coexistence of other associated defects (Baumgartner et al, 2010).

Long-term outcomes for patients with an isolated PS that has been treated using transcatheter intervention and/or surgery is generally considered to be good, and comparable to a healthy normal population with a 97% survival rate at 25 years (Popelova et al, 2008). Mortality rates are higher in patients that have severe PS that has been left untreated into adulthood (Connelly et al, 1998). Some long-term complication in patients with PS may include arrhythmias, heart failure and pulmonary regurgitation (a leaking pulmonary valve) (Gatzoulis, Webb, and Daubeney, 2010).

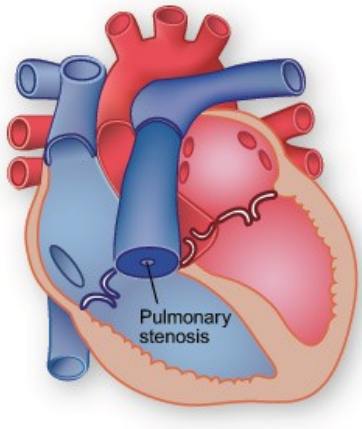

Figure 1.7**:** Image of a heart with PS
© Texas Heart Institute [www.texasheart.org]

1.4.2 Tetralogy of Fallot (ToF)

Tetralogy of Fallot (ToF) is one of the most common cyanotic forms of CHD, accounting for approximately 10% of all CHD, with a slight male to female predominance (Gatzoulis, Webb, and Daubeney, 2010). ToF is characterised by the coexistence of four individual defects (See Figure 1.8 below):

- RVOTO (Pulmonary Stenosis-PS): A narrowing in the way out of the right side of the heart to the lungs
- Ventricular Septal Defect (VSD): A hole in the septum that separates the left and right ventricles
- Over-riding Aorta: The aorta rides over the VSD allowing blood from both ventricles to enter into circulation
- Right Ventricular Hypertrophy: Thickening of the muscle in the right ventricle caused by overworking due to the PS.

The signs and symptoms of ToF can occur across several systems including: cardiovascular, respiratory, neurological and haematological systems (Harrox, 2002). One of the most common symptoms is cyanosis, characterised by blue or purple coloration of the skin due to lack of oxygen supply caused by deoxygenated blood bypassing the lungs and being shunted directly into arterial circulation (Harrox, 2002).

The presentation and severity of cyanosis depends on the degree of RVOTO obstruction. Most ToF patients present with cyanosis in infancy and others with milder RVOTO may have minimal cyanosis (so-called pink Tetralogy or acyanotic Fallot) and present well into adulthood (Gatzoulis, Webb, and Daubeney, 2010). If left untreated, it may lead to complications such as stroke, arrhythmias (irregular heart beat), exercise intolerance and endocarditis (an infection of the inner lining of the heart) in adult patients (Gatzoulis, Webb, and Daubeney, 2010).

The choice of treatment for ToF depends upon the complexity of the condition and the urgency to conduct complete repair. In the past most children underwent staged treatment with palliative procedures before complete repair. The general aim of the palliative procedures is to delay the complete repair and this is achieved using a systemic-to-pulmonary artery shunt (i.e. creating a hole or passage) to enable pulmonary blood flow. However, due to the resultant side effects (e.g.

hypertension), these staged procedures are largely being abandoned for complete repair early on in the baby's life (Harrox, 2002).

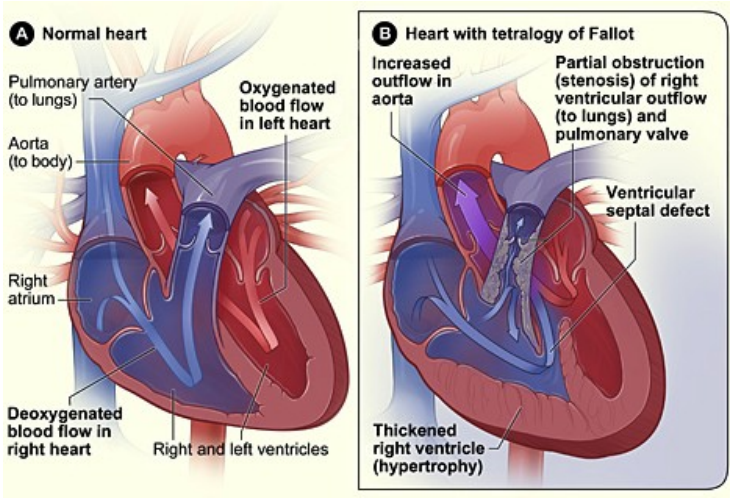

Figure 1.8: Normal heart and heart with ToF
© National Heart, Lung, and Blood Institute (NHLBI) [www.nhlbi.nih.gov/]

Repair surgery for ToF involves two main steps; i) closing the VSD by sewing a patch of fabric or pericardium (the normal lining around the outside of the heart) over the hole to close it completely, and ii) relieving the RVOTO through the right atrium and the pulmonary artery (Gatzoulis, Webb, and Daubeney, 2010). Repair surgery carries approximately 1% risk of mortality in patients with ToF (Baumgartner et al, 2010).

The survival rate for untreated ToF is very low with only 3% of patients reaching over 30 years of age (Brickner, Hills and Lange, 2000). The use of palliative procedures has led to an improvement in early and mid-term outcomes for ToF, however long-term outcomes are limited compared to those undergoing complete repair (Bailliard, 2009; Gatzoulis, Webb, and Daubeney, 2010). The survival rate for patients that had complete repair is approximately 85% after 36 years (Warnes et al., 2008). Long-term complications in patients with ToF are common

and approximately 10% of repaired patients will need to undergo re-intervention over a 20-year follow-up period (Oechslin et al, 1999; Gatzoulis, Webb, and Daubeney, 2010).

1.4.3 Transposition of the Great Arteries (TGA)

TGA accounts for 4-5% of all CHD, and is more prevalent in males than females with a 2:1 ratio (Gatzoulis, Webb, and Daubeney, 2010). TGA is characterised by a ventriculo-arterial discordance which involves an anatomic arrangement whereby the aorta arises from the right ventricle and pulmonary artery from the left ventricle in a fashion that is opposite to that seen in a normal heart (See Figure 1.2 (page 23) for a representation of the normal heart) (Martins and Castela, 2008). Therefore in patients with TGA, the aorta and the pulmonary artery run parallel to each other as opposed to the normal cross over (See Figure 1.9 below). Associated abnormalities are very common in TGA with the most common ones being VSD (40%-45%), LVOTO (25%) and CoA (5%) (Gatzoulis, Webb, and Daubeney, 2010).

With regards to the symptomology, cyanosis is the most common symptom often seen within the first few hours from birth. Other signs and symptoms include shortness of breath, rapid breathing, hyperpnoea (deep breathing using abdominal muscles) and heart failure (Harrox, 2002).

Treatment for TGA usually involves at least one operation in childhood; patients may undergo a palliative procedure to delay the complete repair, as palliative procedures are usually less invasive. This may include balloon atrial septostomy (creating a small hole between the two atria) to increase the blood flow and improve the mixing of the blood, however most patients ultimately require total surgical repair (Popelova et al, 2008). Until recently the most common forms of surgical repair for TGA included Senning and Mustard operations (atrial switch operations) (Gatzoulis, Webb, and Daubeney, 2010). Both these procedures correct the transposed arteries by creating a baffle (tunnel) within the atria to switch the flow of blood thereby correcting the defect, leading to a normal blood flow.

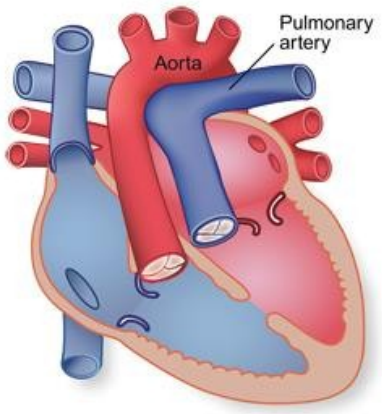

Figure 1.9**:** Image of a heart with TGA
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These procedures were then replaced by the Jatene procedure (arterial switch operation) in the 1990's. It's performed within the first few weeks of a patient's life, and involves switching the main arteries, which are then sutured into the correct position, providing better outcomes than the Mustard and Senning procedures (Gatzoulis, Webb, and Daubeney, 2010). The surgical mortality rate for the arterial switch operation is low (2-7%) for patients without associated defects (Sarris et al, 2006). In TGA patients with coexisting conditions such as VSD or pulmonary outflow track obstruction, the Rastelli procedure (involves the use of tubes to redirect the blood flow) is most frequently used (Rastelli, 1969; Gatzoulis, Webb, and Daubeney, 2010).

The outcomes for TGA patients without surgery are considered quite poor with most patients not surviving beyond the first few months (Gatzoulis, Webb, and Daubeney, 2010). A 90% 10-year survival rate and an 80% 20-year survival rate are reported for those who undergo the atrial switch operation (Wilson et al, 1998). The long-term survival rate for the arterial switch operation is 88% at 10 and 15 years with no deaths reported after 5 years of the operation (Losay et al, 2001). Long-term complications for those undergoing arterial switch operations

and Rastelli procedures may include ventricular dysfunction, arrhythmias, PS and hypertension (Popelova et al, 2008).

1.4.4 Single Ventricle (SV)

SV conditions account for 1%-4% of all CHD (Harrox, 2002). Single ventricle circulation is an umbrella term referring to a group of conditions that are characterized by the absence or poor development of one of the ventricles (hypoplastic left or right ventricle), or inlet valves of the heart (tricuspid and mitral atresia). They are a serious group of conditions that cannot be corrected, as a biventricular repair (restoring a two ventricle circulation) is not possible in patients with SV (Popelova et al, 2008). Some of the most common SV conditions include:

- Tricuspid Atresia (TA): characterized by the absence of a tricuspid valve, and a resultant lack of communication between the right atrium and ventricle
- Double-inlet left ventricle (DILV): characterized by both the left and right atrium draining into one ventricle, which is usually very small in size and has a hole in the ventricular septum
- Hypoplastic Left Heart Syndrome (HLHS): is characterized by the presence of a severely underdeveloped left ventricle (See Figure 1.10 below).

Common co-existing conditions include CoA, interrupted aortic arch, and patent ductus arteriosus (Gatzoulis et al, 2008). Symptoms in patients with SV conditions depend on the level of pulmonary blood flow and the mixing of systemic and pulmonary blood circulation; some of the signs and symptoms include severe congestive heart failure, cyanosis, pulmonary hypertension and chest infections (Harrox, 2002).

Most children diagnosed with SV are treated in childhood. Depending on the level of pulmonary flow, patients may initially undergo a range of palliative procedures such as pulmonary artery banding (to reduce excessive pulmonary blood flow) and systemic-to-

pulmonary artery shunts (a surgically created connection between the systemic and pulmonary artery) to increase the blood flow and relieve pulmonary stenosis (Gatzoulis and Swan, 2009). Treatment for SV is generally staged leading up to a Fontan procedure (Talwar et al, 2014). The Fontan procedure involves three stages leading up to the final Fontan. The aim and outcome of a Fontan operation is near normal arterial oxygen saturation and minimising cyanosis (Jaquiss and Imamura, 2009). For an overview of the different types and variations of the Fontan procedure see McRae, (2013).

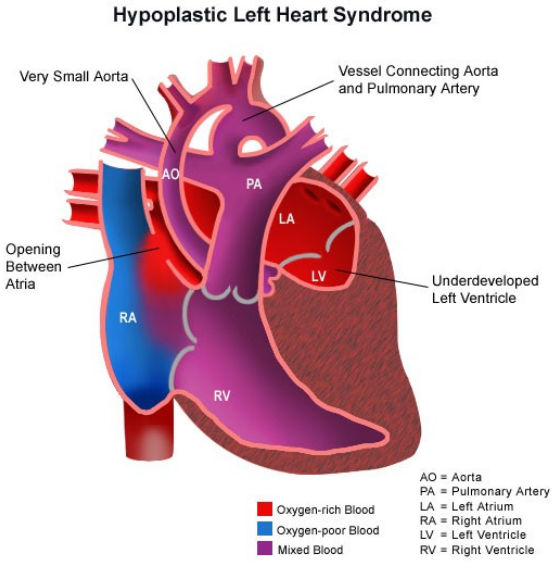

Figure 1.10*:* Image of a heart with with SV (HLHS)
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The prognosis for untreated SV patients is extremely poor (Silversides et al, 2010). Survival rates after a Fontan procedure are reported as 86%-94% at ten years and 82%-87% at 15-20 years (Silversides et al, 2010). The complex and multi-systemic nature of SV conditions can have further complications for patients (operated and un-operated) including congestive heart failure, arrhythmias, chronic cyanosis, and stroke amongst others (Warnes et al., 2008). SV patients generally require frequent follow-ups and constant surveillance to manage their condition.

1.5 Long-term complications of Adult Congenital Heart Disease

Having discussed some of the most common forms of CHD and their associated treatments, this section addresses some of the most common long-term complications affecting patients with ACHD. Long-term complications in ACHD are inevitable; as the heart ages, many forms of ACHD may require re-intervention and further treatment due to recurring problems. A recent review of the ACHD literature reported the most common long-term complications being arrhythmias, endocarditis, hypertension and heart failure (Ministeri et al, 2016).

Some patients with ACHD experience arrhythmias (an irregular heart beat) in the long-term due to several factors, including their underlying cardiac defect and post-operative scarring (Deanfield et al, 2003). When experiencing an arrhythmia patients may have symptoms such as shortness of breath, dizziness, chest pains, loss of consciousness or sudden cardiac death. Arrhythmias are reported to be one of the main factors responsible for hospitalization in ACHD, and are a frequent cause of increased morbidity and mortality (Somerville, 1997).

Another common complication in ACHD is the risk of an infection leading to an inflammation of the inner wall of the heart (endocardium) i.e. infective endocarditis (IE). Patients may experience a range of symptoms including fever, weight loss, joint pains and shortness of breath (Cabell, Abrutyn and Karchmer, 2003). Factors both external (tattooing, piercing and dental treatment/infection) and treatment related (surgical interventions) can be implicated in causing IE in patients with ACHD (Perloff and Warnes, 2001; Deanfield et al, 2003). Antibiotic prophylaxis is usually warranted to manage symptomology, with guidelines varying based on the underlying condition. Untreated IE can lead to damage of the heart valves and reduced pumping capability, which can result in death (Thuny et al, 2005).

Pulmonary Hypertension (PH) refers to a rise in blood pressure within the pulmonary arteries, and is a common complication of ACHD (Ministeri et al, 2016). PH in patients with ACHD is associated with increased morbidity and mortality (Rodriguez-Lopez, 2014). Furthermore Heart

Failure (HF) is another common complication of ACHD and is a known cause of morbidity and mortality in this patient group. HF includes a range of symptoms including difficult and laboured breathing, peripheral edema (accumulation of fluid in tissue) and increased central venous pressure (Ministeri et al, 2016). HF occurs due to the inability of the heart to efficiently deliver blood to other organs and tissues in the body (Mcmurray et al, 2012).

Another potential complication of ACHD is brain injury leading to impairment of neurological and cognitive functioning. Some of the most common causes for these injuries are hypoxic-ischemic/reperfusion injury, referring to the damage and injury caused to the brain, due to changes in cerebral perfusion i.e. cerebral blood flow and metabolism when undergoing cardiac surgery (Busl and Greer 2010). Furthermore, a characteristic symptom of some forms of CHD is cyanosis; the reduced blood oxygen saturation levels in cyanotic conditions may have neurological implications. Evidence related to the relationship between the heart and the brain, and the different types of brain injury and their causes in CHD is presented in Chapter 3. One potential complication of these injuries is cognitive impairment i.e. a decline in cognitive abilities such as memory and attention. Cognitive impairment can have a range of implications for patients, including difficulty and challenges with education and employment and the ability to conduct independent day-to-day activities such as self-care. Despite the growing literature in children with CHD this area of research has remained under explored in adult CHD patients. The aim of this thesis was to explore this area of research and investigate the extent of cognitive impairment and its potential mechanisms in ACHD patients.

1.6 Conclusions

Overall the improvements in treatment techniques have led to an increase in the survival rates of CHD, with an increasing number of patients reaching adulthood. Despite the improvements, this group of patients are often faced with long-term complications. These complications can have widespread implications for patients, including their physical, emotional and functional outcomes. One such complication is cognitive impairment, which can have widespread and

long-term implications for patients with ACHD. Assessing cognitive functioning in ACHD patients is the main focus of this thesis. The following chapter introduces and elaborates the concept of cognitive functioning.

2 COGNITION AND COGNITIVE FUNCTIONING

2.1 Prologue

As discussed in Chapter 1, cognitive impairment is a potential complication affecting some patients with CHD. This chapter provides an introduction to cognitive functioning and an overview of the key cognitive domains that pertain to this thesis. The chapter then discusses some of the challenges associated with cognitive testing.

2.2 Cognitive functioning

Cognitive functioning is an umbrella term encompassing a number of mental processes and abilities. Broadly speaking, cognitive functions can be classified into four areas; i) *receptive functions* involving the ability to acquire and integrate information, ii) *memory and learning* referring to the ability to store and retrieve information, iii) *thinking* which involves the ability to gather and organize information, and iv) *expressive functions* which refer to the ability to communicate and execute information (Lezak et al, 2012).

Each of these broad areas of cognitive function include a wide range of mental processes and abilities that are often referred to as 'domains' of cognitive functioning, such as attention, executive functioning, and motor function (Sections 2.2.2 - 2.2.5 provide a description of the different domains). While these mental processes and abilities can be classified conceptually into different domains, they are often intrinsically co-dependent, for instance attention and memory; whereby an individual must pay attention to a task in order to be able to acquire the relevant information for storing in memory.

2.2.1 Intelligence quotient (IQ)

Interest in assessing different domains of cognitive functioning is a recent development in the cognitive literature, as historically cognition was assessed as a single function, under the umbrella term 'intelligence' which refers to a general cognitive ability. Intelligence Quotient (IQ) is the unit of measurement used to describe this hypothesized general ability (Lezak et al, 2012). IQ tests generally consist of a number of tasks with varying levels of difficulty, that assess different cognitive abilities such as verbal comprehension, processing speed, working memory and perceptual organization. These tasks are then scored individually and cumulated to provide a single score for an individual's overall functional abilities i.e. IQ. IQ scores can range from low to high, with scores below 69 considered very low and score over 130 considered very high. A score of 100 is usually considered as the mean score on most tests of intelligence, representing an average IQ level.

In addition to this overall IQ score, the different subtests of an IQ test battery can also be utilized independently to assess specific areas of cognitive function such as the working memory and verbal abilities. Majority of IQ tests categorize these subtest scores into two broad areas: verbal IQ (VIQ) and performance IQ (PIQ). Verbal IQ is a measure of the individual's ability to apply verbal skills (e.g. language expression, comprehension) to analyze information and solve problems, for example answering questions orally or naming words. Performance IQ is a measure of the individual's ability to solve problems and analyze information using non-verbal skills (e.g. perceptual, visuo-spatial, and organizational) for example solving a puzzle or building a design (Wechsler, 1997).

There are a number of IQ test batteries used in the cognitive literature, for instance the Stanford-Binet Intelligence Scale (Terman and Merril, 1960), Raven's Progressive Matrices (Raven and Court, 1998), the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981), the Wechsler Adult Intelligence Scale – III (WAIS-III) (Wechsler, 1997), and the more recent version the Wechsler Adult Intelligence Scale- IV (WAIS-IV) (Wechsler, 2008). The WAIS

predominates the IQ literature and is one of the most widely used tests of intelligence. The WAIS is also considered 'the gold standard' in intelligence testing (Ivnik et al, 1992). The WAIS measures a range of cognitive abilities such as mental arithmetic, general knowledge and vocabulary; it provides both the PIQ and VIQ scores (Strauss, Sherman and Spreen, 2006).

Despite being widely used the concept of intelligence and measurement of IQ have been criticized as inadequate in the assessment and identification of specific cognitive impairment. IQ scores are cumulative in nature and are derived from assessment of a number of different functions. The use of a cumulative score may obscure the nature of specific impairments preventing the identification of the impaired cognitive domains. Furthermore, some researchers consider IQ scores to be unreliable; such that impairment of specific cognitive functions may lead to an erroneous representation of the overall intellectual ability of an individual (Lezak et al, 2012). For instance if an individual has impaired working memory, a low score on the memory task may pull down the overall average IQ when the individual scores are cumulated to derive a full-scale IQ score.

Critiques of the approach using a single cumulative measure like IQ have led to the development and use of more sophisticated measures aimed at assessing individual domains of cognitive functioning. Despite these criticisms, IQ remains one of the most widely used measures of cognitive functioning. IQ tests may be useful in situations requiring a general measure of an individual's functional abilities, for instance as part of a job or educational placement. IQ has been found in some studies to be predictive of certain forms of achievement including academic, occupational, and financial outcomes (Neisser et al, 1996).

Despite the critique presented above IQ was measured in the present study for two reasons: firstly to gain an insight into the overall functional abilities of this patient group, and secondly for the purposes of comparison to the existing literature.

2.2.2 Executive functioning

Executive function refers to a set of mental processes and abilities, which are thought to be higher order cognitive functions that govern in the overall hierarchy of brain processing (Baron, 2004; Gilbert and Burgess 2008). Executive function includes abilities such as problem solving which is the ability to identify a strategy in a complex situation; cognitive flexibility which is the ability to switch between different concepts; and response inhibition which is the ability to suppress actions that may interfere with a goal driven behaviour (Diamond, 2013).

Executive functions are an essential component of cognitive functioning, which enable an individual to initiate and monitor actions, deal with novel situations, engage in independent self-directed behaviours such as self-care, maintaining social and work relationships, and achieving goal directed behaviour (Strauss, Sherman and Spreen, 2006).

There is a wide range of measures used to assess executive functioning in the cognitive literature. A study surveying the cognitive assessment practices and test usage patterns among clinical psychologists reported the three most common measures used to assess executive functioning as the Wisconsin card sorting test (WCST- Kongs et al, 2000), Rey–Osterrieth complex figure test (Rey, 1941; Osterrieth, 1944), and the Halstead category test (Reitan and Wolfson, 1985) (Rabin, Barr and Burton, 2005). Within the present study executive function was assessed using a range of tests (See Chapter 7 for details).

2.2.3 Attention

Attention refers to the ability of an individual to be receptive to incoming information and stimuli, and to be able to identify and filter the relevant information to the brain for further processing (Cohen, Sparling-Cohen and O'Donnell, 1993). It is comprised of several processes including response selection which is the ability to select an appropriate response in a given situation; sensory selection which involves selecting a sensory modality such as visual, auditory and tactile; attentional capacity which is the extent to which one can focus and process

information; and sustained performance which is the ability to focus on a task for an extended period for time (Strauss, Sherman and Spreen, 2006).

The measurement of attention is complicated, in that impairments in attention may occur due to one or more of the above mentioned processes making it difficult to identify where the impairment lies. Furthermore in order for an individual to pay attention to "a task" one needs to attend to the incoming information that could be visual, verbal or spatial in nature. Similarly the response to this "task" may be in a similar or a different modality, requiring the individual to exercise multiple faculties' simultaneously. Tests of attention often require other additional cognitive skills such as motor speed and verbal abilities to be used (Strauss, Sherman and Spreen, 2006). A good example of this is the Trail Making Test B (TMT) of divided attention which requires the test taker to switch between sequences of numbers and letters (joining the numbers and letters as quickly as possible), and assesses divided attention along with perceptuo-motor skills and motor speed. Given the multiple modalities the nature of the test may involve and the different domains of cognitive functioning that need to be exercised, assessing attention can be a difficult task. Within the present study a range of tests was used to assess different aspects of attention e.g. divided attention and complex visual scanning. A detailed description of the tests utilized in this study is presented in Chapter 7.

2.2.4 Memory

Memory refers to the complex process of encoding, storing and retrieving information (Lezak et al, 2012). Broadly speaking memory can be divided into i) Sensory memory, ii) Working memory (previously referred to as short-term memory), and iii) Long-term memory (Strauss, Sherman and Spreen, 2006). Sensory memory holds information perceived for less than one second; a memory of any information observed only for a split second refers to the concept of sensory memory. Information is then transferred into the working memory, which retains information for a small period of time (1-2 minutes) (Strauss, Sherman and Spreen, 2006). Working memory is considered to include two subsystems; one that is responsible for

processing language (phonological loop) and the other for processing visuospatial data (visuospatial sketch pad) (Baddeley, Kopelman and Wilson, 2004).

Lastly, the information is transferred from working memory to the long-term memory, which is considered a more permanent store for information that can be retrieved at a later date, and can be stored indefinitely. Information transferred from working memory to long-term memory is more likely to be stored if it is rehearsed and/or repeated. Long-term memory is generally divided into i) implicit memory (procedural) which is used at an unconscious level to perform a task without conscious recollection of previous experiences; and ii) explicit memory which on the contrary is used at a conscious level with intentional recollection of past experiences and information (declarative and conscious) (See Strauss, Sherman and Spreen, 2006 for a detailed overview on the sub-types of long-term memory).

There are many types of memory used to store and retrieve different types of information, for instance episodic memory refers to the memory of specific events and experiences in time, which allows one to reconstruct an event that occurred. On the other hand semantic memory is a more structured record of facts, meanings, theories and concepts acquired.

A cognitive skill closely linked to memory is that of 'learning'; which refers to the ability of an individual to acquire new information (Lezak et al, 2012). Memory and learning are two closely related constructs, as learning is a process used to acquire memories and in turn memory is the process used to retrieve and expresses acquired or learnt information that has been stored (Okano, Hirano and Balaban, 2000). The present study includes a measure of verbal learning and memory (See Chapter 7, for details).

2.2.5 Motor functioning and dexterity

Motor functions are physical actions and movements that require the use of muscles. There are two types of motor function: gross motor function and fine motor function. Gross motor function involves actions that use larger muscles, which are responsible for movements such as walking, rolling over and balancing. Fine motor function involves the use of smaller muscles that enable one to do activities such as writing and picking up small objects using fingers (Cuffaro, 2011).

Motor functioning is an essential component of a comprehensive Neuropsychological (NP) assessment. Most tests of motor functioning involve tasks requiring the test taker to use their hands (Strauss, Sherman and Spreen, 2006). These tests assess different aspects of motor functioning including strength, speed, and dexterity, and are usually conducted for both hands.

Generally the performance of test takers is reported to be better with the preferred or dominant hand, however some studies have shown considerable variability in the normal population, with the dominant hand not always being more dexterous or proficient (Benton, Meyers and Polder, 1962, Strauss, Sherman and Spreen, 2006). It may therefore be important to assess both hands independently when testing motor function. The present study includes a measure of motor function that assesses fine motor functioning, visuo-motor co-ordination and dexterity for both hands (See Chapter 7, for more details).

2.3 A note on the specificity of cognitive assessments

As discussed above in Section 2.2, the multifaceted nature of cognition implies that cognitive tests are rarely unitary in nature and in any task are likely to interact with each other (Lezak et al, 2012). While conceptually understandable, it complicates the task of identifying which specific domains are responsible for the performance on any particular test.

Within the present study the NP tests utilized are discussed within four broad domains (executive function, attention, memory and motor function) that these tests fall under, along with IQ (See Chapter 7, for details). Given the complex nature of cognition, and the nature of cognitive tests, it is acknowledged that some of the cognitive tests used in this study may require one or more domains of cognitive functioning to be exercised. Therefore based on the recommendation of the published literature any patterns in the results of tests assessing a similar function are discussed where applicable, to identify specific areas of impairment (Lezak et al, 2012).

2.4 Factors commonly associated with cognitive functioning

When assessing cognitive functioning it is important to consider the range of potential factors that may have the ability to influence cognitive outcomes. These factors could play the role of confounders when assessing the level of cognitive impairment, which may lead to false positive conclusions and/or incorrect diagnosis. Some of the most common demographic factors that are known to influence cognitive functioning are age, gender and level of education.

The association of age and cognitive functioning is well established with changes in cognitive functioning reported with increasing age (Lezak et al, 2012), therefore comparing cognitive functioning in a group of people with different age groups is challenging and incorrect. Another factor that has the ability to influence cognitive functioning and test performance is the level of education achieved. Higher education is generally associated with better cognitive functioning across different domains and IQ and therefore must be taken into consideration (Lezak et al, 2012). Lastly gender differences in cognitive functioning have also been reported with males being better than females on certain domains of cognition and vice versa (Hill, Laird and Robinson, 2014), therefore when assessing cognitive functioning these factors must be taken into consideration and preferably controlled for.

Along with demographic factors some psychosocial factors have also been reported as having an influence on cognitive functioning. Mood related variables such as anxiety, affect and depression have been reported as being potential confounders when assessing cognitive functioning. Poorer cognitive performance has been reported in people experiencing negative moods such as increased anxiety or negative affect (Bartolic et al., 1999). On the contrary positive mood has also been associated with better cognitive performances (Bartolic et al., 1999); therefore making it important to control for factors like mood when assessing cognitive functioning.

Lastly, some extraneous factors that need to be considered when conducting cognitive assessments are the consistency of testing environment and the reliability of the cognitive tests used. The reliability of a test refers to its ability to measure the construct consistently. Therefore when using a cognitive test, good reliability is important to ensure that the test measures the same construct each time it is administered. If the reliability of the measure is poor, it would result in different scores each time it is administered (Mitrushina et al, 2005), making it difficult to drawing inferences about the cognitive ability being assessed. Therefore these factors must be considered when choosing the NP test battery.

2.5 Evaluating cognitive test performance

When evaluating the performance of an individual or group on tests of cognitive functioning, one needs to establish what constitutes a normal score and/or performance. In order to evaluate a test performance an empirical frame of reference is needed, generally normative data provide this frame of reference (Mitrushina et al, 2005). Normative data refers to a set of data (cognitive scores) on different tests gathered from a group of healthy individuals, with similar demographic characteristics. Normative data is generally considered the gold standard for comparing cognitive performance in the cognitive literature (Mitrushina et al, 2005).

An alternative to normative data is the use of control groups that independent studies can recruit. Similar to normative data, control groups include a healthy group of individuals with homogeneous demographic characteristics that match the subject/sample in question. Matching the characteristics of the study sample to that of the normative or control group are essential, as discussed above in Section 2.4 these factors can have the potential to influence cognitive functioning and therefore must be accounted for when drawing comparisons.

Lastly, in order to compare the performance of the patient with a normative/control group an impairment criterion needs to be established in order to assess the relative performance of the participant in comparison to the normal population. There is a wide range of impairment criteria used in the literature to define a cognitive impairment. A detailed description on the subject is presented in Chapter 7 (section 7.7.1).

2.6 Conclusions

This chapter introduced the concept of cognitive functioning, and its measurement. It presented the key domains of cognitive functioning that are fundamental to an individual's ability to function independently on a day-to-day basis. It also highlighted the complexities associated with the measurement and interpretation of cognitive assessments. The current evidence on cognitive functioning within the CHD population will be discussed in the next two chapters.

3 BRAIN DAMAGE, NEURODEVELOPMENTAL AND COGNITIVE IMPAIRMENT IN CHILDREN WITH CHD – AN OVERVIEW

3.1 Prologue

This chapter begins by considering the relationship between the brain and the heart. It then goes on to discuss evidence on both the structural (structural brain damage) and functional (neurodevelopmental and cognitive impairment) outcomes in children with CHD. This is followed by a brief discussion of the findings.

3.2 The brain and the heart

The relationship between the brain and the heart has been subject to much investigation, so much so that the last few decades have seen the emergence of a new medical subspecialty- '*Neurocardiology'* (Samuels, 2007). As the heart and the brain develop in tandem in the human fetus, through a complex genetic process, the development of both organs is codependent. The brain depends on the heart for delivery of oxygen and nutrients; in turn the heart is governed by the autonomic nervous system both during organ development and normal bodily function. Therefore it is not surprising that disruption in the development of one organ could have implications for the other (McQuillen and Miller, 2010).

Evidence in relation to the brain structure and its functioning in children with CHD is reviewed here, as it provides an important background to compare with the adult CHD literature. It helps identify the key areas of impairment in this patient group and enables comparing the outcomes

in childhood with those in adulthood to gain better understanding of whether the impairments identified in childhood persist into adulthood.

As children are not the primary focus of this thesis only a brief overview of key findings, from recent literature reviews and meta-analyses on children are presented. Evidence is discussed under two broad areas i) brain development and brain injury in children with CHD - addressing pathophysiological evidence regarding structural brain damage and ii) functional outcomes in children with CHD - addressing outcomes such as neurodevelopmental and cognitive impairment.

3.3 Brain development and brain injury in children with CHD

Improved imaging techniques such as Magnetic Resonance Imagining (MRI) have increased understanding of structural differences in the brains of children with CHD when compared to healthy controls. These differences can be classified into two categories: i) reduced brain development (referring to an impaired development of the brain in comparison to age matched controls) and ii) acquired brain injury (injury or damage caused to the brain after birth as a result of both internal (e.g. reduced cerebral blood flow) and/or external (e.g. pharmacological agents/surgical procedures such as cardio pulmonary bypass) factors (Martinez-Biarge et al, 2013; McQuillen and Miller, 2010).

3.3.1 Reduced brain development in CHD

Reduced brain development, indicated by reduced brain volume, retarded neuroaxonal development, and reduced cerebral blood flow, has been identified as early as in utero (i.e. foetal stages) in CHD patients, when compared to normal healthy foetuses (Donofrio et al, 2003). Advanced imaging techniques like MRI have enabled clinicians to gain an insight into the timing and nature of these developments. A three-dimensional volumetric MRI study of foetuses with CHD (primarily those with SV and TGA), reported smaller gestational-age-adjusted brain volume and altered brain metabolism relative to healthy foetuses

(Limperopoulous et al, 2010). Furthermore the results showed a slow rise in the level of N-acetylaspartate choline (NAA- an acetylated amino acid fluid that increases with cerebral/brain maturity) in CHD patients particularly in those diagnosed with TGA and HLHS when compared to healthy controls suggesting impairment in brain growth for CHD patients (Limperopoulous et al, 2010).

Reduced brain development in infants and children has been reported across different forms of CHD including SV, PS and TGA; with smaller brain volumes, brain immaturity, and reduced cerebral blood flow observed in these patient groups (Glauser et al, 1990; Tavani et al, 2003; Beca et al, 2009 and Donofrio et al, 2003). Brain growth and development largely depends on the level of oxygen supply, which is determined by the level of cerebral blood flow. One of the factors that may predispose patients with CHD to abnormal brain development is the alteration and disturbance in the blood flow, as a result of certain cardiac defects such as cyanotic conditions (Donofrio et al, 2003).

3.3.2 Acquired brain injury in CHD

3.3.2.1 Acquired brain injury in CHD prior to surgery

Beyond reduced brain development; infants with CHD are also at risk of brain injuries such as white matter injury (WMI), stroke, and haemorrhage, even prior to having any form of cardiac surgery. Some authors suggest the role of reduced brain development in causing this brain injury (Andropoulous et al, 2010). For example, factors such as brain immaturity and reduced cerebral blood flow may lead to lack of oxygen supply to the brain tissue causing it to deteriorate and/or eventually die, in turn causing injuries such as stroke and Periventricular Leukomalacia (PVL) which is a type of a WMI characterized by the death of brain tissue due to the lack of oxygen (Licht et al, 2004; Tabbutt, Gaynor and Newburger 2012).

MRI studies have highlighted the magnitude of brain injury in this patient group, indicating that 28-59**%** of infants experience some degree of brain injury prior to cardiac surgery. More

specifically the review reports the presence of WMI in 7%-27%, haemorrhage in up to 54% and stroke in up to 30% of CHD patients (Owen et al, 2011).

A more recent systematic review and meta-analysis of the literature (13 studies, N=425) showed a high incidence of brain injury in patients with CHD before cardiac surgery, with studies reporting the presence of WMI (PVL), stroke and cerebral atrophy (loss of neurons and connections between them) (Khalil et al, 2014). The overall prevalence of brain injury prior to congenital cardiac surgery is reported as 43% in the meta-analysis conducted by Khalil and colleagues, however the prevalence rates varied with the type of cardiac defect, ranging from 34% in TGA to 49% in left-sided heart defects such as HLHS, aortic stenosis (AS) and CoA (Khalil et al, 2014).

3.3.2.2 Acquired brain injury in CHD associated with cardiac surgery

Evidence shows that cardiac surgery in CHD patients can increase the risk of brain injury due to the risk of reduced cerebral perfusion (oxygen supply to the brain), microemboli (a blood clot/fat globule causing a blockage) and the body's inflammatory response to surgery (Kinney et al, 2005).

Cardiac surgery in patients with CHD can lead to an occurrence or increase in brain damage and/or worsening of existing brain lesions. In a study of 24-neonates with CHD (e.g. TGA, VSD, and HLHS) the presence of PVL and infarcts (a localized area of dead tissue due to lack of blood supply) was reported as 16% and 8% respectively prior to open-heart cardiac surgery (Mahle et al, 2002). Upon re-assessment after cardiac surgery a new PVL, infarct and haemorrhage was reported in 48%, 19% and 33% of the sample respectively; a total of 67% of the cohort presented a new or worsened brain injury after undergoing cardiac surgery (Mahle et al, 2002).

Another study assessing CHD patients both before and after cardiac surgery reported the presence of WMI in 20% of the infants in their study prior to any form of cardiac surgery. A new WMI was reported in 44% of the sample after undergoing cardiac surgery (Beca et al, 2013). These results showed that cardiac surgery in CHD patients may either cause or exacerbate brain damage and/or injury. However in contrast some research in children with CHD (TGA, SV) reports no worsening of preoperative brain injury after undergoing cardiac surgery (Block et al, 2010).

Reduced brain development and brain injury are common complications of both CHD and its related treatments (Snookes et al, 2010). Studies report that brain injuries such as diminished white matter can contribute to impaired cognitive function in domains such as visuo-spatial skills, learning, executive function, and IQ in children and adolescents with CHD (Rollins et al, 2014; Panigrahy et al, 2015). It is important to consider the evidence on the extent to which this reduced brain development and acquired brain injury are associated with functional outcomes in CHD patients, as these can have long lasting implications in the form of neurodevelopmental or cognitive impairment which may affect different areas of the patient's life, such as educational attainment, quality of life and social adaptation. The developmental and cognitive outcomes of patients with CHD are reviewed in the next section.

3.4 Developmental and cognitive outcomes in patients with CHD

There are two key concepts to be considered in the paediatric literature when discussing brain related developmental and functional outcomes in CHD; these are *neurodevelopment outcomes* and *cognitive outcomes*. In this thesis we will consider '*Neurodevelopment*' to refer to the early stages of development and meeting developmental milestones in the areas of learning, speech, motor function, social adaptation and behavioural functioning; impairments in neurodevelopment are presumed to reflect a lack of time-appropriate development (Marino et al, 2012).

As discussed in Chapter two '*Cognitive functioning*' is an umbrella term referring to a set of mental processes and abilities such as problem solving, higher order language skills, attention, executive functioning, motor function, dexterity and memory. In the CHD literature cognitive assessments overlap with neurodevelopment measures, but do not address specific developmental milestones.

Cognition and neurodevelopment have a conceptual overlap, for instance while the term neurodevelopment refers to a wide range of outcomes including behavioural (e.g. hyperactivity) and social (e.g. social adjustment and adaptation), it also includes the assessment of some cognitive functions such as motor function, attention and some elements of language and arithmetic abilities. As the focus of this thesis is on cognitive functioning as opposed to the broader field of neurodevelopment; only the key findings in the neurodevelopment literature relevant to cognition are discussed under the appropriate cognitive domains.

A note on terminology

Interpreting the literature on neurodevelopment and cognitive functioning is challenging owing to the variety of terms used by authors to describe the findings in the paediatric literature. For instance the terms neurodevelopmental or developmental delay and/or deficit are frequently used to describe the performance of those with CHD on traditional developmental measures (e.g. Bayley Scales of Infant and Toddler Development (Bayley, 1993)). This term 'delay' implies that the individuals will at some time in the future recover their performance to the normal level; while the term 'deficit' implies a more permanent impairment that may not recover to within the normal level. However, usually this empirical question is not addressed within these studies, as it requires long-term follow up and therefore there is no consensus on whether the impairments seen in children are delays or deficits. Therefore a more neutral term – 'impairment' was used in this thesis, regardless of the term used in the studies reported. Thus when referring to traditional developmental measures such as language or motor development, the term "neurodevelopment impairment" is used.

Similarly when discussing the evidence on cognitive assessments in this patient group the term used to describe performance below the 'normal' range is "cognitive impairment" as opposed to the commonly used 'cognitive deficit' and 'cognitive defect', as it carries no implication of the potential of the individual to recover (or not) but is descriptive of the findings in the literature and the present study.

A brief summary of the prevalence rates and most common forms of neurodevelopmental impairment in CHD is presented below in Section 3.4.1, before discussing some of the evidence pertinent to each of the cognitive domains assessed in this study (see Section 3.4.2).

3.4.1 Neurodevelopmental impairment in CHD

Several reviews of the literature have summarized the evidence on neurodevelopmental impairments in infants and children with CHD (Martinez-Biarge et al 2013; Tabbutt, Gaynor and Newburger, 2012). The systematic review and meta-analysis conducted by Khalil and colleagues reported a high risk of neurodevelopmental impairment in CHD patients (9 studies, N=512, age range= 4 days to 10 months), with a prevalence rate of 206/512 cases (~40%). Some of the most commonly reported neurodevelopmental impairments include altered muscle tone, reduced consciousness and retardation in motor development (Khalil et al, 2014).

Many studies using neurodevelopmental measures showed the presence of motor and cognitive impairment in patients with CHD within the first 2-3 years, with motor impairment being more pronounced in the first year (Tabbutt, Gaynor and Newburger, 2012). As children grow older a wider range of neurodevelopmental impairments, including poorer visual-motor skills, language, fine motor function and social maladjustment, are reported in school aged children and adolescents (Wray, 2006; Snookes et al, 2010). These findings could be explained by the fact that, with increasing age children may be confronted with more complex demands requiring a wider range of functions to be exercised. These more complex cognitive functions may not be

assessed in the formative years, making long-term follow up of these children critical (Martinez-Biarge et al, 2013). Evidence related to specific cognitive functions is discussed below in more detail.

3.4.2 Cognitive impairment in CHD

There is extensive evidence regarding cognition and possible cognitive impairments in children with different forms of CHD. A number of systematic reviews and meta-analyses have attempted to synthesize this evidence (Karsdorp et al, 2007; Bellinger and Newburger, 2010; Miatton et al, 2006; Sterken et al, 2015; Latal, 2016). Evidence relating to IQ and some of the key domains of cognitive functioning affected in children with CHD are discussed below.

3.4.2.1 Intelligence Quotient (IQ)

The literature on IQ in children with CHD is inconsistent; some studies report IQ in CHD patients to be lower than a healthy normative or control group (Miatton et al, 2007; Wernovsky et al, 2000) while other studies report IQ in CHD patients as comparable to normative groups (Goldberg et al, 2000). Generally the literature on cognitive functioning in CHD patients reports IQ levels within the average IQ range, even when the scores are lower in comparison to the age matched normative/control group data (Bellinger et al, 2003; Krueger et al, 2015).

3.4.2.2 Motor functioning

Studies report motor impairment in children with CHD across a range of conditions, including SV, ToF and TGA (Marinez-Biarge et al, 2013; Sarajuuri et al, 2012). In a study assessing children with SV 21.4% of the sample exhibited impairment in visual-motor integration, which is the ability of the hands and eyes to function simultaneously in co-ordination (Uzark et al, 1998). Similar findings were reported in another study, which reported 25% of children with different forms of CHD exhibiting impairment in motor function when compared to normative data, particularly in the areas of visual-motor integration and motor speed (Miatton et al, 2007b).

Impairment of both gross and fine motor function have been observed in children with CHD when compared to normative data, with one study reporting 42% of children with CHD exhibiting gross motor impairment and 42% fine motor impairment (Limperopoulos et al, 2002). The odds of motor impairment in children with CHD are reported as being three times higher for more structurally complex forms of CHD and two times higher for less structurally complex/Simple forms when compared to healthy controls (Brandlistuen et al, 2011).

3.4.2.3 Attention

Studies of children with CHD report impairments in some aspects of attention when compared to age matched normative data (Miatton et al, 2007a). A study assessing attention in school-aged TGA patients reported impairments (using a measure of inattention), in comparison to age matched normative data, with response times (measure of how fast /slow information is processed and responded to) being 1Standard Deviation (SD) slower in TGA patients when compared to the normative group (Bellinger et al, 2003).

Hovels-Gurich et al, (2007) assessed children with VSD and ToF using the computerized Attention Network Test (Adólfsdóttir, Sorensen and Lundervold, 2008) which provided performance measures on three functions of attention; alerting (continuous performance and vigilance tasks that require different levels of alertness), orienting (tasks requiring directing attention to a cued location) and executive control (tasks involving cognitive conflict i.e. two simultaneously competing tasks). ToF patients performed worse on the function of executive control in comparison to children with VSD and a healthy control group; the other two functions, including alerting and orienting, were reported to be normal in comparison to the control group, and performance did not differ between the groups (Hovels-Gurich et al, 2007). These results showed impaired attention (executive control) in patients with more complex forms of CHD in comparison to less complex conditions and control groups.

3.4.2.4 Memory

Evidence with regards to memory in CHD patients is inconclusive, as some studies of children with CHD show impairments in memory when compared to normal healthy controls, while others do not show any differences. A study investigating cognitive functioning in school-aged children with surgically corrected CHD, reported impairment in memory when compared to healthy controls, particularly with regards to memory for names i.e. recalling correct name associated with faces and learning (Miatton et al, 2007a).

On the contrary other studies have reported memory function in children with CHD (TGA, and ToF) to be within the normal range when compared to healthy controls (Miatton et al, 2006). A study assessing memory in children with different forms of CHD (such as SV, TGA, ToF, ASD, CoA) who have undergone cardiac surgery, reported memory function in the areas of picture memory, design memory, verbal memory and story memory as being within the normal range (Forbess et al, 2002). However the only exception reported in the study conducted by Forbess and colleagues was that patients with SV conditions performed below average on the picture memory test (Forbess et al, 2002).

3.4.2.5 Executive functioning

Relatively few studies have focused on assessing executive functioning in patients with CHD (Bellinger and Newburger, 2010). Amongst the studies that have, executive function is reported as being impaired in children with CHD. The Boston Circulatory Arrest Trial reported cognitive impairments in children with TGA that are collectively indicative of problems in executive functioning, which may affect the ability to organize and implement strategies and plans (Bellinger et al, 2003). School aged children diagnosed with ToF have been reported to perform lower on executive functioning tasks, in comparison to healthy peers (Miatton et al, 2007b).

More recently the occurrence of impaired executive functioning in a group of CHD patients with structurally complex forms of CHD (SV, TGA, & ToF) was found to be approximately

twice as high (75-81%) as healthy controls (43%) (Cassidy et al, 2015). All CHD groups in the Cassidy study showed impairment in the areas of cognitive flexibility, problem solving and verbally mediated executive functioning, while the SV and ToF groups also demonstrated impairment in visuo-spatially mediated executive functioning skills (Cassidy et al, 2015).

3.5 Cognitive impairment and the structural complexity of CHD

Literature on cognitive functioning in CHD generally reports that patients with more structurally complex forms of CHD exhibit greater cognitive impairment, in comparison to less structurally complex forms of CHD (Bellinger et al, 2003) (See Table 1.1 for the structural complexity classification used within this thesis). A meta-analysis of the literature on cognitive functioning in children and adolescents with CHD reported that patients with structurally complex conditions such as SV (HLHS), and TGA demonstrated impaired cognitive functioning when compared to normative data and control groups (Karsdorp et al, 2007); while those with less structurally complex conditions such as ASD and VSD demonstrated cognitive functioning within the normative range (Karsdorp et al, 2007). Similarly, with regards to IQ, more structurally complex forms of CHD exhibited both, impaired verbal and performance IQ when compared to normative data (Karsdorp et al, 2007).

A possible explanation for these findings is that complex forms of CHD are generally cyanotic in nature; and those with cyanotic conditions are at an increased risk of cognitive impairment compared to those with acyanotic conditions (Nass and Frank, 2010). Cyanotic conditions are characterized by low levels of oxygen in the blood, and this lack of oxygen supply may have detrimental effects for the brain causing impairments in cognitive functioning (Bass et al, 2004). Furthermore as seen in Section 3.3.2, the treatment techniques such as surgery associated with structurally complex forms of CHD may cause brain damage, which may in turn cause cognitive impairment (Kinney et al, 2005). Additionally patients with structurally complex forms of CHD are more likely to undergo multiple surgical procedures to correct their heart

defect, which increases their risk for brain damage and cognitive impairment in comparison to less complex forms of CHD.

3.6 Discussion

Both structural and functional impairments of the brain occur in children with CHD, with brain damage and cognitive impairment being common long-term complications (Newburger and Bellinger, 2006). While there is extensive empirical evidence regarding cognitive impairment in children with CHD, some caution is warranted when drawing conclusions. There is a large amount of variability in the findings across the literature with inconclusive results regarding the presence of impairment in some domains such as executive function and IQ; with studies reporting both poorer and similar performance in CHD patients when compared to the normative data and control groups. This variability could be attributed to the different measures used to assess these domains across the studies. Furthermore there are considerable differences in sampling across studies with some studies focusing on a single diagnosis while others include a more heterogeneous group of CHD patients.

Furthermore drawing comparisons between studies is challenging as the majority of the paediatric literature involves samples ranging from 4-18 years of age. This wide age-range makes drawing comparisons and inferences across studies challenging, given the difference in measures used to assess cognitive functioning in the different age groups.

There is also variability in the studies discussed with regards to the comparator group used to compare performance with the normal population; with some studies using established normative data and others a study control group. Each of these factors could potentially explain the differences in the results. Future studies may benefit from establishing a gold standard with regards to the assessment and measurement of cognitive functioning in patients with CHD, to enable drawing comparisons across the literature.

Lastly, the extrapolation from studies of cognitive impairment in children with CHD to the current era of CHD patients is challenging and perhaps inaccurate, due to the on-going advent and improvements in anesthetics, prenatal diagnosis, treatment techniques, and post-operative care; as the outcomes of patients born in the current era are likely to be very different from, and perhaps better than, the previous generation.

3.7 Conclusions

Despite the extensive evidence of cognitive impairment amongst infants and children with CHD; drawing conclusions regarding the long-term trajectory of these impairments is challenging in the absence of longitudinal data. The cross-sectional nature of these studies limits the ability to determine whether the performances observed persist over time and development, or whether children with CHD do at some time point catch up with their peers, albeit somewhat later in their development. Studies assessing adult CHD patients could help determine if these impairments indicate a delay in the development of functional abilities that will eventually develop to their full capacity, or are they in fact deficits that will not improve and persist well into adulthood. In order to address this issue the next chapter reviews the available evidence on cognitive functioning in the adult CHD population.

4 EXTENT OF COGNITIVE IMPAIRMENT IN ADULT CONGENITAL HEART DISEASE (ACHD) – A SYSTEMATIC REVIEW

4.1 Prologue

In Chapter 3 the relationship between the brain and the heart was introduced and evidence regarding neurodevelopmental and cognitive impairment in infants and children with CHD was presented. This chapter presents the findings of a systematic review of studies that have examined cognitive functioning specifically in ACHD patients, which is the main focus of this thesis. The chapter begins by detailing the focus, aims and objectives of the review followed by the methodology adopted. Thereafter the main findings of the review are presented and discussed.

4.2 Background

Given the increase in survival rates of CHD patients, there has been a shift in the focus from morbidity and mortality onto long-term functional abilities and outcomes such as their emotional health and wellbeing, cognitive functioning and Quality of Life (QoL). While there are a number of systematic reviews and meta-analyses that have aimed to synthesise the evidence on cognitive functioning in the paediatric CHD population (Sterken et al, 2015; Karsdorp et al, 2007), the literature on cognitive functioning in ACHD patients has not had such an extensive examination.

As discussed in Chapter 3, children with CHD exhibit a wide range of cognitive impairments in domains such as executive function, attention and motor function. However, given the lack of

longitudinal data the child literature does not allow any conclusions to be drawn regarding the persistence or not of these impairments. Therefore, it is difficult to determine whether the impairments seen in childhood, are delays in development that will eventually recover to within the normal range or if they are more permanent cognitive deficits that persist into adulthood. In order to address this question, cognitive functioning in the ACHD population needs to be assessed.

This systematic literature review aims to summarize and synthesize the existing empirical evidence on cognitive functioning in ACHD patients.

4.3 Aims of the systematic review

The primary focus of this review was on cognitive functioning in ACHD patients; therefore studies assessing only the paediatric CHD population were not included. The specific aims of the review were:

i) To examine the evidence on the extent and nature of cognitive impairment in ACHD, including the areas of cognitive functioning most affected.

ii) To identify factors which may influence and/or impact cognitive functioning in ACHD patients

4.4 Methodology

In accordance with the reporting guidelines for systematic reviews, a Preferred Reporting Items for Systematic reviews and Meta- Analyses (PRISMA) checklist was used and can be found in Appendix-A (Moher et al, 2009). According to the PRISMA checklist a systematic review of the literature must consist of certain methodological aspects such as a literature search strategy, information sources, eligibility inclusion and exclusion criteria, literature selection processes, a flow chart, study quality assessment and the analysis and synthesis of the evidence.

4.4.1 Literature search strategy

The electronic databases listed below were searched in 2011 and a literature review was published (Tyagi et al, 2013- See Appendix-B). In 2016 an updated systematic review was conducted for the purpose of this thesis. All databases were searched from inception through to August 2016. Furthermore a bibliographic search of the relevant articles was conducted to identify any additional articles for inclusion.

Databases searched via the OVID interface

- Embase (1974 – August 2016)
- Amed (1985 – August 2016)
- Cochrane database for systematic reviews (2005 – August 2016)

Databases searched via the EBSCOHost interface

- Psychinfo (1806 – August 2016)
- Medline (1948 – August 2016)
- Cinhal (1937 – August 2016)

Databases searched from other Sources

- Web of Science (1970 – August 2016)
- Google scholar (2004 – August 2016)

The literature searches were conducted using both key word and subject heading searches (e.g. MESH terms). The key words used to search all databases were ("Cogniti* " **OR** "neuropsycholog*" **OR** "neurocogniti*" **OR** "intelligence" **OR** "IQ") AND ("adult" **OR** "grown-up") **AND** ("congenital heart*" **OR** "congenital heart disease" **OR** "congenital heart defect"). The subject headings identified varied based on the database being reviewed; the detailed search strategy for each database is presented in Appendix-C and an example of the full electronic search for one database is presented in Appendix-D.

4.4.2 Inclusion and exclusion criteria for articles included in the systematic review

Given the limited number of studies assessing cognitive functioning in ACHD patients, the inclusion and exclusion criteria for the systematic review were deliberately not stringent, with the aim of being as inclusive as possible. The specific criteria applied within the review are discussed below.

4.4.2.1 Publication type

Articles were included only if they were written in English language, and published in an academic peer reviewed journal.

4.4.2.2 Study design and purpose

Articles were only included if they utilized a quantitative methodology to assess cognitive functioning in ACHD; including both cross-sectional and longitudinal study designs. Qualitative studies, literature reviews, meta-analyses and commentaries were excluded. Studies were included if their purpose was to i) assess the extent of cognitive impairment in ACHD patients, ii) assess the association of disease complexity with cognitive functioning in ACHD iii) identify predictors of cognitive functioning in ACHD.

4.4.2.3 Measures and outcomes

Only articles that assessed cognitive functioning as a primary outcome variable were included. Studies that only considered cognitive function, as a confounding variable and/or predictor variable were not included. Studies that included an objective assessment of cognitive functioning using an established and validated neuropsychological assessment tool were included. Articles were excluded if they assessed cognitive function using observational ratings and/or only recorded the participant's subjective reports of cognitive functioning in the absence of an objective evaluation of their cognitive abilities.

4.4.2.4 Participants

Only articles with an adult congenital heart disease sample were included, ACHD patients were defined as those ≥18 of age for the purpose of this review. Articles that only included patients ≤18 years of age were considered to be paediatric literature and were therefore not included. However articles that had both children (≤18 yrs) and adults (≥18 yrs) were included and reviewed with the aim of being as inclusive as possible.

Articles that only assessed patients with chromosomal abnormalities such as Williams's syndrome, Noonan syndrome and 22q11 syndrome, where CHD could be considered a secondary diagnosis were excluded. The presence of such chromosomal abnormalities has been associated with impaired cognitive functioning (Lott and Dierssen, 2010), which may obscure the association between congenital heart disease and the cognitive outcomes, which was the primary focus of this review. Therefore only studies that include a sample with CHD as a primary diagnosis were included in this review.

4.4.3 Systematic review procedure

4.4.3.1 Initial assessment of article relevance

The titles of all identified articles were assessed for relevance to the systematic review. Those that were not related to the research question and/or did not meet the inclusion and exclusion criteria were rejected at this stage and the reasons for exclusion were recorded. In instances where the article relevance was unclear based on the title alone, the article abstracts were reviewed. Abstracts of articles with relevant titles were then reviewed and assessed using the review inclusion and exclusion criteria. Any uncertainties regarding the inclusion of an article based on the abstract were resolved in liaison with a member of the supervisory team. Reasons for exclusion after reviewing article abstracts were recorded and are presented in Figure 4.1 (below). Full texts of all articles with relevant abstracts were then reviewed. Lastly a bibliographic search of relevant articles was also conducted, in order to identify potential articles for inclusion in the systematic review.

4.4.3.2 Analysis of selected articles

This review did not include a quantitative meta-analysis of the evidence. A narrative synthesis of the data was planned and considered more appropriate given the small number of studies, and the heterogeneity of the measures and samples used across the studies. To enable a systematic synthesis of the data the characteristics and results of the studies included were tabulated in Table 4.1.

4.4.3.3 Data extraction and synthesis

A data extraction form was designed to extract key information from the articles included in the systematic review. The data extraction form recorded general article information (title, authors and source of article), sample characteristics (sample size, inclusion and exclusion criteria, control/normative group, structural complexity groups), study characteristics (aims, design, measures used, cognitive impairment criteria used, analysis conducted) and the main findings and conclusions for each study (See Appendix-E).

The findings of the included studies are discussed under three broad areas, with aim of synthesising the literature: i) *measurement of cognitive functioning,* detailing the range of measures used across the studies included, ii) *the extent of cognitive impairment in ACHD,* detailing the results of the cognitive tests and the performance of ACHD patients in comparison to normative/control group data and iii) *factors that may influence and/or impact cognitive functioning in ACHD,* detailing any evidence on factors that may have an association with cognitive functioning.

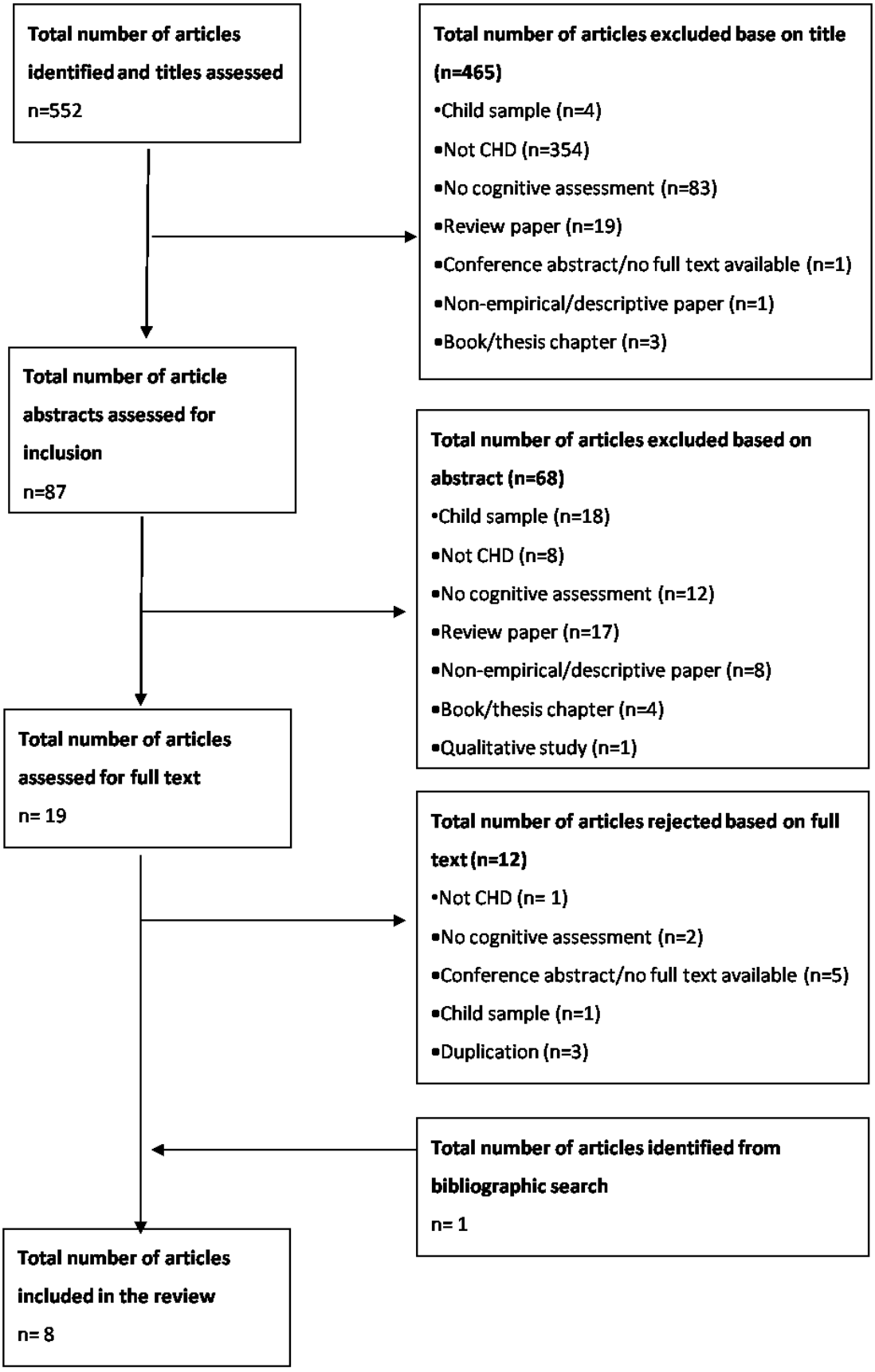


Figure 4.1 The study selection process for the systematic review search (2016)

4.4.3.4 Quality assessment

A quality assessment tool developed by Downs and Black (1998) was chosen to evaluate the methodological quality of the studies included in this systematic review. This quality assessment tool was chosen as it is designed for use with both randomized control trials (RCT) and observational studies. Furthermore it provides a total cumulative score for study quality, which enables comparison across studies. It includes 4 areas of assessment including: i) reporting, ii) external validity, iii) internal validity (both control of bias and confounding), and iv) power.

Given the nature of the research question, no RCT's were included in the review, consequently some of the items in the measure were not considered relevant. Following other studies that amended the measure to better fit their research (Hignett, Otter and Keen, 2016) the items pertinent to RCT's were excluded from the measure (e.g. was an attempt made to blind study subjects to the intervention they received?) and some items were adapted to better fit this area of research (e.g. "are interventions of interest clearly defined?" was replaced with "was the criteria for cognitive impairment clearly defined?"). The method for scoring was kept consistent to the original measure. All items on the scale were given a score of 2 (yes), 1 (partially) or 0 (no/unable to determine). The highest score possible for the quality assessment was 38, with a higher score representing better quality (Appendix-F).

4.5 Results of the systematic review

4.5.1 Identified papers

Using the search strategy detailed in Appendix-C a total of 552 articles were retrieved. Figure 4.1 illustrates the number of articles identified at each stage. The titles of each one of these articles was assessed and after rejecting papers based on title relevance a total of 87 articles remained. The abstracts of these remaining 87 articles were assessed and after exclusion a total

of 19 articles remained. The full-texts of the remaining articles were examined in detail for inclusion in the systematic review.

A total of 8 articles were finally included in the systematic review. Seven articles were identified from the literature searches, and one from the bibliography search. Two of the studies included were based on the same sample (Utens et al 1994; 1998). Utens et al (1998) only included a subset (19-25 year olds) of the original participants. Within the systematic review both these studies were included and treated separately with the aim of being as inclusive as possible, given the dearth of literature assessing cognitive functioning in ACHD.

4.5.2 Characteristics of the studies included in the systematic review

The characteristics of all the studies included in the systematic review are presented in Table 4.1 (page no. 82). All included studies (8/8) were cross-sectional in design and assessed cognitive functioning as a main outcome measure. Across the 8 studies a total of 1023 patients with CHD were assessed. The majority of the patients included across the studies were male (N=645 63.05%). Seven out of the eight studies included both males and females, with the exception of Eide et al, (2006), which included only male participants. The articles included were published between the years 1994 and 2015. Majority of the studies (6/8) were conducted in Europe, and the other two in the United States of America (2/8).

4.5.3 Quality assessment of studies included in the systematic review

The results of the quality assessment undertaken (Downs and Blacks, 1998) showed that the reviewed studies varied considerable with regards to the methodological quality (mean score =27/38; range of scores= 21-32), with higher scores indicating superior quality.

The most common issues related to study quality were the exclusion of critical information about recruitment procedures. Details about the recruitment procedures and how patients were invited and why certain patients declined were not presented (Utens et al, 1994). Further, some

studies did not report the sample size calculations and discuss the statistical power of the study (Utens et al, 1994; Heinrichs et al, 2014). Some studies did not describe the patient characteristics clearly (e.g. gender), which made it challenging to evaluate the representativeness of their study sample (Wernovsky et al, 2000).

With regards to the reporting of results, some studies failed to include the exact values and proportions and only provided approximations of the results for instance up to 10% of the patients experienced impairment in the domain of memory (Daliento et al, 2005). The lack of exact results made it difficult to draw conclusions regarding the magnitude of the problem observed within these studies. Furthermore, some studies included both children and adults in their study sample but combined the results of the different age groups and did not provide specific results for each age groups, which did not enable any conclusions to be drawn with regards to the adult population included in the study (Wernovsky et al, 2000). It also made it difficult to determine whether it was the performance of the child, adult or both groups of patients that led to the impaired scores. Overall given the lack of critical information and fundamental results and statistics, the majority of the identified studies scored low on the quality assessment measure with most studies ranging from poor to moderate quality.

4.5.4 Measures of cognitive functioning

The studies reviewed showed the most common form of cognitive assessment (7/8 studies) was the use of IQ tests, although there was considerable variability with regards to the measures utilized to assess IQ across the studies. Six out of the eight studies assessed IQ as the only measure of cognitive functioning. Two studies assessed domains of cognitive functioning beyond IQ and included the assessment of cognitive speed, executive functioning, memory, attention and language (Idorn et al, 2013; Daliento et al, 2005). Specific measures used in each study are detailed in Table 4.1 below.

Table 4.1 Details of studies included in the systematic review

Study author	Sample size and sample characteristics	Study design	Normative data used for NP comparison	Structural complexity groups included (N)	NP Measures used to assess cognitive function	Key findings	Quality score
Utens et al, (1994)*	N: 288 Mean age: 22.7 (18-35) Gender: M=147, F=141	Cross-sectional	Normed population data	Simple (ASD=91, VSD=67), TOF=52, TGA=15,PS=29, Other unspecified= 35	Groninger Intelligence Test (GIT) short form Subtests:: i)Visualisation ii)Verbal induction/deduction iii)Numbers	Patients had higher IQ than normative data (Mean IQ=105.5 vs. 100.0) 17% scored <86 indicating borderline mental functioning	24
Utens et al, (1998)*	Total N: 166, final included in analysis=146 Mean age: 21.7 (19-25) Gender: M=84, F=82	Cross-sectional (Sample from Utens et al, 1994)	Not available	Simple (ASD=50, VSD=40, PS=15), TOF=28, TGA=13	GIT short form	Patients had higher IQ than normative data (Mean IQ=105 vs. 100.0) 12.7% scored <86 indicating borderline mental functioning	21

Study author	Sample size and sample characteristics	Study design	Normative data used for NP comparison	Structural complexity groups included	NP Measures used	Key findings	Quality score
Wernovsky et al, (2000)	N: 133 Mean age: 14.1 ±8.8 (3.7-41.0) Gender: M=73, F=60	Cross-sectional	Normed population data	LV-TGA, SV (HLHS, Fontan LV-NRGA, Heterotaxy)[a]	Age appropriate IQ test: Wechsler Preschool and Primary Scale of Intelligence Revised. Wechsler Intelligence Scale for Children – Third Edition Wechsler Adult Intelligence	Patients had lower IQ than normative data (Mean IQ=95.7 ±17.4) 7.8% participants scored >2SD below normative data	30
Daliento et al, (2005)	N: 54 Mean age: 32 Gender: M=24, F=30	Cross-sectional	Control group	TOF= 54	Cognitive measures: i) Tower of London ii) Raven Progressive iii) Matrices iv) Trail making test A and B v) Calculation vi) Verbal fluency vii) Attentive Matrices viii) Digit Span ix) Logical story x) Corsi Blocks xi) Paired Associate learning	More than 2/3 of the sample had IQ scores in the normal range. Small proportion had impaired memory (0-10%)attention (10-20%) and learning (0-10%) and a larger proportion had impaired executive functioning (up to 53% on tower of London test)	22

Study author	Sample size and sample characteristics	Study design	Normative data used for NP comparison	Structural complexity groups included (N)	NP Measures used	Key findings	Quality score
Eide et al, (2006)	N: 166 (heart defect patients) Mean age: 18.7 Gender: M=166 (only males included)	Cross-sectional	384 healthy army recruits	TGA=2, Simple (dextrocardia=6, VSD/ASD =17) Unspecified cyanotic patients=141	Validated IQ test designed for the Norwegian draft board in 1953. Sub scales: i) Verbal analogues ii) Number series (calculation) iii) Geometrical figures (abbreviated version)	Patients had lower IQ scores in comparison to normative data (Mean 'stanine' IQ score (i.e. 1-9)= 5.30)	31
Idorn et al, (2013)	N=158 Median age = 13.9 (IQR=10.2-19.3) Gender: M=93, F=65	Cross-sectional	Control group	AVSD=15 DILV=39 HLHS=12 PA-IVS=12 TA=43 Other unspecified Fontan patients=37	A quick test of cognitive speed (AQT) Subtests i) Colour ii) Form iii) Colour-form	The adult patients included in the study performed lower in comparison to the control group on all three tests included in the AQT: colour ($p<0.001$), form ($p<0.001$) and colour-form ($p<0.001$).	27

Study author	Sample size and sample characteristics	Study design	Normative data used for NP comparison	Structural complexity groups included	NP Measures used	Key findings	Quality score
Heinrichs et al, (2014)	N: 60 Mean age: 16.9 ± 1.7 (14- 21.1) Gender: M=47, F= 13	Cross-sectional	Normed population data	TGA=74%, Simple (VSD=18%, VSD closed during Atrial switch operation=5%)CoA corrected in infancy=3%	Hamburg-Wechsler intelligence test (German version of the Wechsler Adult Intelligence Scale, revised) Subscales (6/11) i) Information ii) Arithmetic iii) Similarities iv) Vocabulary v) Picture completion vi) Block design vii) Leistungsprufsytem nach Horn test	Patients had higher IQ scores than normative data (FSIQ=106.7 vs. 100.0). 9% and 5% scored 1 and 2 SD below the mean on FSIQ	28
Murphy et al, (2015)	N= 18 (case and sibling pairs) Mean age: 16.1(SD=3.5) Gender: M=11, F=7	Cross-sectional	Sibling controls and normed population data	ToF=12, TGA=6	Wechsler Intelligence Scale for Children – Fourth Edition Wechsler Adult Intelligence Scale – Fourth Edition	Patients scored lower than their siblings and normative data on the FSIQ ($p<0.05$), and Processing Speed Index ($p<0.05$) and Perceptual Reasoning Index ($p<0.05$)	32

Note- *Studies using the same sample, [a]= exact proportion of patients in each structural complexity group unspecified, AVSD-Atrioventriclar Septal Defect, DILV- Double Inlet Left Ventricle, PA-IVS-pulmonary atresia with intact ventricular septum, TA- tricuspid atresia

Two of the articles included in the systematic review (Utens et al, 1994, 1998) examined IQ using the Groninger Intelligence Test (Luteijn and Van der Ploeg, 1983), a standardized Dutch measure of IQ; the short version of the test assessed three sub-tests; verbal induction/deduction, numbers and visualization. Normative reference group scores were used for the purpose of comparison with the general population.

In total 4/8 studies included both children and adults in their study cohort. Two of the four studies used age specific measures to assess IQ in the different age groups (See Table 4.1 above for details of measures used). The Wechsler Adult Intelligence scale –Revised (WAIS-R) was used for those >17 years of age (Wechsler, 1981) in the study conducted by Wernovsky et al, (2000) and the Wechsler Adult Intelligence scale – Fourth Edition (Weschsler, 2008) was used to assess IQ by Murphy et al, (2015). The other two studies utilized a single measure to assess all age groups. One study used the Hamburg-Wechsler intelligence test (Tewes, 1994) (German version of the Wechsler Adult Intelligence Scale, revised) (Heinrichs et al, 2014) and another used A Quick Test of cognitive speed (AQT) (Wiig et al, 2002) to assess cognitive speed (Idorn et al, 2013). The AQT involves three subtests: colour, form and colour form. The colour and form subtests assess perceptual speed and the colour-form test assesses cognitive speed, along with some aspects of executive functioning including the ability to shift sets (i.e. shift attention from one task to the other) and working memory. All four studies utilized normative data or control groups for the purposes of comparison to the normal population.

Eide et al, (2006) utilized a measure of general IQ performance that was designed and developed in 1953 for the Norwegian military draft board and was revised in 1962. It is a timed test involving categories of items; verbal analogue, number series (calculation) and geometrical figures (an abbreviated version of the Ravens Progressive Matrices) (Sundet et al, 1988; Raven, Raven and De Lemos, 1990). The test comprises 120 questions with increasing levels of difficulty. The measure is highly correlated with the well-established Wechsler Adult Intelligence Scale (r=0.73) (Sundet et al, 1988). This study utilized a group of healthy army

recruits as a control group to compare the performance of the patient group to the normal population.

In contrast to the studies discussed above, Daliento et al, (2005) utilized a range of measures to assess different domains of cognitive functioning using specific neuropsychological tests; Trail Making Tests (Reitan, 1958) to evaluate motor speed, attention and switching ability, the digit span subtest of the Wechsler Memory Scale to measure the span of immediate verbal recall (Wechsler, 1974). Verbal memory and learning was assessed using the verbal paired associates test (Wechsler, 1987) (from the revised edition of the Wechsler memory scale). The Corsi block test (Milner, 1971) was used to assess orientation and spatial attention, while the Attentive matrices test (Spinnler and Tognoni, 1987) was used to assess selective and sustained attention. Lastly, the Calculation test (arithmetic abilities) (Basso, 1979), the Tower of London test (Shallice, 1982) and the Ravens progressive matrices test (Raven, 1978) were used to assess executive function. The Ravens progressive matrices test also provided a measure of the patients' IQ. The patient data was compared to the scores of a reference control group to enable comparison with the general population.

Overall a wide range of measures was used across the different studies to assess cognitive functioning. This variability in choice of measures increases the difficulty in drawing comparisons across studies. The specific results and impairments identified within these studies are discussed in the following section and a summary is presented in Table 4.1 (page no. 82).

4.5.5 The extent of cognitive impairment in ACHD

The results of the reviewed studies showed mixed findings with regards to IQ in adults with CHD. Some studies reported IQ in ACHD patients as being higher in comparison to the normative/control group data. Utens et al, (1994) reported the level of IQ in their cohort as being higher (IQ= 105.5) than that of the normative group (Normative data mean IQ on the GIT; IQ=100), however the exact proportion of participants scoring above the normative mean was

not reported. Of the total sample the authors reported 17% of patients with borderline mental functioning classified by a score lower than 86 on the IQ test. The authors also reported including some patients with chromosomal anomalies such as Down's syndrome (N=1), Marfan's syndrome (N=1), and Reifenstein's syndrome (N=1). The interpretation of the findings in this study is complicated by the large amount of missing data (> 15%) and the inclusion of patients with intellectual disability (i.e. IQ<86) and chromosomal abnormalities.

Utens et al, (1998) utilized the same sample as Utens et al, (1994) but only included the 19-25 year olds from the sample (N=166, mean age=21.7 yrs). The mean IQ score of the sample was 105 (SD=15). As with the full sample a similar proportion of participants (12.7%) showed borderline mental functioning with low IQ levels (<70-85). The authors reported that normative data for the IQ scores were not available for comparison within their study, although no reasons were reported (Utens et al, 1998). However, they presumed that since a normative group would consist of the general normal population its scores should be normally distributed (i.e. IQ=100, SD=15). Based on this assumption the authors concluded that the results of their ACHD sample (IQ=105) were more 'favourable' (as stated by the author) as compared to a healthy normative group.

With regards to the level of cognitive performance in the different structural complexity groups, a significant difference in IQ (p=<0.01) was reported (Utens et al, 1998). The authors concluded that patients with more structurally complex conditions such as TGA (IQ=96) and ToF (IQ=96) exhibited the lowest level of IQ in comparison to the less structurally complex conditions such as ASD (IQ=107), VSD (IQ=106) and Pulmonary Stenosis (IQ=113). However when interpreting the results of both studies conducted by Utens and colleagues some caution is warranted, due to the poor methodological quality of these studies, including problems such as the high level of missing data and small cell sizes, inclusion of participants with intellectual disability and chromosomal anomalies, and the lack of established normative data for the purpose of comparison. Although the higher IQ reported in this study seems contrary to

expectation, given the inclusion of patients with intellectual disability chromosomal anomalies, it could perhaps be explained by the fact that a very small number of these patients were included in this study, which may not have been enough to affect the overall results.

Similar findings were reported more recently in the study conducted by Heinrichs et al, (2014), which found the average full-scale (106.7 ± 23.1), verbal (104.2 ± 22.6) and performance (105.4 ± 27.5) IQ in adolescent and adult TGA patients as being higher in comparison to the normative data (100 ± 15) (Heinrichs et al, 2014). With regards to the proportion of patients scoring 1 and 2 SD below the mean, the authors reported 9% and 5% for full scale IQ, 9% and 2% for verbal IQ and 14% and 11% for performance IQ respectively (Heinrichs et al, 2014). It must be noted that the study conducted by Heinrichs et al, (2014) did not have the same methodological problems reported by Utens and colleagues, such as large amounts of missing data and lack of normative data for comparison.

Contrary to the findings of Utens et al, (1994; 1998) and Heinrichs et al, (2014), other studies reported IQ scores in ACHD patients as being lower in comparison to normative data. Wernovsky et al, (2000) assessed cognitive functioning specifically in patients who underwent the Fontan operation. They assessed cognitive functioning in their cohort based on different age groups (<6yrs, 6-16yrs, >17yrs). Patients >17 years of age scored 95.7± 17.4 on the full scale IQ, 94.3± 14.2 on the verbal IQ, and 99.7± 16.0 on performance IQ respectively. However, the findings showed no significant differences in the IQ scores of the different age groups (Full-scale p=0.7, verbal p=0.2, and performance p= 0.2). In the absence of any significant differences in the mean full scale IQ, the authors combined the scores of the different age groups to achieve a single score. This combined score was then used for all further analyses.

The mean IQ of the combined age groups was 95.7±17.4, which was significantly lower than that of the published normative data for the WAIS test used (p=0.006). Of the total sample 7.8% scored <70 (i.e. more than 2 standard deviations (SD) below the normative mean of 100) on the

full scale IQ. Furthermore 6.3% and 8.5% of participants scored <70 on the verbal and performance IQ scores respectively. While the majority of the patients scored within the normal range, the cohort performed lower in comparison to the normative data (Wernovsky et al, 2000). However, the author's treatment of the data by combining scores for the different age groups makes it difficult to independently assess the performance of the adult patients in their cohort without the influence of the other age groups. This makes drawing specific conclusions difficult; as it remains unclear as to whether it is the scores of the children or the adults that are below the normative mean, in turn pulling down the average of the entire study sample.

Similar to the findings of Wernovsky and colleagues, Eide et al, (2006) also reported that patients CHD had lower IQ compared to a healthy control group. Eide et al, (2006) recruited only male participants in their study with a range of birth defects such as cleft pallet, cleft lip and CHD. Only the results of the CHD subgroup from this study are discussed in this systematic review. The authors reported significantly lower levels of IQ ($p=0.007$) in CHD patients when compared to the control group even after controlling for confounding factors such as birth order, maternal age, maternal education and marital status. Furthermore, the authors reported that patients with multiple heart defects did not exhibit any additional cognitive impairments in comparison to those with a single heart defect ($p=0.7$); to some extent these findings could be considered contrary to those of Utens et al, (1998) as having multiple heart defects could be considered more complex in comparison to a single heart defect.

Another study reported similar findings in adolescent and adult patients with TGA and ToF, with lower IQ in the areas of Verbal Comprehension (VCI), Working Memory (WMI), Processing Speed (PSI), Perceptual Reasoning (PRI) and Full Scale IQ (FSIQ) as measured by the WAIS- 4^{th} edition; when compared to their sibling controls (matched by age and gender) and normative data (Murphy et al, 2015). Patients with CHD consistently scored lower than their siblings on all indexes, with scores being significantly lower on the FSIQ ($p<0.05$), and PSI

($p<0.05$). Similarly, when compared to normative data CHD patients scored lower on all IQ indexes with significant differences on PRI ($p<0.05$).

In contrast to the other studies Daliento et al, (2005) conducted a more comprehensive cognitive assessment, examining several cognitive domains using neuropsychological tests, in a group of ToF patients. The authors report IQ scores within the normal range for majority (> ⅔) their study sample; however other specific domains of cognitive functioning showed impairment. A small proportion of patients showed impairment in memory (between 0-10%), attention (between 10-20%) and learning (between 0-10%); however, the authors do not report the exact proportion of patients scoring below the normative data on these tests. A larger proportion of patients exhibited problems in executive function, problem solving, and planning strategies (Verbal fluency test, Ravens test, Trail making test A and B, Tower of London test). In particular 53% of patients were reported as experiencing difficulties in the Tower of London test, which requires planning abilities. These results suggest that ToF patients experienced more difficulty in dealing with complex situations and finding solutions to them when compared to a normative sample. The lack of information regarding the exact proportion (%) of participants with impairments on the domains of attention and memory restricts conclusions being drawn about the magnitude of the problem in these domains.

Another study that assessed individual domains of cognitive functioning, reported impairment in cognitive and perceptual speed and executive functioning in patients with SV conditions (Idorn et al, 2013). ACHD patients performed poorer than the control group in all three subtests of the AQT, including the colour, form and colour-form. However, when interpreting the findings of this study some caution is warranted as the authors report severe cognitive impairment as one of the exclusion criteria within their study; which may have potentially resulted in a selection bias (i.e. not randomly selected) and suppressed the actual extent of impairment within this patient group.

Overall the results do not show a consistent pattern of impairment in IQ across the studies reviewed. While there is some indication of impairment in specific domains of cognitive functioning it is difficult to draw any conclusions based on a limited number of studies. Furthermore, given that the studies conducted by Daliento et al, (2005) and Idorn et al, (2013) only included patients diagnosed with ToF and SV respectively the findings may not be generalizable to ACHD patients as a group.

4.5.6 Factors that may influence and/or impact cognitive functioning in ACHD

Some of the studies examined in this systematic review showed the presence of cognitive impairment in ACHD patients. Five of the eight studies also examined possible factors that may influence and/or impact cognitive functioning. Of those, three studies reported an association between demographic factors and cognitive functioning. One study reported higher socio-economic status (SES) as a strong predictor of higher IQ ($p<0.001$), with SES explaining 16.1% of the total variance in IQ (Wernovsky et al, 2000). Two studies reported that lower levels of education were associated with poor performance on the Trail Making Test (TMT A and B) of attention, and IQ respectively (Daliento et al, 2005; Eide et al, 2006). Furthermore, another study reported a positive association between maternal age and IQ, which implies that higher the maternal age at the time of birth the higher the IQ; and a negative association between marital status and IQ, with an unmarried status being associated with lower IQ ($p<0.0005$) (Eide et al, 2006).

Three of the studies reviewed, reported an association between clinical variables and cognitive functioning. Wernovsky et al, (2000) reported a significant association between lower full scale IQ and the use of circulatory arrest before a Fontan operation ($p=0.002$), the use of circulatory arrest explained 6.1% of the variance in IQ. When the different structural complexity groups included in the study (TGA, SV, HLHS and "other complex conditions") was added to the model, the condition Hypoplastic left heart syndrome ($p <0.001$) and the variable 'other complex conditions' were reported to be associated with full-scale IQ ($p=0.05$) (Wernovsky et

al, 2000). Further, the addition of the structural complexity groups to the model rendered circulatory arrest not significant in the analysis. These results could be explained by an overlap between the variables given that hypothermic arrest is often used as a support strategy in the treatment of HLHS and complex forms of CHD.

A significant association between preoperative clinical factors (cyanosis), and cognitive functioning (executive functioning) has also been reported (Daliento et al, 2005). In particular ToF patients with a history of cyanosis in infancy performed poorly on the Trail Making Test (A and B) of attention and the Tower of London test of executive function ($U = 104.00$, $p < 0.005$, and $U = 184.00$, $p < 0.05$, respectively).

In another study neurological dysfunction (in patients with abnormal cranial nerves, motor dyspraxia, ataxia, sensory dysfunction, palsy, clinical seizures) was reported as being correlated with poor full scale ($p=0.001$), performance ($p<0.0001$) and verbal ($p=0.15$) IQ in patients with ACHD (Heinrichs et al, 2014). Furthermore, the authors also reported a significant correlation between reduced brain volume (measured through an MRI examination) and poor average full scale IQ in ACHD ($p=0.009$) (Heinrichs et al, 2014).

The third study reported a significant correlation between cognitive functioning and psychosocial outcomes, reporting a medium but significant negative correlation between cognitive speed and QoL; suggesting that poorer cognitive speed was associated with poorer QoL in patients with ACHD (Idorn et al, 2013).

These findings collectively suggest the role of both demographic and patient related clinical factors in influencing cognitive functioning in ACHD patients and the impact cognitive function may have on long-term outcomes such as QoL. However, the cross-sectional nature of these 3 studies only suggests correlations between these variables, but do not allow determining causality. Further work is needed in order to explore a wider range of clinical, psychosocial, and

demographic factors and their impact on cognitive functioning, for instance the impact of different, surgical procedures, implications of hospitalization, anesthetics and gender. Longitudinal assessment of these factors would allow examination of the stability of cognitive functions and the underlying causality of these impairments to be established.

4.6 Discussion

Given the only recent increase in survival rate of CHD patients, the majority of the literature and research in CHD has focused on the paediatric population. Consequently, there is an understandable lack of evidence regarding cognitive functioning in ACHD. The literature review published in 2013 was the first to assess and synthesize the literature on cognitive functioning in ACHD (Tyagi et al, 2013). Both the published review and this updated systematic review found a limited number of studies in this area of research.

The existing literature shows the presence of some cognitive impairment in patients with different forms of ACHD. The evidence with regards to IQ is inconclusive with some studies reporting IQ in the ACHD sample being lower than the normative data (Wernovsky et al, 2000; Murphy et al, 2015), while other studies reported IQ comparable to or better than the normative data (Utens et al, 1998; Heinrichs et al, 2014). Two studies investigated and reported impairments in specific domains of cognition such as cognitive speed, executive functioning, attention and memory (Daliento et al, 2005; Idorn et al, 2013). However the samples utilized within these two studies were limited to ToF (Daliento et al, 2005) and SV patients (Idorn et al, 2013), thereby limiting the generalizability of the findings. Collectively, the findings of the adult literature helps address the delay versus deficit argument discussed earlier in Section 4.2, showing that the cognitive impairments seen in childhood may in fact be deficits as opposed to delays, which persist well into adulthood (A fuller discussion on the subject is presented in Chapter 15).

Overall when interpreting the adult literature, there are some methodological challenges that limit the conclusions that can be drawn about the level of cognitive functioning in ACHD. There is considerable variability in the methodology adopted across the studies, both with regards to the assessment and measurement of cognitive functioning and sample selection.

With regards to the assessment of cognition, the systematic review showed an overreliance on the measures of IQ, as a global or cumulative measure of cognitive functioning in the ACHD literature. Furthermore, when interpreting the findings with regards to IQ it is difficult to draw comparisons across studies owing to the variety of instruments used to assess IQ. As discussed in Chapter 2, while IQ scores can be useful and informative, they are limited in the assessment and identification of specific cognitive impairments. As a result of this some of the subtle cognitive impairments in the ACHD population may not be identified. For instance, in the study conducted by Daliento and colleagues, the IQ scores of most patients (two-thirds) were within the normal range, however a considerable proportion of patients (>50%) showed impairments in specific domains such a executive functioning and problem solving, thus indicating the need to assess each domain of cognitive functioning independently.

Given that different forms of CHD show impairments in different areas of cognitive functioning, for instance more structurally complex and cyanotic conditions (ToF, SV) show more impairment in domains such as executive functioning and attention as compared to the less structurally complex conditions (ASD, VSD) (Utens et al, 1998; Daliento et al 2005, Idorn et al, 2013), and that the use of a cumulative measure such as IQ may obscure specific impairments in different domains, it is considered essential to undertake a more exploratory approach to investigate each domain independently, as opposed to a cumulative score.

Furthermore, there is considerable variability in the normative data used to compare the performance of the ACHD patients with the normal healthy population. Some studies utilized established normative data, while others recruited an independent control groups. This

variability makes it difficult to draw conclusive judgments as some groups were matched to the normative data by age, while others were matched by age and gender. Therefore, there is lack of standardization in the process of evaluation, which makes the interpretation and comparison between studies challenging. Furthermore, this variability in the source of the normative data may also help explain the contrary findings observed within the studies reviewed.

Another distinction between the reviewed studies is the variability in the complexity of the heart disease within the sample. While some studies include and assess a range of different forms of ACHD both structurally complex and simple (Utens et al, 1998), others included patients from a single structural complexity group, for instance ToF (Daliento et al, 2005) and SV (Idorn et al, 2013). The heterogeneity of the different levels of structural complexity amongst the study samples makes comparison across studies difficult, as there is some evidence to suggest that different types of ACHD show a different likelihood of demonstrating cognitive impairments. For instance, one of the studies in the systematic review reported more structurally complex forms of CHD exhibiting more cognitive impairment in comparison to those with less structurally complex forms (Utens et al, 1998), however no differences were noted between patients that were diagnosed with a single versus multiple forms of CHD (Eide et al, 2006). Although no inferences can be drawn with regards to the increase in structural complexity of those with multiple conditions, the fact that the different diagnosis may each be accompanied by their own associated treatments and complications, they could be considered more complex in comparison those with a single defect.

Similarly, in a meta-analysis of the literature it was reported that children and adolescents with more structurally complex forms of CHD exhibit more cognitive impairment as compared to their counterparts (Karsdorp et al, 2007). The authors attribute these differences to the fact that more complex forms of CHD are associated with specific risk factors such as the number and complexity of surgeries undergone and the pre and post operative cerebral perfusion that may have a cumulative adverse effect on cognition (Karsdorp et al, 2007).

This heterogeneity of sample selection further raises an interesting question regarding the value of assessing each complexity group independently versus assessing a heterogeneous group with a range of ACHD conditions together. Assessment of independent structural complexity groups would allow specific analysis of the issues and challenges faced by the different conditions, which would enable a clearer understanding of the impact of these different forms of CHD. This may also enable more specific provision of care and support. Although the single condition approach does allow more specific assessment of the group in question it does restrict generalizability to ACHD patients as a group. Although assessing a heterogeneous group of patients collectively may allow wider generalizability, it may lead to dilution of specific effects if differential impairment exists.

In light of the evidence discussed above and the presence of more cognitive impairments in structurally complex forms of CHD in comparison to those less complex, the former approach may have more merit and allow a better understanding of the level of impairment across different complexity levels. Therefore, future studies may benfit from undertaking a more exploratory approach to investigating cognitive functioning in ACHD by investigating different types of CHD independently while also conducting a comparative analysis to identify differences in cognitive functioning across different forms of CHD, which may get obscured if different conditions are grouped together.

Another important question relates to sample selection. Critical here is whether to include or exclude patients with co-morbidities and other chromosomal anomalies inherent in some forms of CHD; including Down's syndrome, and Di Georges syndrome. Within the systematic review most studies did not report including patients with chromosomal anomalies, with the exception of one study (Utens et al, 1994). However, the proportion of these patients was too small (N=3) to draw any conclusions, and as a result their inclusion did not seem to impact the results of the study. Down's syndrome is one of the most common genetic causes of impaired intellectual and

cognitive functioning commonly found in CHD patients (Lott and Dierssen, 2010). Therefore, inclusion of these patients may bring down the average intelligence quotient and cognitive test performance in a study. Furthermore, the inclusion of these patients may obscure the impact of CHD and its related treatments on cognitive function, making it difficult to identify the exact cause of impairment. Alternatively, not including these patients may restrict understanding of those CHD patients that have these additional anomalies. Furthermore, it could be argued that the exclusion of these specific patients may result in the findings being more positively skewed with most patients performing in the normal range.

The overall conclusions of the review conducted in 2016 did not differ from the review conducted in 2011 (See Appendix-B for published literature review). While collectively the available literature allows some insight into the cognitive functioning of ACHD patients, the methodological limitations of these studies should ideally be addressed in future research. First, larger sample sizes would provide more statistical power, which would in turn enable assessment of different surgical, and intervention related factors with a lot more precision. It would allow controlling for type-II error rate, which implies the identification of false-negative findings, which may result in the missed identification of impaired patients. Second, studies may benefit from assessing patients with different levels of structural complexity and comparing cognitive outcomes within different complexity groups, to get a better understanding of the impact of the different forms of ACHD on cognitive outcomes.

Third, future studies may benefit from a more comprehensive assessment of cognitive functioning including both tests of IQ and independent cognitive domains, in order to identify impairments in cognitive functioning with more specificity. Lastly, adopting a longitudinal design would enable assessment of the stability of these functions and identify any intervening factors. For example, medical and/or psychosocial factors that may influence change in cognitive functioning over time. In addition, while there was some indication of the impact of reduced cognitive functioning on QoL, further research is needed to be able to evaluate the

influence of cognitive impairment on QoL outcomes in this patient group. The current study aimed to address some of these limitations. The specific aims and objectives of this study are presented in Chapter 6.

4.7 Limitations of the systematic review

In addition to the limitations of the reviewed studies, discussed in the previous section, the limitations of the systematic review need to be acknowledged. This systematic review was limited to studies written in English language, and published in peer-reviewed journals. It is acknowledged that the use of translational services may have expanded the scope of the review with the inclusion of articles published in other languages; however the lack of funding and access to translational services made this unavoidable. Furthermore while the literature searches aimed to be comprehensive up to August 2016; research papers may have been published since the searches were undertaken. Examining the evidence on the impact of impaired cognitive functioning on other patient related long-term outcomes was outside the scope of this review, but remains an important area of research for future studies to investigate.

4.8 Conclusions

The published literature review and this updated systematic review were the first to synthesize the evidence on cognitive functioning in ACHD. The findings of the review showed the presence of cognitive impairment in ACHD patients, particularly in the areas of executive function, attention, cognitive speed and IQ. However the findings with regards to IQ were inconclusive. The review identified methodological limitations of the existing literature. These limitations have important implications for future research. Although the existing literature is characterized by mixed findings and methodological limitations, it does address an important area of research that has previously been neglected. It highlights the functional limitations of patients with ACHD, and presents an insight into the potential long-term implications of developmental impairment seen in children with CHD. Lastly it showed the potential impact of

cognitive functioning on long-term psychosocial outcomes such as QoL, however further research is warranted.

5 COGNTIVE FUNCTIONING AND QUALITY OF LIFE IN ACHD

5.1 Prologue

This chapter introduces the concept of Quality of Life (QoL), and discusses the evidence available on QoL in ACHD patients. It also discusses and presents the available evidence on the association between QoL outcomes and cognitive functioning in ACHD.

5.2 Background

As previously discussed in Chapter 4, the increasing survival rates of ACHD patients have lead to greater attention being focused on long-term outcomes other than morbidity and mortality; for instance, employment, emotional wellbeing, and cognitive functioning. One such outcome is QoL, which is emerging as an important patient reported psychosocial outcome in the ACHD literature (Uzark, 2016). Quality of life is a multidimensional construct that is conceptualized into broad domains, namely, physical, psychosocial, occupational and environmental (Ware et al, 2000).

The congenital and chronic nature of CHD implies that some patients may have to undergo a lifetime of on-going medical care and treatment, particularly for those with more structurally complex forms of CHD that require constant monitoring. Furthermore the chronic nature of CHD not only poses physical challenges such as morbidity and mortality but may also present psychosocial challenges resulting from the illness such as poor emotional health and wellbeing including depression, anxiety and reduced QoL (Webb, 2005; Eslami et al, 2012). The British Cardiac Society Working Party and American College of Cardiology have recognized these

psychosocial challenges, and provide guidelines and recommendations for the management of ACHD patients (Webb & Williams, 2001; Report of the British Cardiac Society, 2002). These guidelines emphasize the importance of emotional and psychosocial health and recommend that emotional wellbeing should be a priority in the overall care provided to these patients.

Impaired cognitive functioning has been associated with poorer physical and mental QoL in ACHD patients; suggesting the potential impact impaired cognitive functioning may have on different areas of the patient's life (Idorn et al, 2013). This association between cognitive functioning and QoL has been reported both in the paediatric and adult CHD population (See Section 5.4 for details).

The following section discusses QoL outcomes in ACHD. Given that QoL in ACHD is not the primary focus of the present study only a brief summary of the literature is presented below.

5.3 Quality of Life in ACHD

Some studies have indicated that quality of life in ACHD patients is lower in all domains except social functioning, when compared to the general population (Rose et al, 2005). Significantly worse physical QoL has been reported in ACHD patients when compared to the normal population across several studies (Lane, Lip and Millane, 2002; Kamphuis et al, 2002). These findings are understandable given that some forms of ACHD may include on-going morbidity and symptoms such as cyanosis, palpitations and arrhythmias, which may impact the patients' general physical health and well-being, in turn affecting their physical QoL. Furthermore, some of these patients may also experience physical limitations due to their condition and/or are advised to follow certain restrictions in the intensity and type of physical activity they undertake on a day-to-day basis, leading to reduced physical QoL in comparison to the normal population.

However, other studies have reported QoL in ACHD as being comparable to or better than the general population (Moons et al, 2006; Silva et al, 2011; Daliento et al, 2005). Fekkes et al,

(2001) assessed QoL in a group of ACHD patients with and without social impediments (i.e. social life limitations in relation to CHD as measured by a disease specific QoL measure, QoL-CHD) and reported that patients experiencing social impediments have overall QoL comparable to that of the general population. Moreover, patients not experiencing any social impediments reported better QoL in comparison to general population in areas including daily activities, vitality and social functioning (Fekkes et al, 2001). Several studies have reported better QoL in ACHD patients in comparison to a healthy normal population in the areas of psychosocial, physical and environment QoL (Silva et al, 2011; Chen et al, 2011).

Overall the findings with regards to the QoL in ACHD appear inconclusive with conflicting evidence which could be attributed to a number of factors, such as the different complexity groups assessed across studies and the variability in measures used to assess QoL (see Fteropoulli et al, 2013, and Kahr et al, 2014).

5.3.1 QoL and the structural complexity of CHD

Recently conducted systematic reviews of the QoL literature in ACHD reported that patients with more structurally complex forms of CHD such as TGA and SV generally report poorer QoL in comparison to less structurally complex forms such as ASD and VSD, mainly in the areas of physical, environmental and occupational QoL (Fteropoulli et al, 2013; Kahr et al, 2014). Furthermore, patients with cyanotic forms of CHD have been reported as having poorer QoL in comparison to those with acyanotic forms (Lane, Lip and Millane, 2002).

However, this association between the increased complexity of the heart conditions and reduced QoL outcomes is not always evident in the ACHD literature. The literature review by Fteropoulli and colleagues also found some studies that showed more structurally complex forms of CHD (such as ToF and SV patients) reporting better QoL in comparison to those with a less complex forms (ASD). This is especially notable, as the more complex forms will have had multiple surgical interventions, hospital admissions and everyday health related

complications (Saliba et al 2001; Ternestedt et al, 2001). A plausible explanation for these findings could be that patients with complex forms of CHD who perceive themselves as doing relatively well with regards to their QoL may score themselves higher, as their expectation of having a good QoL may have been lower than that of the general population, given the chronic nature of their condition and its associated limitations and complications.

In order to improve QoL it is fundamental to identify and understand the factors that may have the potential to influence QoL outcomes. Quality of life may be influenced by a number of factors, both internal (e.g. physical health, emotional and cognitive functioning) and external (e.g. education, employment, social support) (Rose et al, 2005). As discussed above, one such factor that has the potential to influence QoL outcomes is cognitive functioning (Idorn et al, 2013). The next section aims to present the literature examining the relationship between cognitive functioning and QoL outcomes in CHD patients.

5.4 Relationship between cognitive functioning and QoL in CHD patients

The majority of the available evidence on the association between cognitive functioning and QoL in CHD has focused on the child and adolescent population (DeMaso et al, 1990). The paediatric literature reported some association between cognition and QoL, with impaired cognitive functioning being associated with reduced QoL outcomes (DeMaso et al, 1990). For instance a study assessing children and adolescent patients with ToF, TGA and SV conditions reported mood and cognitive domains of executive functioning and gross motor ability as being key drivers of poorer QoL. The results showed demographic factors explaining 8-14% of the variance in QoL and executive function, gross motor skills, and mood predicting an additional 11-37% of the variance (Marino et al, 2011). Similarly, with regards to IQ, a positive association between lower levels of verbal, performance and full scale IQ and the psychosocial domain of QoL in children with TGA has been reported, with lower levels of IQ being associated with poorer psychosocial QoL (Dunbar-Masterson, 2001).

With regards to ACHD literature, a recent study reported a significant correlation between cognitive functioning and psychosocial outcomes including QoL. A medium but significant negative correlation between cognitive speed and physical and psychosocial QoL was reported in adult SV patients. These results suggested that impaired cognitive speed was associated with poorer QoL outcomes in patients with different forms of SV conditions (Idorn et al, 2013).

A systematic review assessing QoL in those born at high risk (including pre-term and CHD patients) reported that young adults living with childhood onset of developmental impairment including cognitive impairment are restricted in life roles, such as employment and interpersonal relationships, social adaptation, which may have a negative impact on their QoL (Dahan-Oliel, Majnemer and Mazer, 2011). These findings appear understandable if one assumes that those with CHD may, during their early years of education, be restricted by neurodevelopmental and cognitive impairments, as well as school absences due to recurring hospital appointments and admissions. These difficulties during their formative years may lead to challenges in social adaptation, education and employment in the adult years of these patients' lives, which may in turn affect their QoL and well-being. Some support for this view is apparent in a study which reported that as ToF and ASD patients grow older they report a greater negative impact of their condition on their general well-being and QoL (Ternestedt et al, 2001).

The available evidence indicates an association between cognitive functioning and QoL in CHD patients, but warrants further investigation in the ACHD population that has not been adequately investigated. Assessing QoL in the adult population may provide more specific insight into the QoL issues pertinent to this patient group in adulthood, for instance employment and socio economic status etc. Furthermore, the lack of adult literature in this area restricts an understanding of whether the associations noted in childhood carry forward into adulthood and affect patient QoL, as they grow older.

5.5 Conclusions

Overall there is lack of literature investigating the association between cognitive functioning and QoL in ACHD. There is evidence of an association between cognitive functioning and QoL in other chronic conditions. For instance patients undergoing coronary artery bypass grafting report a significant association between impaired cognitive outcomes and reduced QoL after cardiac surgery (Newman et al, 2001; Phillips-Bute et al, 2006). Evidence in other non-cardiac conditions such as multiple sclerosis (Benito-León, Morales and Rivera-Navarro, 2002; Samartzis et al, 2014), Huntington's disease (Eddy and Rickards, 2013) and mild cognitive impairment (Teng, Tassniyom and Lu, 2012) also report an association between impaired cognitive functioning and reduced QoL. Given the evidence in other areas and that cognitive functioning is critical to an individual's ability to function independently on a day-to-day basis (including abilities such as problem solving, decision making and reasoning) and may have the potential to affect different areas of a patient's life for instance, educational attainment, employment, social adaptation, it could be considered critical in influencing QoL, warranting further research and investigation in the ACHD population.

This study aimed to assess the relationship between cognition and QoL specifically in ACHD patients, and the related findings can be found in Chapters 8.

6 INTRODUCTION TO CROSS-SECTIONAL STUDY AND AIMS AND OBJECTIVES

6.1 Summary of the background chapters and literature review

ACHD is a heterogeneous group of conditions that vary in the level of structural complexity and severity. With improvements in treatments and surgical techniques the proportion of ACHD patients has escalated in recent times, with adults becoming the fastest growing segment of CHD population. Given the only recent increase in survival rates, research in CHD has largely focused on the paediatric population.

As discussed in chapter 3 impairments in cognitive functioning have been reported in children with CHD, across a range of cognitive domains including attention, executive function and motor function when compared to normative data or a healthy control group. However, there is lack of clarity around the nature and longevity of these impairments noted in the paediatric population and how these could be extended to the adult population. In remains unclear from the available evidence if the impairments seen in children are deficits that last into adulthood or delays that will eventually develop to within the normal range.

In order to address this gap in the literature cognitive functioning in the ACHD population needs to be investigated. A systematic review of the literature was conducted, and the results showed a limited number of studies assessing cognitive functioning in ACHD patients. The available evidence showed mixed findings with regards to the extent of cognitive impairment in ACHD patients. Inconclusive findings were reported with regards to IQ, and only two studies investigated and reported impairments in specific domains of cognitive functioning such

executive functioning, attention and cognitive speed. Furthermore, there was lack of research on the potential impact of cognitive impairment on long-term outcomes such as QoL.

Overall a dearth of good quality evidence investigating cognitive impairment in ACHD patients was noted, and the need to comprehensively investigate the extent and impact of cognitive functioning in ACHD was highlighted.

6.2 Limitations of the existing literature

There were a number of methodological limitations in the studies reviewed. Some of the key issues that arose from the systematic review were;

- ***Measurement of cognitive impairment***

The majority of the existing studies relied on a composite measure of cognitive functioning in the form of an IQ test. This method of assessment limited the information available on the specific impairment of cognitive functioning in different domains of cognition. More comprehensive evaluation of the specific domains of cognitive functioning is warranted.

- ***Heterogeneous versus more homogeneous sampling***

Another limitation of the existing literature was the difference in sampling across the existing studies. While some studies utilized a heterogeneous sample and assessed cognition in a group of ACHD conditions with varying levels of complexity collectively, others only investigated a single condition. This discrepancy in the studies highlighted the lack of a gold standard for classifying the different forms of CHD, and also limited the generalizability of the findings to ACHD patients as a whole.

- ***Factors influencing cognitive functioning***

There is a lack of research investigating the factors that may have the potential to impact cognitive functioning in ACHD. Very few studies have investigated this and those that have, include a limited number of factors (usually clinical factors) that do now allow a complete

understand of the range of variables that may have the potential to impact cognitive functioning. A more comprehensive investigation of the causality of these impairments in the adult population is warranted.

6.3 Justification of the research

This study addresses a novel area of research that has received little attention, but given the fast growing ACHD patient population, requires further research and investigation. The present study is designed to comprehensively investigate cognitive functioning in ACHD patients. At present there are no studies that investigate and compare cognitive impairment in different forms of ACHD with different levels of structural complexity, across different domains of cognitive functioning.

In order to move away from the trend in the current literature to assess cognitive function using a composite measure such as IQ, this study included a wider range of measures assessing independent domains of cognition, with the aim of providing a more holistic overview of the extent of cognitive impairment in this patient group. Given that cognitive functioning is critical to an individual's ability to be able to function independently, work, solve problems and maintain social relationships on a day-to-day basis, it is an important area to assess, as it may have the potential to impact the long-term outcomes such as the patient's education, employment and QoL.

Within this study a range of different ACHD conditions that vary in their levels of structural complexity were assessed. Each of these conditions is investigated independently, acknowledging the variability in each of their symptomologies, prognosis and treatments; and the differential impact these factors may have on the patient's long-term outcomes such as cognitive functioning and QoL.

Furthermore, to enable a fuller examination of the potential factors that may have the ability to influence cognitive outcomes in this patient group, a wide range of clinical, psychosocial and demographic variables are included in the study when compared to existing literature.

It is hoped that the findings of this study would help in the development of specific supportive and rehabilitative interventions to help patients that may be impacted.

6.4 Research questions and objectives of the cross-sectional study

Research question 1

What is the extent of cognitive impairment in ACHD patients?

Specific objectives related to the research question 1 included:

- To investigate the extent of cognitive impairment in ACHD patients, in comparison to age matched normative data.
- To investigate the most commonly affected domains of cognitive functioning in ACHD patients.
- To investigate differences in cognitive functioning among different structural complexity groups.

Research question 2

What factors have the ability to influence and or impact cognitive functioning in ACHD patients?

Specific objectives related to the research question 2 included:

- To investigate the influence of demographic, clinical and psychosocial factors on cognitive functioning in ACHD patients as a group
- To investigate the influence of demographic, clinical and psychosocial factors on cognitive functioning in different structural complexity groups

Research question 3

Is cognitive functioning in ACHD patients associated with QoL?

Specific objectives related to the research question 3 included:

- To investigate if cognitive functioning is associated with physical and mental QoL in ACHD patients as group
- To investigate if cognitive functioning is associated with physical and mental QoL in different structural complexity groups.

7 CROSS-SECTIONAL STUDY METHODOLOGY

7.1 Prologue

This chapter presents the methodology adopted for the cross-sectional study, including the study design, measures and the statistical strategy adopted for data analysis of each research objective.

7.2 Design and setting of the cross sectional study

A cross-sectional study was conducted at the Heart Hospital, London (University College London Hospitals (UCLH) NHS Foundation Trust). The NRES Committee London – Bentham and the University College Hospital Ethical Committee granted ethical approval for this study (Study Ref. No - 08/HO715/105). Relevant approvals were also gained from the Research & Development (R&D) department at UCLH.

7.2.1 Participants and sampling procedures

7.2.1.1 Inclusion and exclusion criteria

Patients attending routine follow-up outpatient appointments (OPA) at the Grown-up Congenital Heart (GUCH) unit at the Heart Hospital, London were considered eligible for the present study. Specific inclusion/exclusion criteria were set for participation in the study.

Inclusion criteria:

- Aged 16 years and over
- No major visual and hearing impairments or other sensory or motor impairments that could prohibit them for undertaking the neuropsychological assessments.
- Fluent in spoken and written English language, sufficient to complete a self-report questionnaire and neuropsychological assessments

- Currently in a stable condition defined as not being critically ill, hospitalized or due to undergo any surgical procedures
- Not pregnant at the time of the study
- Diagnosed with one of the following conditions: ToF, TGA, SV, VSD, ASD, CoA, AS, PS (See Chapter 1 for details).

Exclusion criteria:

- Diagnosed with a Patent Foramen Ovale (PFO) in the absence of any other form of CHD; which is characterized by the presence of a hole between the left and right atria (upper chambers). PFO is known to be associated with cognitive dysfunction (Reisman & Fuller, 2009) and could potentially obscure other factors associated with cognitive functioning.
- Patients with an arterial switch operation (as this procedure was adopted in late 1980's, and majority of the study sample would not have had this procedure)
- Immediately prior to or post (6-months) a surgical intervention
- Diagnosed with chromosomal anomalies such as Trisomy21 (Downs syndrome) and 22q11 deletion (DiGeorge syndrome), as chromosomal anomalies can cause cognitive impairment which could obscure the impairment caused due to the CHD
- Diagnosed with learning difficulties
- History of stroke

7.2.1.2 Structural complexity groups

As discussed in Chapter 1 Congenital Heart Disease (CHD) is a composite term for a group of conditions, which range from simple to very complex; and this study set out to examine the different forms of CHD. The sample was divided into four groups based on the level of the structural complexity of the condition determined by the anatomical complexity of the heart defect. The different structural complexity groups varied in their symptomology, prognosis and

treatment. This classification was established following deliberation, evaluation and agreement by two expert consultant cardiologists who treat and manage ACHD patients at the Heart Hospital, London.

Participants were purposively sampled into the four groups (structural complexity groups): ***Tetralogy of Fallot*** ("TOF" group*)*: patients in this group were diagnosed with ToF. Patients with pulmonary valve replacement, pulmonary atresia, and major aortopulmonary collateral arteries (MAPCAS) were also included in this group. ToF patients usually experience cyanosis (or blue baby syndrome), with ToF being one of the most common cyanotic conditions (Breitbart and Fyler, 2006).

Transposition of the great arteries ("TGA" group): These patients are often born cyanotic. Patients in this group were diagnosed with TGA and had undergone a Mustard or Senning procedure (atrial switch) including those with implantable cardioverter defibrillators and pacemakers.

Single ventricle physiology ("SV" group): This group of patients were born cyanotic and included all patients with a single ventricle physiology and those with repairs including: Fontan operation and Total Cavopulmonary Connection (TCPC).

Simple lesions ("Simple" group): The "Simple" group comprises of patients in this group are acyanotic as they were born pink (without cyanosis). It included the following conditions- Atrial septal defect, Ventricular septal defect, Left Ventricular Outflow Track Obstruction-LVOTO (Valvular aortic stenosis and Coarctation of the aorta), and Right Ventricular Outflow Track Obstruction-RVOTO (Pulmonary valve stenosis). These conditions are collectively labelled as "Simple" to reflect their lower level of structural complexity in comparison to the other three groups (See Table 1.1 for details of the structural complexity group classification adopted in the present study).

7.2.1.3 Sample size calculation

In order to estimate a statistically adequate sample size for the cross-sectional study, G-Power software was used to establish the number of participants needed in each group (Faul et al, 2007). The sample size calculation was based on a four group cross sectional study to detect a significant group difference (using ANCOVA) in the level of cognitive functioning. A total of 280 participants (70 in each group) were required in order to attain 80% power to detect a difference at 0.05 significance level, and a small to medium effect size of 0.25 (α =0.05, β =0.80, ES= 0.25).

7.2.2 Participant recruitment procedures

All participants were recruited from a single site (Grown-Up Congenital Heart disease (GUCH) unit) at the Heart Hospital, London. All patients who had routine follow-up appointments at the GUCH unit of The Heart Hospital between March 2009 and June 2011 were potentially eligible for the cross-sectional study. At the time of the present study a new electronic record system was being established at the Heart Hospital, however these electronic records were not complete and did not include all the patients seen at the hospital. As a result of this, two different methods of patient recruitment were adopted; these included i) the use of paper records and ii) the use of clinic lists.

Paper records

Hospital paper records were used to identify potential participants for the cross-sectional study. These paper records listed all patients actively being seen at the Heart Hospital, GUCH unit; all potential participants were identified in alphabetic order (Surname, name). Once identified a clinical GUCH nurse specialists reviewed the latest clinical notes for each potential participant to assess their eligibility using the study inclusion and exclusion criteria. Details of patients that met the inclusion criteria were entered into an electronic database and those that did not meet

the inclusion criteria were excluded at this stage and their details were recorded. Each participant was given a unique identification number in the database.

All eligible participants were categorized into the four structural complexity groups (ToF, TGA, SV and Simple). In instances where the participants had two diagnoses, they were allocated into a group based on their more structurally complex diagnosis, so as to avoid including patients with complex conditions into the "simple" group. For instance, if a patient was diagnosed with both SV and VSD, they were allocated into the SV group. Clinical details of the four structural complexity groups are discussed in Chapter 1.

Both randomized and purposive sampling were undertaken to recruit participants in the present study. Eligible participants meeting the criteria for the Simple and ToF groups, in the database prepared above, were selected randomly (using a random number generator) and invited to participate in the study. Random selection continued until a sufficient sample size was attained within these two groups. Purposive sampling was used to recruit patients for the TGA and SV groups as they had a limited number of patients meeting the eligibility criteria. To meet the sample size requirement all eligible participants in these two groups were purposively invited to participate in the study.

Clinic lists

Along with paper records, the outpatient clinic lists were reviewed monthly through the course of the study, in order to identify any more potential patients from the TGA and SV groups. These clinic lists were mainly reviewed to identify any potential participants that may not have been identified in the paper records. These participants were usually those that were only recently referred to the UCLH GUCH clinic from other clinics around the UK; hence, no paper records of them were available at the time. These identified patient were then added into the recruitment database and recruitment continued until the required sample size was obtained.

All potential participants were invited by post and were sent an invitation letter by their cardiologist along with an information sheet, and an interest form with a freepost return envelope, to indicate interest in participation (See Appendix-G for information sheet). The information sheet explained to the participant the purpose of the study and the procedures involved in it. It also informed the participant about data confidentiality and their right to participate and/or withdraw at any time. Patients were given two weeks to consider participation before a reminder letter was sent along with all the same documents. Lastly, a reminder telephone call was made to all participants a week before their prescheduled OPA as all assessments were conducted on the same day as the participants OPA in order to avoid additional travelling and expenses for the participants.

The participation rates and study sample:

Although the lack of comprehensive electronic patient record prevented an accurate estimation of the number of patients attending regular follow up appointments at the heart hospital, review by the clinic staff led to an estimation of approximately 5000 patients. Of these a total of 1199 patients were identified for assessment of eligibility based on the inclusion and exclusion criteria discussed above. Seven hundred and eight patients meeting the study inclusion criteria were invited to take part in the study (See Figure 7.1 below for details). Two hundred and seventy three declined the invitation and 81 did not respond. Of the 354 consenting participants 40 withdrew (without providing a reason) before their study appointment and 4 did not complete the neuropsychological assessment.

In total, data from 310 participants were included in the analyses (Please see Figure 7.1 below for recruitment details).

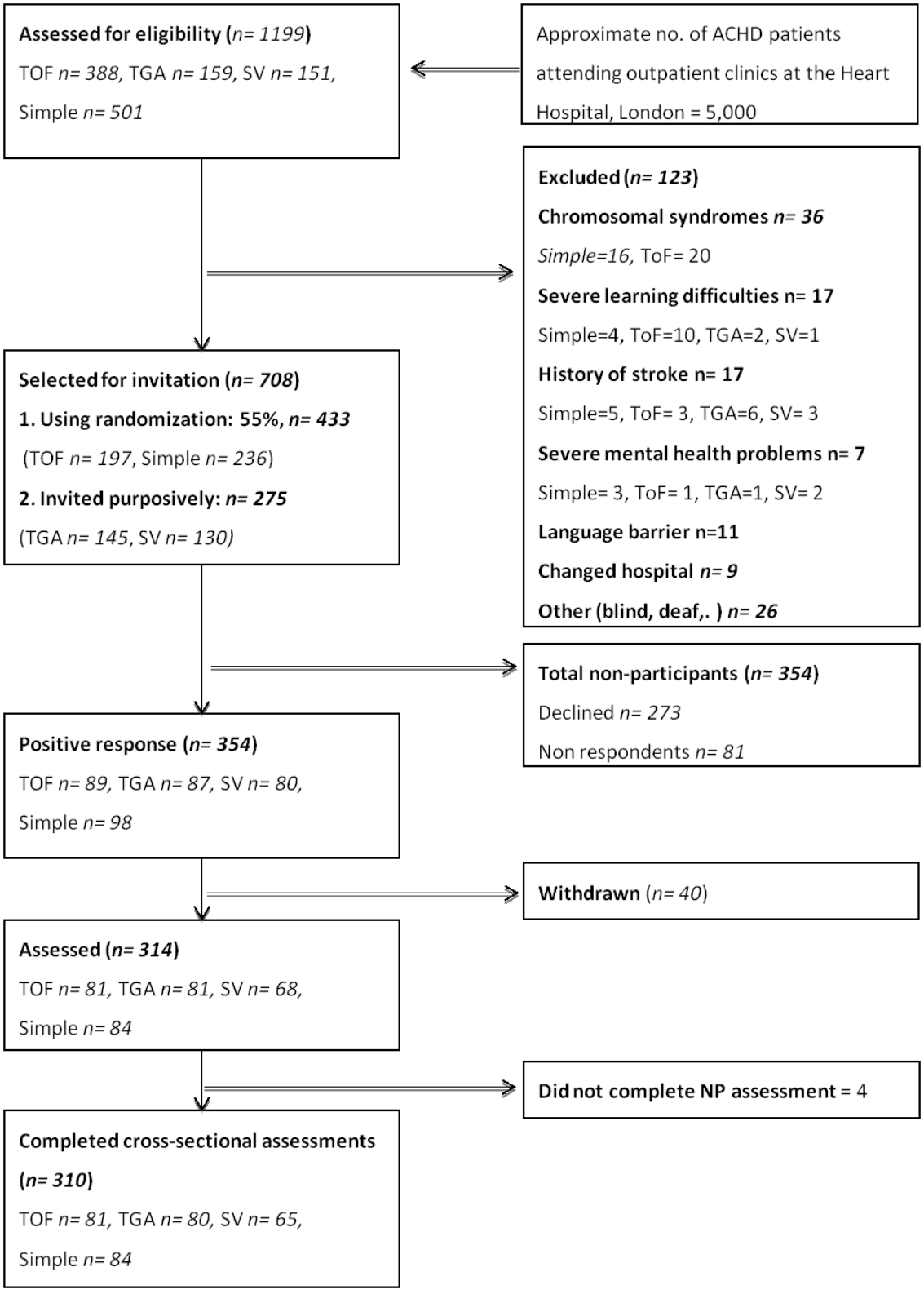


Figure 7.1: Flow chart of the cross-sectional study recruitment procedure

7.3 Measures included in the cross-sectional study

A wide range of measures were utilized in the cross-sectional study to assess cognitive and psychosocial outcomes. Detailed demographic and clinical information was also gathered for each participant. Details of the information collected and the measures utilized are presented in the following sections.

Neuropsychological (NP) Measures

All participants underwent a detailed NP assessment. A brief summary of each of the NP tests used is presented below (See Table 7.1 on page 131). The order in which the NP tests were conducted was; Trail Making Test (Part A and B), WAIS-III digit symbol coding, Controlled Oral Word Association Test, Stroop test, WAIS-III Arithmetic subtest, Grooved pegboard test, WAIS-III knowledge subtest, Wisconsin Card Sorting Test, Rey Auditory Verbal Learning Test and the Symbol Digit Modalities test (written and oral subtest) (See Appendix H for NP test battery). The order of the test was chosen such as to alternate and distribute the more difficult (cognitively challenging) tasks with the less difficult tasks across the test battery. This alternating order of the NP tests allowed switching between the different domains assessed to avoid any influence of practice on a particular cognitive function. Lastly, the ordering of the tests also helped prevent participants from being exposed to prolonged periods of complex demanding tasks, thus reducing patient burden. The psychometric properties of the measures will be stated where appropriate and reliable data is available; an omission indicates a lack of available data. Short forms of tests (WAIS-III- IQ, WCST-64- executive functioning) were used where available and appropriate for their brevity, with the aim of reducing participant burden.

Given the large number of tests utilized and the overlap in the cognitive domains assessed (as discussed in Chapter two), tests were classified into overarching domains adapted from Strauss, Sherman and Spreen, (2006). These overarching domains included tests that largely assess some aspect of a similar cognitive function. For instance, executive functioning is a broad term encompassing a number of cognitive abilities, including problem solving and response

inhibition, therefore tests assessing these abilities were grouped under 'measures of executive function'. The overarching domains (and tests) used in this study are described below.

7.3.1 Measure of IQ

7.3.1.1 Sub-scales from the Wechsler Adult Intelligence Scale-III (WAIS – III)

Description

The WAIS-III is a modified version of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) and is used to measure general intellectual function in adolescents and adults (16-68 years). The WAIS is considered the 'gold standard' in the measurement of IQ (Ivnik et al, 1992). The WAIS III comprises of 12 subtests and provides summary scores for full scale IQ, verbal IQ and performance IQ, along with four secondary indices including verbal comprehension, working memory, perceptual organization and processing speed. The completion of all 12 subtests requires approximately 50-60 minutes (Axelrod, 2001).

To reduce patient burden, this study utilized a selected number of the subtests (N=3) of the WAIS-III to estimate the full scale IQ. Methods to calculate an estimated full-scale IQ from a limited number of sub-tests have been established in the literature (Jeyakumar et al, 2004, Schoenberg et al, 2003). The three subtests included in the present study were information, mental arithmetic and digit symbol. This method of reducing the number of subscales rather than items per subscale was considered to be a more reliable technique to reduce test burden without compromising the overall assessment (Jeyakumar et al, 2004).

The information subtest involves the examiner asking the participant questions to test their general knowledge (E.g. – Could you name all the continents for me please? Who was Mahatma Gandhi?). The arithmetic subtest assesses the participant's ability to do mental arithmetic. Lastly the digit symbol subtest requires the participant to copy a number of symbols into blank squares with corresponding numbers on a sheet of paper, using a key provided with numbers

and matching symbols. The examiner records the responses and the time taken to complete the test on a response booklet.

Scoring

Estimated Full-scale IQ (estimated FSIQ) scores were derived from three subtests of the WAIS-III using a specific formula and reference table provided by Jeyakumar and Colleagues, (2004). A score 1Standard Deviation (SD) below the mean (100) was considered a marker of impairment, as opposed to the 1.5 SD markers for all other NP tests (see Section 7.7.1 for details). This was done as the WAIS tests utilize "deviation IQ" as the standard scoring classification with the normative sample mean raw score defined as 100 and one standard deviation (defined as 15 points above or below the mean) used as a marker to indicate impairment. A marker of 1 SD below the mean also enables comparison to the published literature, which usually assesses IQ using 1SD below the mean to indicate impairment.

Psychometric properties

The median subtest reliability of the entire WAIS-III test has been established as (r=0.86). The composite reliabilities of the indexes have been reported as (0.94-0.95) and the verbal and performance IQ's (0.94-0.97) thus demonstrating a good reliability of the measure (Ryan, Sattler and Lopez, 2000).

The test-retest reliability (stability of the measure to assess the same concept upon re-administration) of the subtests included in this study has been shown to be very high for the information subtest (>.90) and high for the arithmetic and digit symbol subtest (.80-.90) (Strauss, Sherman, and Spreen, 2006). The internal consistency is reported as being very high for the information subtest (>.90), and high for the arithmetic subtest (.80-.90). The authors do not provide the internal consistency measure of the digit symbol test as it is a timed test (Strauss, Sherman, and Spreen, 2006).

7.3.2 Measure of executive functioning

7.3.2.1 Wisconsin Card Sorting Test- 64 (WCST-64)

Description

The WCST-64 (Kongs et al, 2000) is a short form of the original WCST test (128 cards) (Heaton et al, 1993). The WCST is designed to assess abstract reasoning ability and the ability to shift cognitive sets (the ability to switch between two distinct concepts, and to think and process different concepts simultaneously) (Luria, 1976). It requires concentration, attention, organization and cognitive flexibility (Welsh, Groisser and Pennington, 1988). The WCST is particularly sensitive to frontal lobe impairment (Demakis, 2003).

The test involves four stimulus cards and a set of 64 response cards. Each of the cards depicts figures of varying shapes (triangles, stars, crosses, and circles), colours (red, green, yellow and blue) and numbers (one, two, three and four). The four stimulus cards are first placed in front of the participant (one red triangle, two green stars, three yellow crosses and four blue circles - See Figure 7.2 below).

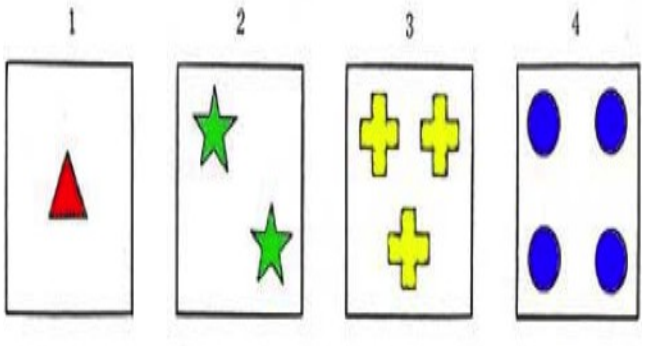


Figure 7.2**:** Wisconsin Card Sorting Test -64
(Source: Jonides and Nee, 2005)

The participant is then handed a deck of 64 cards, and instructed to match each consecutive card to one of the stimulus cards. The participant is not told how to match the cards but is told each time whether they were right or wrong. There are three sorting principles (by colour, shape and

number). After a set of 10 correct responses the examiner changes the sorting principle until all the cards are used. The researcher does not inform the participant of the change in principles. This process is continued until all cards have been utilized.

Scoring

Multiple scores can be generated from the WCST including: the respondent's ability/failure to maintain a set (the number of times one makes five or more correct responses in a row and then makes an error before successful completion of a category), number of trials required to complete the first category (i.e. total number of trials needed before attaining 10 consecutive correct responses), and total correct/error responses (total number of correct/incorrect responses made) (Kongs et al, 2000). A higher score on the failure to maintain score represents poorer performance, while on the categories completed and correct responses a higher score represents better performance.

Five scores were calculated in the present study to reflect different aspects of executive function. 1) Total number of errors 2) conceptual level responses (consecutive correct responses occurring in runs of three), which reflects some insight into the correct sorting principle, 3) trials to complete first category, and 4) failure to maintain set which indicated the inability to continue using a successful strategy 5) total number of categories (total number of correctly completed categories upon completion of the test).

Psychometric properties

The generalizability coefficients for the WCST-64 (single administration) have been reported as ranging from 0.60-0.85 averaging at 0.74, thus demonstrating good scale reliability (Kongs et al, 2000).

7.3.2.2 Stroop Neuropsychological Screening Test (SNST)

Description

The Stroop test has many versions; the one used in this study was the Stroop Neuropsychological Screening Testing (SNST) (Trenerry et al, 1989). The SNST is a two-part test, which assesses selective attention and executive functioning (cognitive flexibility and response inhibition) in 18-79 year olds. The test comprises a sheet of paper with a list of words (colour names) (N=112) randomly printed in 4 distinct colours; red, green, blue and tan (brown). At the beginning of the test a colour test is conducted to check for colour blindness, if a participant is found to be colour blind the test is discontinued. This is followed by the first half of the task; 'Stroop colour' which involves the participant reading aloud the list of words in a given time frame (2 minutes). The next half of the task 'Stroop colour word' involves the participant reading the colour of the ink in which the words are printed in the same time span (2 minutes).

Scoring

Two scores are recorded for each task: the number of words/colour names correctly recited, and the time to complete the task. A higher score on the words correctly recited represents better performance but a higher score represents poorer performance on the time to completion. The score for the total number of colour names correctly recited was utilized in this study.

Psychometric properties

The test reportedly differentiates >79% of brain-damaged adults from normal adults (Trenerry et al, 1989). The measure has been shown to demonstrate good test-retest reliability i.e. 0.90 (Trenerry et al, 1989)

7.3.2.3 Controlled Oral Word Association Test (COWA)

Description

The COWA is a test of executive functioning, verbal association and fluency (Benton et al, 1994). It evaluates the spontaneous production of words under restricted conditions. The participant is asked to produce as many words as they can, beginning with each of the letters 'F', 'A' and 'S' individually. They are instructed to exclude proper nouns, numbers and the same words ending with a different suffix (e.g. long, longer and longest). Participants are allocated one minute for each letter (F, A, S). The researcher records a list of all the words named by the participant.

Scoring

The total score is the sum of all admissible words for all three letters. A higher score indicates better performance.

Psychometric properties

The COWA-FAS has been shown to have moderate to high internal reliability (r=0.83) and high test-retest reliability(r=0.74) after 5 years (Tombaugh, Kozak and Rees, 1999).

7.3.3 Measures of Attention

7.3.3.1 Symbol Digit Modalities Test (SDMT)

Description

The SDMT (Smith, 2002) assesses divided attention, complex visual scanning, hand-eye coordination, and reading-writing ability. It is known to be sensitive for detecting acquired, acute or chronic cerebral dysfunction but is not specific for localization of the dysfunction (Smith, 2002).

It is a paper and pencil test that comprises rows of 110 blank squares each with an assigned symbol. Above the rows there is a printed key with numbers from 1-9, each paired with a

randomly assigned abstract symbol. The task requires the respondent to match each symbol (110) with a corresponding number with the help of the key and write these down as rapidly as they can, consecutively in the order presented (it involves the opposite procedure to the WAIS-III as discussed in Section 7.3.1.1 which requires copying symbols). Participants are asked to perform a practice trial on the first 10 symbols (See Figure 7.3 below). Following the practice session participants are given 90 seconds to complete the test.

The SDMT test has two parts: written (SDMT-W) and oral (SDMT-O). This allows drawing comparisons between visual-motor and oral responses. The written assessment was presented first followed by the oral assessment in accordance with the test instructions (Lezak, 1995; Strauss, Sherman and Spreen, 2006).

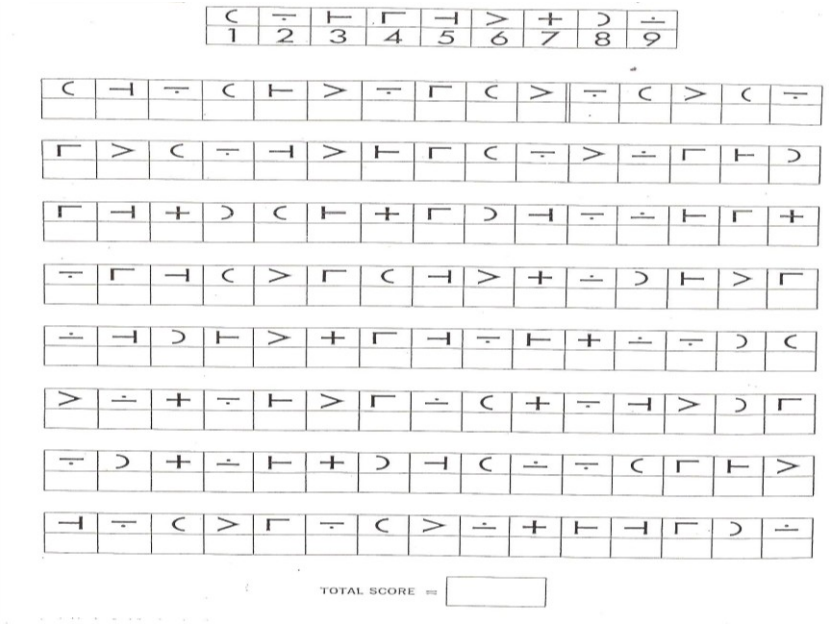


Figure 7.3 Symbol Digit Modalities Test
(Source: Original scanned form)

Scoring

The score is the total number of correct responses within the specified time frame. A separate score is calculated for each part of the test (written and oral). A higher score on each part of the test is indicative of better performance.

Psychometric properties

The test-retest reliability of the SDMT has been shown to be high (0.91) (Hinton-Bayre et al, 1999).

7.3.3.2 Trail Making Test: Forms A and B (TMT)

Description

The TMT (Reitan & Wolfson, 1995) is a two-part paper and pencil measure of divided attention, visual scanning, motor speed and mental flexibility. It is considered a good measure of generalized brain functioning (Reitan and Wolfson, 1995). Part A (TMT-A) requires participants to connect 25 randomly arranged numbers (in circles) in ascending order without lifting the pencil from the paper (no restrictions on lines crossing). Part B (TMT-B) requires the participant to connect randomly arranged letters and numbers in an alternate sequence (1-A, 2-B, 3-C . . . 13) as quickly as possible (See Figure 7.4 below). Respondents are given a (short) practice trial prior to both parts to ensure familiarity with the test and comprehension of the test instructions. Both parts of the test are timed to completion. The TMT-B subtest is terminated if the respondent takes over 5 minutes to complete.

Scoring

The score is the total amount of time taken to complete the test, with lower scores indicating better cognitive functioning. Higher scores (time taken) on either part (A and B) have been used as an indicator of diffused brain damage. A high score on part A indicates difficulty in cognitive perceptual tracking and attention. Part B is more complex than Part A and may indicate difficulties in divided attention, executive functioning and cognitive flexibility along with conceptual motor tracking (Bremer et al, 1997). Both scores (TMT-A and TMT-B) are reported in this study.

Psychometric properties

The test-retest reliability of the TMT varies with age-range and population, but is generally considered adequate, at least for the Part B (Strauss, Spreen and Sherman, 2006). The test-retest reliability coefficients over 11 months have been reported as 0.79 for Part 'A' and 0.89 for Part 'B' (Dikmen et al, 1999). The inter-rater reliability has been reported as 0.94 for part A and 0.90 for part B (Fals Stewart, 1992).

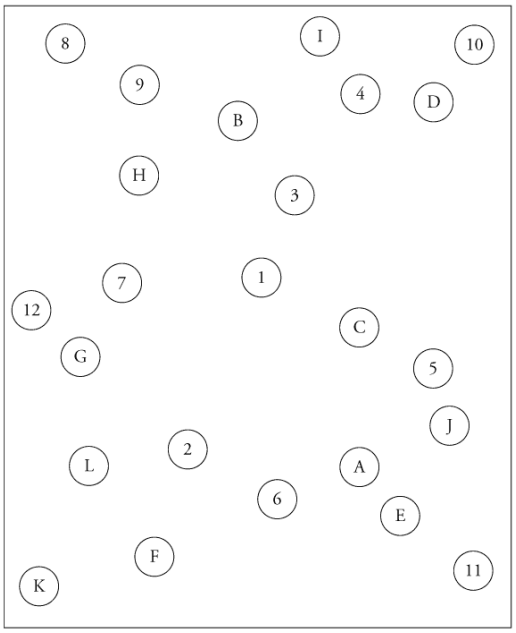


Figure 7.4: Trail making (Part B)
(Source: Original scanned form)

7.3.4 Measures of motor functioning and dexterity

7.3.4.1 Grooved Pegboard (GP)

Description

The Grooved Pegboard task (Matthews & Klove, 1964) measures motor function, dexterity and motor speed requiring manual precision and hand-eye coordination. It is known to be sensitive to both focal and diffused cerebral damage and can aid the detection of any lateralized disability or motor dysfunction even in the presence of a normal range of movement and motor functioning.

The test consists of a metal board with a grid matrix of 25 randomly positioned slots and 25 metal pegs that are ridged to one side. Participants are required to match the groove/ridge on the pegs with that of the slots and insert them as fast as possible consecutively across and down the grid (right to left for the left hand and vice versa) (See Figure 7.5 below). The participant continues until all pegs have been placed. The examiner records the time taken to correctly insert all the pegs and the number of pegs dropped in the process. A maximum of 5 minutes are allowed for test completion, after which the test is terminated.

Figure 7.5: Grooved Pegboard and the pegs
(Source: www.lafayetteeevaluation.com)

Scoring

The most commonly recorded score for the GP is the total time required to complete the task using either hand. Two other scores can be calculated: number of pegs dropped and number of pegs inserted correctly. These two scores are considered critical for clinical use as these errors are rarely seen in neurologically intact individuals, but less useful for population research purposes (Heaton et al, 2004; Strauss, Sherman and Spreen, 2006). Time taken to completion was the only score utilized in the present study. A higher score on each hand indicates poorer performance.

Psychometric properties

The test re-test reliability of the GP has been shown to be marginal/high (0.67 to 0.86) in normal populations aged 15 years and over (Strauss, Sherman, and Spreen, 2006).

7.3.5 Measures of memory

7.3.5.1 Rey Auditory Verbal Learning Test (RAVLT)

Description

The RAVLT is an auditory verbal memory and learning task that assesses immediate memory, working memory, and interference (Schmidt, 1996). It is a verbal test that consists of a list of 15 words (nouns) (List- A), which are read aloud one second apart. Participants are asked to repeat as many words as they can remember in any order after each presentation. This is done a maximum of 5 consecutive times (fewer if participant recalls all 15 words). The instructions are repeated each time to ensure clarity. Following this, a new 15-word list (List –B) is presented and the participant is asked to recall as many words as possible from the new list. Finally, the participant is asked to again recall as many words as he/she can from List-A without being given any prompts.

Scoring

The score for each trial is the total number of words correctly recalled. Several different scores can be derived from the RAVLT including learning, forgetting, proactive and retroactive interference, and learning curve (Strauss, Sherman and Spreen, 2006). The total number of words recalled from trial 1 – trial 5 were summed to produce a total acquisition score which was the one score used in this study. This score was chosen as it represents the level of verbal learning and working memory. Furthermore, appropriate normative data applicable to this study sample was only available for this score.

Table 7.1 Details of the neuropsychological test battery used for assessment

Tests utilized	Cognitive function assessed	Definition of cognitive function assessed	Scoring	Number of scores generated
IQ				
Wechsler Adult Intelligence Scale – III	Intelligence Quotient	Measure of general intellectual function	Estimated total intellectual quotient score	1
Executive functioning				
Controlled Oral Word Association test (COWAT-FAS)	Verbal fluency	Speed and ease of verbal production	Total number of words produced per letter	1
Wisconsin Card Sorting Test -64 (WCST-64)	Executive function: problem-solving	Ability to respond appropriately in novel situations; ability to plan and use initiative	Number of errors made, conceptual level responses, failure to maintain set, and trials to complete first category, total number of categories completed	5
Stroop Neuropsychological Screening test (SNST)	Executive function: response inhibition	Ability to respond appropriately in novel situations. To perform an action when faced with a competing and more familiar action	Correct number of words recited in 2 minutes	2
Attention				
Symbol Digit Modalities Test (SDMT)	Complex visual scanning	The ability to visually locate a target within a range of complex figures	Total number of symbols & numbers correctly written and recited	2
Trail making test (TMT) A and B	Divided attention	The ability to respond to multiple tasks simultaneously and cognitive processing Speed	Time taken to completion in seconds	2

Tests utilized	Cognitive function assessed	Definition of cognitive function assessed	Scoring	Number of scores generated
		Motor functioning		
Grooved Pegboard (GP)	Manual and motor dexterity and functioning	Speed and accuracy of manipulation of fine objects with the hands	Total time taken to complete task in seconds.	2
		Memory		
Rey Auditory Verbal Learning Test (RAVLT)	Verbal learning and memory, delayed and immediate recall	Ability to learn new information and to store and retrieve information	Total number of words correctly recalled. Total acquisition = Sum of Trial 1-Trial 5	1

Psychometric properties

The internal reliability of the total score for the RAVLT has been shown to be high (0.90) (Van Den Burg & Kingma, 1999).

Table 7.1 **(**above**)** summarizes the NP tests used and the cognitive domains assessed by each. It also details the scoring procedures and the total number of scores generated by each of the tests utilized; for NP test battery see Appendix-H.

Psychosocial Measures (mood and quality of life)

Psychosocial self-report questionnaires assessing mood and quality of life were included in the present study. These measures were included to assess their relationship with cognitive functioning. Some of these measures, such as depression and anxiety are known to have the potential to influence cognitive functioning and hence were selected to assess their relationship to cognition and use as covariates (Lezak et al, 2012). See Appendix-I for psychosocial questionnaires used in the study.

7.3.6 Measures of Mood

7.3.6.1 The Positive and Negative Affect Scale (PANAS)

Description

PANAS is a 20-item self-report measure of positive (PA) and negative affect (NA) (Watson, Clark and Tellegen, 1988). It includes 20 adjectives describing emotions of which 10 items describe negative affect (e.g. upset, guilty, scared) and 10 items describe positive affect (e.g. proud, alert, inspired). The respondent is asked to indicate the extent to which they have experienced these emotions on a 5-point scale, ranging from 'very slightly or not at all' to 'extremely'. The scale can be used to refer to 6 time-points from ('right now' to 'the past year') or generally depending on the aims of the study. In the current study the time frame adopted was 'generally', as the objective of the study was to understand the general effect of the patient's health on their mood as opposed to over a specific time frame. The scale takes approximately 5 minutes to complete.

Scoring

The scores are calculated by summing the item scores (1 to 5) for each scale (NA and PA) respectively to achieve an overall NA and PA score. The total score can range from 10-50. A higher score represents a higher level of positive / negative affect.

Psychometric properties

Both subscales of the PANAS have shown satisfactory internal consistency: PA (Cronbach's alpha=0.89) and NA (Cronbach's alpha=0.85). The test-retest reliability is reported as 0.68 (PA) and 0.71(NA) respectively (Watson, Clark and Tellegen, 1988). The correlation of the short form and the original version is reported as $r=0.92$ ($p < .01$) for PA and $r=0.95$ ($p < .01$) for NA (Thompson, 2007).

7.3.6.2 Spielberger State Anxiety Inventory-6 (STAI-6)

Description

The short version of the STAI (6 items) was used in the study to assess the level of state anxiety (Marteau and Bekker, 1992). The STAI was designed to measure anxiety as 'state like' referring to a situation related anxiety, and 'trait like' referring to the anxiety being more persistent and a personality trait. It is used in this study as a measure to assess state anxiety and the stress associated with a medical condition. The STAI-6 involves 6 items: three items are Anxiety-Present e.g. "I feel tense" and three Anxiety- absent e.g. "I feel calm". The response scale is a 4-point Likert scale range from "not at all" to "very much".

Scoring

The three anxiety-absent items (positively framed) require reverse scoring. The summed score of the scale is obtained from the 6 items, which ranges from 6-24. A higher score on the measure represents greater state anxiety levels.

Psychometric properties

The short version of the scale demonstrates satisfactory levels of internal consistency and is highly correlated with the original measure with all internal consistency reliabilities reported to be greater than 0.90 (Tluczek, Henriques & Brown, 2009). The reliability coefficient of the measure has been reported as adequate at 0.82 (Marteau and Bekker, 1992).

7.3.6.3 Centre for Epidemiological studies Short Depression Scale (CESD-10)

Description

The CESD-10 was used as a measure of depressive symptomology; it is a short version of the CESD-20 developed by Andresen et al, (1994). Respondents rate the level of depressive symptoms they experienced over the last week on a 4 point scale ranging from "0= rarely/none of the time" to "3= All of the time". Some of the items are framed negatively and some

positively for instance “I felt that everything I did was an effort” (negative) and “I feel hopeful about the future” (positive).

Scoring

The two positively framed items (5&8) of the questionnaire are reversed scored (3-0). Items 1-4, 6-7, 9, 10 are scored from 0-3. The summed scale score ranges from 0-30. A higher score represents higher depressive symptomology (<10=without depressive symptomology, 10-14 =mild depression, and >14= severe depressive symptomology) (Swenson et al, 2008). The cut-off score for clinical level of depression for the CESD-10 version has been established as ≥ 10 (Andresen et al, 1994).

Psychometric properties

The test-retest correlations of the CESD-10 ranged from r=0.21 to 0.84, with an overall score correlation being r=0.71 (Andresen et al, 1994). The correlation between the original version and the short-form was reported to be high (r=0.97, p=0.001) (Zhang et al, 2012).

7.3.7 Health Related Quality of Life measure (HRQoL):

7.3.7.1 The Medical Outcome Survey 36-item Short-Form Health Survey Version 1® (SF-36 v1®)

Description

The SF-36v1® is an extensively used generic multidimensional measure of Health Related Quality of Life (HRQoL) (Ware et al, 2000). It comprises 36 items that measure health status with eight subscales that represent both physical and mental health status. The subscales include: physical functioning, social functioning, role-physical (role limitation due to physical health problems), role-emotional (role limitation due to emotional problems), mental health, vitality, bodily pain, and general health perceptions. Participants rate their health status in the last month using a Likert-scale.

Scoring

The SF-36v1® and associated data scoring software is licensed by the Quality Metric Company. For the purpose of scoring the questionnaire, norm based scoring was undertaken using the official Quality Metric Health Outcomes™ Scoring software 4.0 in this study (Saris-Baglama et al, 2010). The software uses the 1998 general U.S. population norms. Norm based scoring was undertaken as it allows drawing comparisons with the general population norms and facilitates interpretability. Each scale is scored to have a standardized mean and standard deviation, relative to the general population scores/norms. The eight sub-scales are combined into two component scores: physical component and mental component summary score (PCS, MCS). Norm based scores are more advantageous as they simplify interpretation and allow direct comparison between the different scores including the two summary scores; PCS and MCS. The eight subscales were linearly transformed into T-scores with a mean of 50 and a standard deviation of 10. A score ranging from 0-100 was obtained for each subscale.

Psychometric properties

The reliability and validity of the SF-36v1® has been well established in the literature. A review of relevant literature reported the median reliability coefficient for each of the 8 subscales as 0.80 and above (Ware et al, 2000). The SF-36 v1® questionnaire will be refered to as the SF-36 from this point onwards.

7.4 Clinical and demographic characteristics

7.4.1 Medical history

A consultant cardiologist and a clinical nurse specialist at the Heart Hospital collected clinical data from patient medical records (both paper and electronic records). A comprehensive and detailed account of the patient's clinical information was collected using a standard medical form.

Cardiac treatments were recorded for each patient including details of previous medical interventions (number, time since last intervention, age at repair) and the types of interventions (palliative, repair, and catheter laboratory). Peri-operative details of surgical interventions were recorded (duration of Cardiopulmonary bypass-CPB, duration of Deep Hypothermic Circulatory Arrest-DHCA, number of days spent in the Intensive Care Unit (ICU) along with post-operative complications where relevant (central nervous system related complications, infections and ventricular dysfunction).

Table 7.2: A summary of the clinical variables measured in the study

Type of clinical variable	**Clinical factors measured**	**Measurement details of the variables assessed**
Structural complexity group	Native diagnosis	Groups: 1) Tetralogy of Fallot 2) Transposition of the great arteries 3) Single ventricle physiology 4) Simple lesions
Treatment (interventions history/profile)	Interventions total (total number incl. repairs, palliations, cath labs)	Count of the total number
	Reparative procedures	Count of the total number
	Palliative procedures	Count of the total number
	Catheterisation (cath) lab (non-invasive) procedures	Count of the total number
	Palliation before repair	Yes/No
	Age at the time of repair (i.e. 1st surgery of reparative nature)	Age in months
	Years since last intervention (since the most recent)	Count of years past since
Operations (peri-operative)	Cardiopulmonary bypass (includes the use of extracorporeal circulation (ECC), which is used to take over the function of the heart and the lungs temporarily during surgery)	Total count in minutes totalled for all interventions
	Hypothermic arrest (refers to cooling the body and stopping blood circulation for the purpose of surgery)	Total count in minutes totalled for all interventions
	Intensive care unit (ICU) days (after operations)	Count of days spent in ICU after surgical procedures
Operations (post-operative)	Central nervous system complications	Yes/No
	Infection	Yes/No
	Ventricular dysfunction	Yes/No
Treatment (medication+)	Medication total	Total count of medications taken
	Pacemaker	Yes/No
	ACE inhibitors	Yes/No
	Diuretics	Yes/No
	Beta blockers	Yes/No
	Anti-arrhythmia	Yes/No
	Anti-coagulant	Yes/No

Table 7.2 – A summary of the clinical variables measured in the study (Continued.)

Type of clinical variable	**Clinical factors measured**	**Measurement details of the variables assessed**
Cyanosis	Cyanosis days (up 'till data collection date)	Total number of days cyanosed up until the day of study data collection
	Current saturation	Percentage (%)
Hospitalization history	Hospitalization days	Total count of days spent in hospital
Co-morbidities	Co-morbidities total	Count of the total number
	Heart failure	Yes/No
	Arrhythmias	Yes/No
	Hypertension	Yes/No
Functional status	New York Health Assessment (NYHA)	Groups Class I, II, III, IV
	Left Ventricular Ejection Fraction (LVEF)	Percentage %
	Right Ventricular Ejection Fraction (RVEF)	

Details of the patient's current medications (Beta-blockers, ACE medication, Diuretic, anti-arrhythmia medications) and co-morbidities (arrhythmias, heart failure, and hypertension) were also recorded. Information regarding cyanosis was gathered including number of days (across life span) patients were cyanosed, and their latest blood oxygen saturation levels. Functional status was measured using the New York Health Assessment (NYHA) classification as part of the patient's routine examination (New York Heart Association, 1964). Further details of clinical variables (e.g. unit of measurement) collected as part of this study can be found in Table 7.2 (above).

7.4.2 Demographic details

Demographic information was collected from each participant using a standard self-report form. Information gathered included: age, gender, marital status, living status, education, ethnicity and employment status. Study procedures

7.5 Study procedures

7.5.1 Data Collection

Patients were seen on the day of their regular outpatient appointment (OPA). Written consent was obtained from all participants prior to assessments. Each participant was explained the purpose of the study and taken through the information sheet prior to signing an informed consent form. The informed consent form stated that the participant had enough time to consider participation in the study and was willing to participate. A copy of the consent form was given to each participant for his or her records (see Appendix-J). Each participant was given a £5 voucher to use for meals and refreshments.

Following consent the assessments were conducted prior to the participants OPA where possible in order to avoid fatigue having an impact on the participant's performance. Demographic information was collected at the start of the session followed by administration of the NP test battery. Finally, participants completed the self-report psychosocial questionnaires (mood and quality of life). This sequence of assessment was standard across all participants, and was

chosen in order to minimize any impact of fatigue on cognitive performance. Participants were given an optional break of 5 minutes between the NP assessment and completion of the psychosocial questionnaires. They were also advised to inform the examiner if they felt fatigued and needed a break between any of the assessments.

All NP assessments were conducted in a standardized manner keeping the testing conditions similar for all participants. The assessments were conducted in a quiet and private room at the Heart Hospital London. Prior to commencing the assessment the examiner spent time talking to each participant asking them questions about themselves and their day, letting them know how long the study may take and what it would involve, with the aim of building a rapport with each participant and to put them at ease. Each participant was offered water, reminded to wear their glasses (if any) and made to feel comfortable before the assessment commenced. The NP assessment was discontinued temporarily (5-10 minutes) if the participant felt fatigued and required a break; the aim was to elicit optimum performance from participants. The NP assessment took approximately 45-60 minutes and administering the psychosocial questionnaires took approximately 60 minutes depending on the participant's speed.

7.6 Preliminary Analysis

All the data collected was entered into SPSS and all analysis within this study was conducted using IBM SPSS (Statistical Package for the Social Sciences) version 21.

7.6.1 Missing Values Analysis

After checking the data for inconsistencies such as manual errors in data entry, incorrect missing values and scores outside of the normal range on any measure, a missing values analysis was conducted; both at item and scale level (Field, 2009). The types of missing data that emerged included:

- NP raw scores missing
- Individual items missing within sub-scales of questionnaires (psychosocial measures)
- Entire sub-scales missing within a single administration of the questionnaires

- No questionnaires completed

The overall amount of missing data was under 5% in the cross-sectional study (See Appendix-K for proportion of missing data on each variable). Although the level of missing data was not large a decision was made to carry out an imputation to obtain a complete data set, minimize loss of sample size and avoid different sample sizes across analyses.

In the psychosocial measures where participants left blank items within a scale or an entire scale and reported the items as not applicable, these scores were labelled as 888 in the database. Similarly in the neuropsychological tests some scores were not applicable to all participants, one example of this is the WCST-64 - Failure to maintain set score, which can only be calculated if the participant has completed at least 2 categories and attempted a third. Therefore for those that did not complete adequate categories the score was considered not applicable and labelled as 888. These scores were considered not applicable as opposed to missing and were not subject to imputation.

In the case of missing data at the item level, mean substitution (within a participant) was carried out in order to reduce the amount of missing data, followed by the calculation of scale level scores. Scale scores were calculated from the items within each case with the average score substituting the missing value. In cases with more than 50% of items missing the scale score was considered missing and treated at scale level. In the case of the SF-36 missing data was dealt with using the built-in algorithms provided (maximum data recovery) in the scoring software (QualityMetric health outcomes scoring software 4.0) (Saris-Baglama et al, 2010).

Multiple imputation procedures were conducted for data missing at scale level. During the imputation process, one imputation was performed. Imputation models were conducted on the basis of predictive mean matching (PMM). PMM is a variant of linear regression that ensures that the imputed values are plausible and match an observed value (specifically, the observed value that is closest to the value drawn by the imputation model). The imputation process, for logistical reasons (i.e. processing power and time) was conducted in batches of

variables (clinical, demographic, psychosocial questionnaires, and NP assessment). However, the predictive model for all imputations had the same predictors i.e. all other variables within the dataset (clinical, demographic, psychosocial and NP assessment). The imputed values were then collated into a single dataset. Imputed values for items that were deemed non-applicable for particular cases (see above) were then replaced with an 888 code.

7.6.2 Distribution of variables

The assessment of the normality of data is a prerequisite for many statistical analyses, and is a key assumption in parametric tests. The distribution of all variables within this study was examined to assess normality. This was done visually using histograms, and statistically, by performing the Kolmogorov-Smirnov test for which a statistical significance level of $p < 0.001$ was used to detect non-normality (The Kolmogorov-Smirnov statistic for each variable is provided in Appendix-L).

When conducting statistical analyses non-normally distributed or skewed data is often transformed using mathematic formulas to attain a more normal data distribution. However, the non-normally distributed data in this study was not transformed. There were two main reasons for this decision. First, when preliminary transformations (e.g. logarithmic base 10 and square root) were applied to non-normal variables it did not render the data correct (normally distributed). Second, transformations transform the nature of the variables (each data point) making the interpretation of data more complex (Osborne, 2005). Based on the data distribution non-parametric tests were used where the data was non-normally distributed, unless stated otherwise.

7.6.3 A note on the level of statistical significance

A significance level of $p<0.01$ was used for all main effects in the study, unless otherwise stated. This more conservative significance level was used due to the large number of tests performed and the risk of obtaining a false-positive result i.e. rejecting the null hypothesis when it is in fact true (Type 1 error). While the main effects were only considered significant at

$p<0.01$, a less conservative significance level of $p<0.05$ was adopted for all preliminary analyses (identifying covariates for ANCOVA's and identifying univariate predictor variables for regression analyses). This approach was deemed appropriate for this exploratory study as it reduced the risk of removing any potential predictor variables based on stringent significance levels alone. Furthermore, it allowed for the observation of any critical interactions between the range of variables included within the present study.

7.7 Statistical analysis strategy for each research question

This section details the statistical analyses adopted for each of the research objectives of the study.

7.7.1 Research question 1- What is the extent of cognitive impairment in ACHD patients?

In order to examine the extent of cognitive impairment in ACHD, the participant data within this study was compared to age matched normative data from healthy individuals. In order to do so the study data was transformed into standardized scores to allow comparability to normative data. The procedures adopted to calculate these scores and the criteria established to indicate impairment in cognitive functioning is discussed below in the following sections.

NP data scoring

The NP data (raw scores) were transformed into standardized scores (z-scores). The reasons for this transformation were firstly that z-scores are standardized and enable comparison across different tests with different units of measurement (time taken, number of words etc.) and different distributions. Secondly, standardized scores enabled comparisons across studies. Z-scores were calculated by subtracting the participant's raw score from the mean value of the age-matched normative data, and dividing it by the Standard Deviation (SD) of the normative data (See formula below). This plots the participant's performance in comparison to age matched normative samples, allowing the participant to be positioned relative to the normative data. Details of the normative data are presented in Appendix-M. The z-scores for all NP tests were used for all subsequent analyses.

$$Z = (X - M) \div SD$$

X= Raw score
M= Normative group mean score
SD= Normative group Standard Deviation

Establishing a criterion for cognitive impairment

In order to compare the sample's cognitive performance to normative data a criterion for cognitive impairment was established. Within the research literature, several cut-off criteria are used to define cognitive impairment including 1, 1.5 and 2 Standard Deviations (SD) below the normative group mean score on a neuropsychological assessment (Lezak et al, 2012). However, there is no established gold standard for defining cognitive impairment. Assuming a normal distribution the likelihood of a healthy individual scoring greater than 1 SD below the mean on one neuropsychological test is approximately 15%. Using 1SD as the criterion for cognitive impairment may increase the number of false-positive results (more cognitively intact individuals will be classified as impaired) (Lezak et al, 2012). Conversely the use of a more stringent criterion of 2 or more SD below the normative data may increase the number of individuals with impairments that are 'missed' and judged as normal (False-negative) (Lezak et al, 2012).

To try and balance the Type I and Type II errors while identifying individuals with impairment on a particular NP test a cut-off score of 1.5 or more SD below/above (depending on the direction of scoring) the respective age matched normative mean score on all NP tests was used to define impairment in this study. This criterion (1.5 SD) has also been used to diagnose Mild Cognitive Impairment (MCI) in different patient groups within the cognitive literature (Schinka et al, 2010, Petersen et al, 1999, Petersen, 2004). Impairment on the IQ test was defined as a score 1SD below the normative mean score (See Section 7.3.1.1 for details). For ease of interpretation and consistency in this study, poor performance will be described as 1.5 SD *below*

the mean irrespective of direction of scoring on all NP tests, and 1SD *below* the mean on the IQ test.

As previously stated, within a normal distribution approximately 15% of individuals would be expected to fall below the 1 SD cut-off and 7% below the 1.5 SD cut-off point. Therefore in the present study, if more than 7% of the sample scored 1.5 SD below the normative mean score on a NP test and more than 15% scored 1 SD below the normative mean score on the IQ test the sample were considered to show significant impairment (See Chapter 8, Section 8.3 further details).

While these figures (15% and 7%) allow assessment of a participant on a single test in comparison to normative data, when using a large cognitive test battery additional factors need consideration. It has been reported that a normal healthy individual may score in the impaired range by chance on 1-2 tests in any given cognitive test battery (Taylor and Heaton, 2001, Lezak, et al, 2004). Further given that 7% of the sample can be expected to score in the impaired range on one test, this proportion would be expected to inflate when a larger number of tests are included in the battery, as the same 7% of the participants are not likely to exhibit impairment across all tests included. For instance, if 5 tests are included the chances of scoring in the impaired range on one of those tests is inflated and 35% (i.e. 7x5) of the sample can be expected to score in the impaired range on one of those tests. In order to correct for this inflation Ingraham and Aieken, (1996) provide a mathematical formula based on binominal theory to calculate the probability of finding impairment in the normal population based on the number of tests utilized, and the established cut-off criteria for cognitive impairment employed (i.e. 1, 1.5 and 2SD). This approach however assumes independence between the tests utilized and when the tests are not independent it is advised that the user exercise some caution, as the estimates of the percentage of the population exhibiting impairment may be reported as being higher than expected.

The technique provided by Ingraham and Aieken, (1996) was applied within this study, using cut-off criteria of 1.5 SD below the normative mean score on three or more tests, to establish what proportion of the ACHD patients exhibited impairment even after taking account of the number of tests. The present study included a total of 8 tests which produced 16 scores in total (See Chapter 8, Section 8.5 for details).

Along with individual NP tests a mean z score was calculated to provide a mean total composite NP score. This score was computed in order to assess the overall level of cognitive functioning across the total sample and the different complexity groups, as assessed by the different measures used in this study. The total mean composite score was calculated by summing up the z-scores from all the tests, and dividing by the total number of scores included. All test scores were included with the exception of the WCST and WAIS-III. The WCST tests scores are not considered independent of each other and therefore including all the scores could cause imbalanced weighting amongst these variables. In order to deal with this problem, only one WCST score (total number of categories achieved) was included in the computation of the mean composite NP score. There were two main reasons for this decision; firstly the total number of categories completed scores is considered one of the most clinically useful WCST scores (Lezak et al, 2012). Secondly the association between the total number of categories completed score and the other WCST scores indicated a medium to strong association ($p<0.001$, range= -0.408 – 0.869); thus suggesting that this score could be considered representative of the other scores. Further the measure of IQ was not included in this score as IQ in itself is considered a composite measure of cognitive functioning rather than an independent domain. When calculating the composite measure, scores on tests such as TMT A and B, and the GP where a higher score indicated poorer performance were reverse scored so a higher score in these tests, as well as in the cumulative score, indicated a better performance consistently.

7.7.1.1 Testing structural complexity group differences in cognitive functioning

The study aimed to assess the differences in the level of cognitive functioning across the different structural complexity groups. Group differences in demographic, cognitive and clinical

variables were tested using the Chi-square test (frequency / categorical data), the Kruskal-Wallis test (non-parametric continuously outcomes) and ANCOVA's (parametric continuous outcomes) where appropriate. The values of the Fisher's exact test are reported where the cell count is less than 5. The reported effect size for the continuous variables is 'r' and for the categorical variable is a Cramer's V.

ANCOVA's were used to assess between-group differences on the NP test scores and the mean total composite score irrespective of the non-normal distribution, as the need to control for certain covariates was considered important and there are no non-parametric equivalents of an ANCOVA (Pallant, 2007). Potential covariates for these analyses were initially selected based on a theoretical rationale and their established association with the outcome variable in past empirical research (Lezak et al, 2012). Identified covariates were retained in the analyses if they were significantly ($p<0.05$) associated with the outcome variable. For post-hoc comparisons between the four groups, the Sidak test was used, as it is less conservative than its alternatives such as the Bonferonni correction and does not result in the loss of power (Field, 2009). The effect size of the ANCOVA analysis as determined based on Cohen's guidelines (Cohen, 1988), whereby 0.01 is a small effect, 0.06 moderate and 0.14 large.

7.7.2 Research question 2: Are demographic, clinical and mood factors associated with cognitive performance in ACHD patients?

This study aimed to identify the demographic, clinical, and mood factors associated with cognitive functioning in ACHD patients. Hierarchical multiple regressions were conducted with IQ and each of the NP scores as dependent variables. Each NP score was used as a dependent variable, as opposed to a cumulative score for each domain, as domains of cognitive functioning are multidimensional and different tests assess different micro-skills within each of these domains, which may potentially be differentially affected by ACHD. Therefore, using a cumulative score may obscure or conceal these differences. Furthermore, assessing each independent score allowed more specificity with regards to identifying the factors that have the ability to influence and or impact different areas of cognitive function assessed.

Given the exploratory nature of this study, a more detailed approach to analysis was undertaken, including the assessment of the total group, and each sub-group independently. It was considered important to assess each group independently to be able to understand the impact of different structural complexity levels on different cognitive outcomes. These differences could have been obscured if the group was assessed as a whole. It is acknowledged that this may have led to a large number of analyses, and a loss of power given the smaller sample sizes in the sub-groups. However, given the lack of evidence in this area of research, the benefits of this exploratory approach were considered to outweigh the risks associated with multiple analyses. To account for the large number of analyses conducted, a more stringent p-value ($p<0.01$) was chosen. However, some caution is warranted when interpreting the results of these analyses.

Two sets of analyses were undertaken to identify factors significantly associated with cognitive functioning:

(1) The entire cohort was analyzed to identify factors associated with cognitive functioning in ACHD patients in general

(2) Subgroup analyses in which each structural complexity group was analyzed separately to identify any unique factors associated with a particular complexity group.

The assumptions tested and the procedural aspects of the regression analysis are discussed below.

7.7.2.1 Collinearity and Multi-collinearity

Bivariate correlation analysis was used to identify significant correlations between the independent variables (IV's) that would be indicative of collinearity, which may weaken the multivariate model by reducing the stability of parameter estimates and increasing standard error. In pairs of variables correlated at r=>.8, one was removed after careful consideration (e.g. the variable total number of days spent in hospital days was retained over number of hospital admissions, as the previous variable has been associated with cognitive functioning in the literature and provides more detailed information regarding the participants time spent in

hospital) (Tyagi et al, 2013). Multicollinearity was also assessed in the regression analysis by conducting tolerance tests and checking the Variance Inflation Factor values (ideally <4).

7.7.2.2 Dummy coding of variables

Categorical variables in the study were dummy coded, with all but one (to represent the reference category) of the dummy coded variables entered into the equation, following procedures recommended by Field, (2009). Further the distribution of some of the clinical variables (cyanosis, CPB minutes, HA minutes, age at repair) was such that the majority of the scores were concentrated on one end of the distribution given that the variable wasn't applicable to all groups included in the study; for instance cyanosis, was only applicable to the cyanotic conditions and not the acyanotic. This caused the data to be severely skewed (See Figure 7.6a as example), and at risk of being unable to reliably explain variance in the regression analyses. Therefore, these variables were transformed into quartiles for two reasons i) to allow a more normal distribution (See Figure 7.6b below), and ii) to allow predictors to explain more variability in the outcome. Quartiles were computed separately for the total group as a whole and for each of the four complexity groups individually.

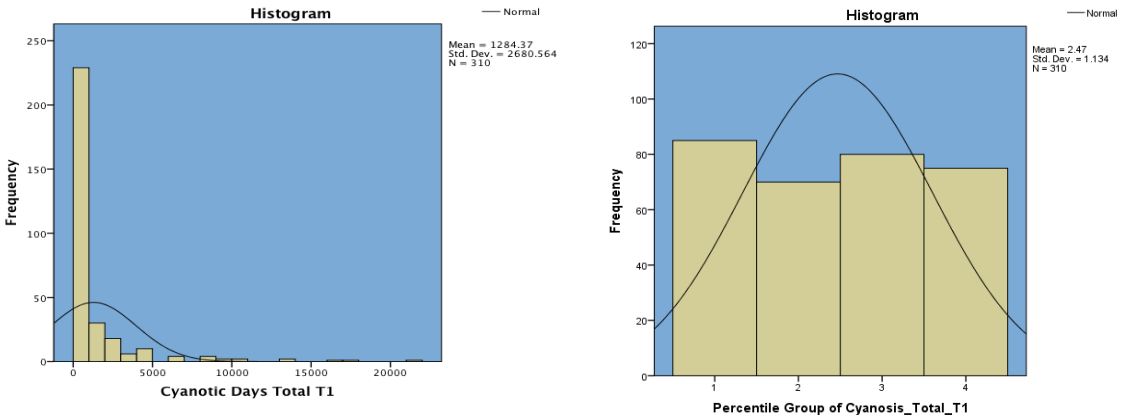


Figure 7.6: Example of frequency distribution before (a) & after (b) transformation into quartiles

7.7.2.3 Screening for univariate predictors of cognitive functioning

In order to identify factors potentially associated with cognitive function to enter into the multiple regression models, a univariate regression was run for each predictor and dependent variable. Only factors significantly associated with cognition at $p<0.05$, were entered into the multivariate regression models, this was done to reduce the number of redundant variables in the model. A significance level of $p<0.05$ was chosen for the univariate screen to allow the maximum number of variables to explain variance in the outcome. Univariate predictors were identified for the group as a whole and for each structural complexity groups separately (Please see Appendix-N for results of the univariate screening). Only results for the outcome variables with at least one significant predictor variable in the univariate screening will be presented.

7.7.2.4 Order of the hierarchical regression blocks

Significant variables were entered into a hierarchical multivariate regression model in 6 blocks. The first block included the participants' demographic variables, which were followed by a block for the structural complexity groupings and functional health status variables. Once these variables were entered into the model the surgery related variables were added, to account for any procedural predictors of variance over and above the structural complexity groups. Oxygen saturation related variables (cyanosis and current saturation) were entered into the fourth block to assess its influence over and above surgery related variables, followed by the current health related variables in the fifth block. Lastly, Mood variables were entered to assess their impact on cognitive functioning having accounted for all clinical variables (See Figure 7.7).

The rationale for the order of the regression blocks was to firstly take into account the demographic variables and the patient's clinical history and structural complexity before assessing the impact of current health related variables for e.g. their current oxygen saturation levels and lastly mood variables. The objective was to identify unique predictors of cognitive functioning over and above the clinical history and diagnosis (Structural complexity groups) of the participants. It aimed to evaluate the association of both clinical and psychosocial factors with cognitive outcomes.

7.7.2.5 Dealing with outliers

Outliers are defined as observations that deviate so much from other observations, that they arouse suspicion that they were generated by a different mechanism, implying that the deviated value is potentially an error of measurement or an invalid data point (Hawkins, 1980). Within this study it was ensured that all outliers were legitimate scores, and not mistakes in data entry. Multivariate outliers were identified using Cook's distance. This index was chosen, as it accounts for the change in the predicted values when influential data cases with large residuals and/or a high leverage are excluded. Further it also takes into consideration the distance of the observed value from the others (Hair et al, 1998). A Cook's distance >1 is considered large and a cause of concern (Stevens, 1984). If a Cook's distance of >1 was identified; analyses were re-run with and without the outliers to see if their inclusion affected results. If differences are noted the results will be presented in Chapter 8.

7.7.2.6 Examination of residuals

While regression analysis does not make any assumptions about the data being normally distributed, it does expect a fairly normal distribution of the residuals after the analysis. For each of the regression analyses the distribution of the residuals was assessed visually using scatter plots. Scatter plots were assessed for a random distribution, the presence of any patterns e.g. funnelling and skewness at either end of the distribution was considered problematic and indicative of non-normally distributed residuals. While non-normally distributed residuals do not invalidate the analyses, it weakens it and thus caution is warranted when drawing conclusions (Tabachnick and Fidel, 2013). If non-normal residuals are noted the results will be presented in Chapter 8.

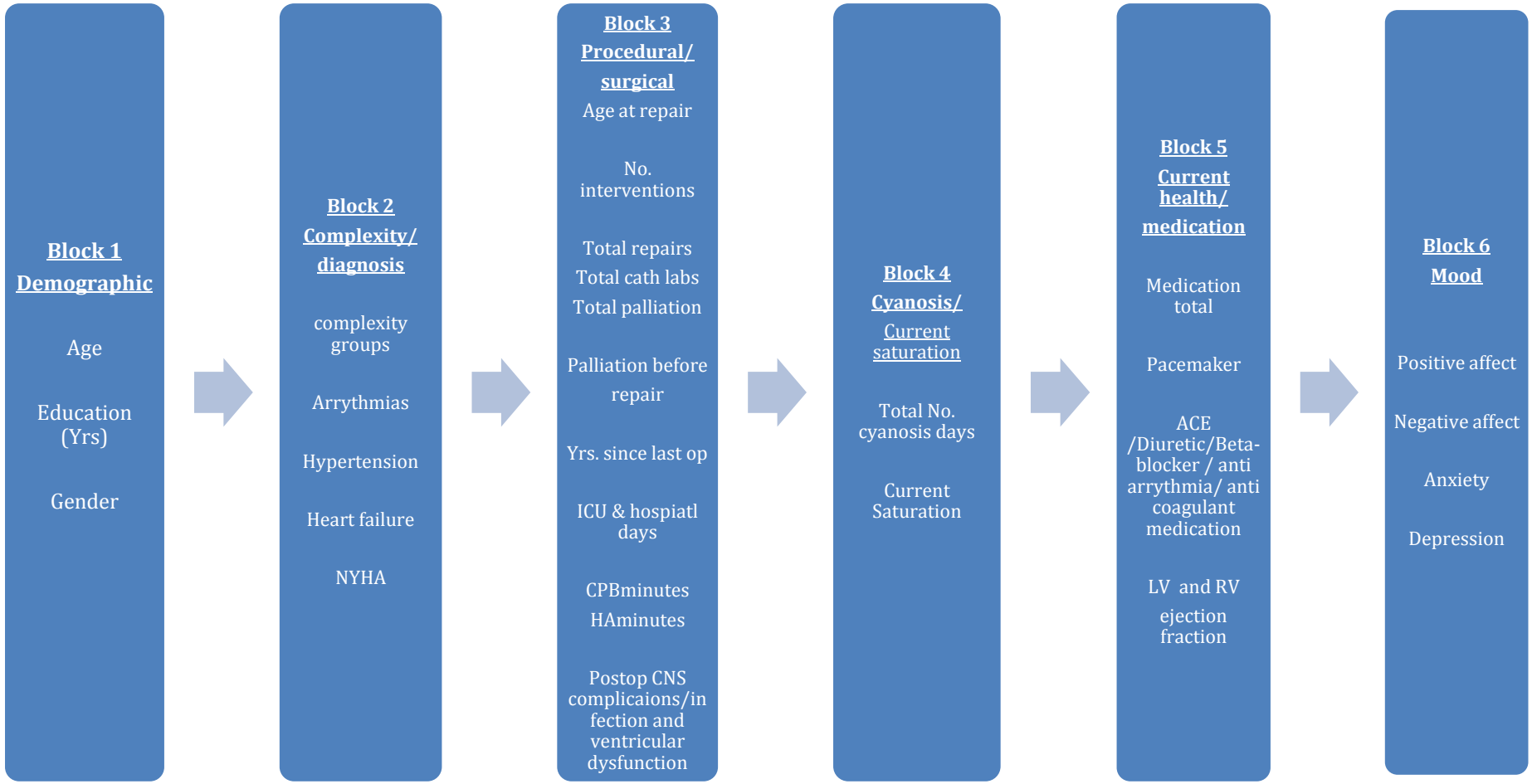
7.7.3 Research question 3: Is cognitive functioning in ACHD patients associated with QoL?

The association between QoL and the demographic, clinical factors and total mean composite NP score was assessed using hierarchical multiple regression. Again to explore the association

between cognitive functioning and QoL in ACHD patients as a group, but also to be able to investigate factors associated with QoL in specific structural complexity groups. A univariate screening using simple linear regressions was conducted for each outcome variable (PCS and MCS) and variables significant at <0.05 were entered into the multivariate regression models. Two sets of analyses were run for each outcome; one on the total sample, and another for each structural complexity group. Procedures and assumptions of the regression analysis were tested similar to the analysis discussed in the previous section (Section 7.7.2), and therefore have not been repeated here.

The variables were entered into three regression blocks for the multivariate analyses. These consisted of the demographic variables, followed by the clinical and lastly cognition variable. The order of the regression blocks was chosen to be able to assess the unique variance in QoL explained by cognitive functioning after accounting for the patient related demographic and clinical characteristics.

The next chapter, Chapter 8 discusses the results of the analysis discussed above.



Note: NYHA= New York Health Assessment, CPB= Cardio Pulmonary Bypass, HA= Hypothermic Arrest, CNS= Central Nervous System, ACE= angiotensin-converting-enzyme , LV= Left Ventricle, RV= Right Ventricle

Figure 7.7: The order of the hierarchical multiple regression blocks for Research question 2

8 CROSS -SECTIONAL STUDY RESULTS

8.1 Prologue

This chapter presents the findings of the cross-sectional study. Each section of the chapter aims to address the research questions detailed in Chapter 6. Firstly, the demographic and clinical characteristics of the sample are described, and assessed for group differences. Secondly, cognitive functioning in this sample is assessed in comparison to normative data. Thirdly, comparisons are made between the four structural complexity groups on cognitive outcomes. This is followed by an examination of possible factors (demographic, clinical and mood) associated with cognitive functioning. Finally, the relationship between cognitive functioning and QoL is examined.

8.2 Demographic and clinical characteristics of the study sample

The total study sample included 314 participants of whom 310 had complete neuropsychological assessment data and were included in the final analyses; the other 4 participants were unable to complete NP tests due to time constraints. The final sample (N=310) consisted of 174 (56.13%) males and 136 (43.87%) females. The median age of the cohort was 31 years ranging from 18-76 years. The demographic characteristics of the sample are presented in Table 8.1 (below). There were similar numbers of participants across three of the structural complexity groups (ToF= 81, TGA= 80, Simple=84), but fewer participants in the SV group (SV=65).

Table 8.1 Demographic characteristics of the sample by structural complexity groups

Variable N (%)	ToF	TGA	SV	Simple	Total sample	χ2/H	V/r (ES)	p-value	df
Gender									
Male	43 (53.1)	51 (63.8)	43 (66.2)	37 (44)	174 (56.1)	9.82	0.17	0.020	3
Female	38 (46.9)	29 (36.3)	22 (33.8)	47 (56)	136 (43.9)				
Ethnicity †									
White British	72 (88.9)	71 (88.8)	51 (78.5)	68 (81)	262 (84.5)	4.91	0.12	0.178	3
Others	9 (11.1)	9 (11.3)	14 (21.5)	16 (19)	48 (15.5)				
Living status									
Cohabiting (with parent/spouse/friend)	72 (88.9)	63 (78.8)	58 (89.2)	68 (81)	261 (84.2)	5.02	0.12	0.170	3
Alone-on their own	9 (11.1)	17 21.3)	7 (10.8)	16 (19)	49 (15.8)				
Employment									
Employed/ student/in training	63 (77.8)	66 (82.5)	51 (78.5)	64 (76.2)	244 (78.7)	2.18	0.08	0.530	3
Unemployed/ retired/ unable to work	18 (22.2)	14 (17.5)	14 (21.5)	20 (23.8)	66 (21.3)				
Occupation level ‡									
Managerial/ Professional	19 (23.5)	17 (21.3)	15 (23.1)	23 (27.4)	74 (23.9)	0.9	0.05	0.820	3
Intermediate	14 (17.3)	18 (22.5)	9 (13.8)	10 (11.9)	51 (16.5)				
Lower	26 (32.1)	25 (31.3)	20 (30.8)	24 (28.6)	95 (30.6)				
Never worked/unemployed	22 (27.2)	20 (25.0)	21 (32.3)	27 (32.1)	90 (29.0)				
Marital Status									
Married	44 (54.3)	36 (45)	33 (50.8)	45 (53.6)	158 (51)	1.73	0.07	0.630	3
Unmarried/divorced/single	37 (45.7)	44 (55)	32 (49.2)	39 (46.4)	152 (49)				
Age									
Age (Median, interquartile range)	33.0 (25-41)	31.50 (27-36)	28.60 (23-32)	37.0 (23-32)	31.0 (26-45)	22.03	-.343 – 0.293	**<.001**	**3**
Education									
Yrs of education (Median, interquartile range)	13.0 (11-16)	13.3 (11-16)	13.7 (11-16)	13.5 (11-16)	13.4 (11-16)	3.08	n/a	0.370	3

V= Cramer's V, r= effect size for Kruskal Wallis, ES=Effect Size, † =the ethnicity variable was collapsed into a dichotomous variable due to low cell counts within categories (N=11). ‡= The National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010) (Rose and Pevalin, 2010)

The ethnicity of the study sample was initially classified into 11 sub-groups but due to the small proportion in many categories (e.g. Asian, African American, White- British) groups were combined into a dichotomous variable (White British vs. Others), with most of the study sample being British. The majority of the study sample was employed and/or studying, and cohabiting with family and friends. A Kruskal-Wallis test revealed a significant difference between the groups in age. The SV group was significantly younger than the Simple ($p < 0.001$, $r = -.343$) and ToF groups ($p = .002$ $r = 0.293$). No other demographic variables differed significantly between the groups at $p < 0.01$.

The clinical characteristics of the study sample are presented in Figure 8.1– Figure 8.16 (box plots of the median values of each continuous variable) and Table 8.2 (for categorical variables). The reported effect size for the continuous variables is 'r' and for the categorical variable is a Cramer's V. The pairwise comparisons conducted to identify significant group differences between the groups on the continuous variables (as seen in Figures 8.1-8.16) are presented in Appendix-P

Figure 8.1 – 8.16 Boxplots with error bars for each continuous clinical variable by structural complexity group

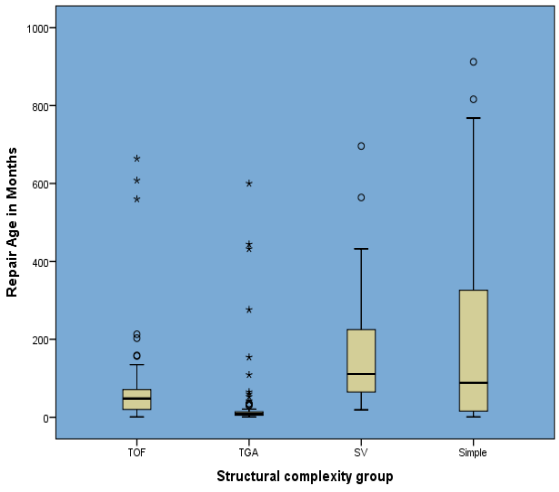


Figure 8.1: Data distribution for age at surgical repair by complexity group

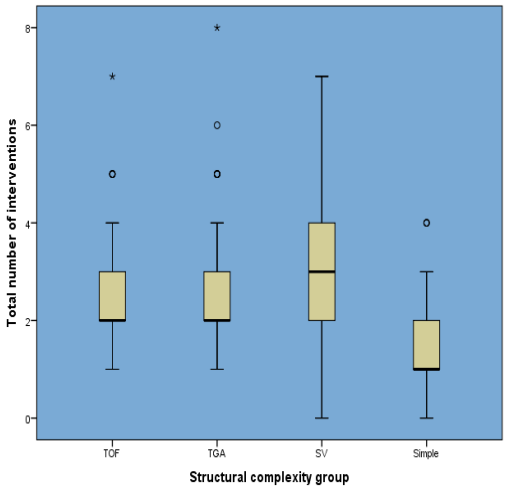


Figure 8.2: Data distribution for number of interventions by complexity group

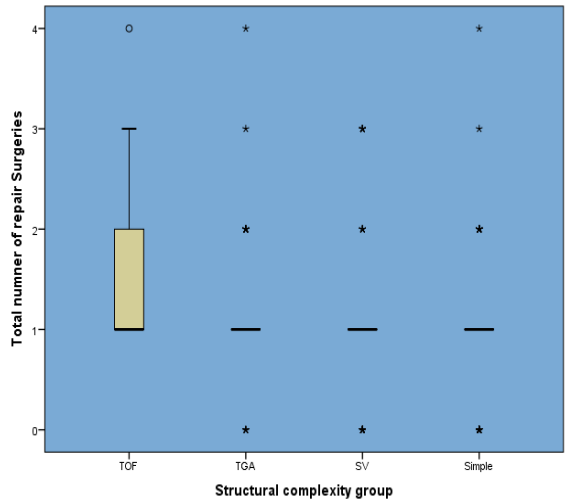


Figure 8.3: Data distribution for number of repair surgeries by complexity group

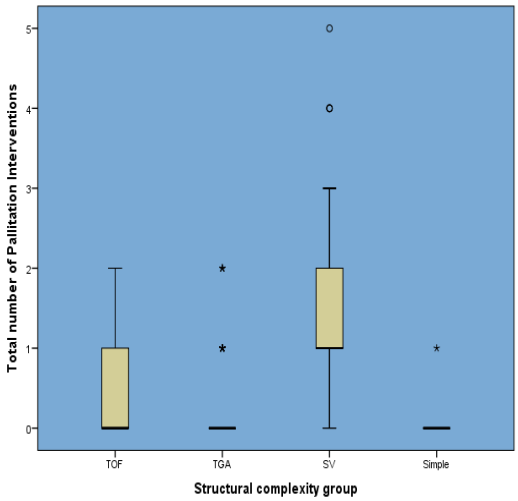


Figure 8.4: Data distribution for number of palliation procedures by complexity group

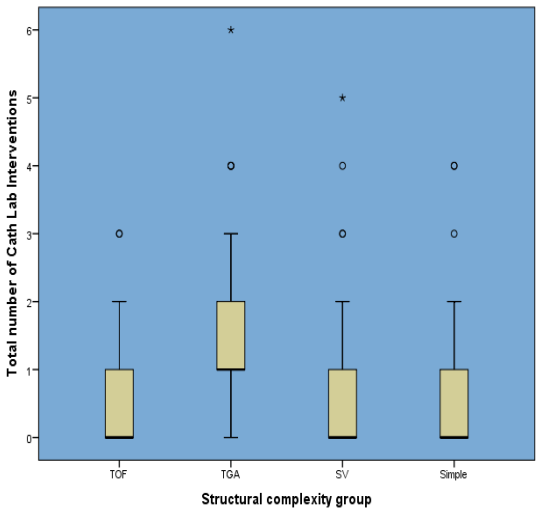


Figure 8.5 Data distribution for number of catheter lab interventions by complexity group

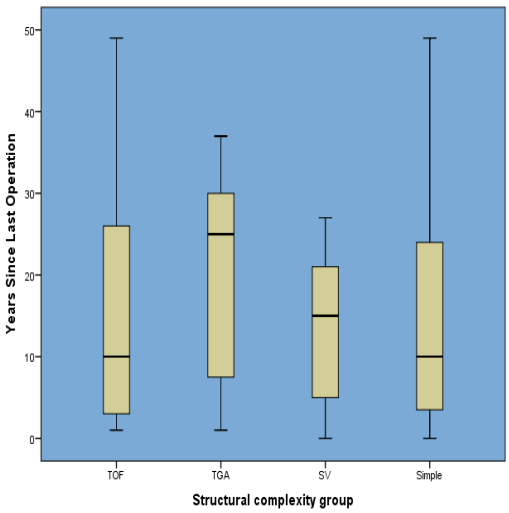


Figure 8.6 Data distribution for number of years since last surgery by complexity group

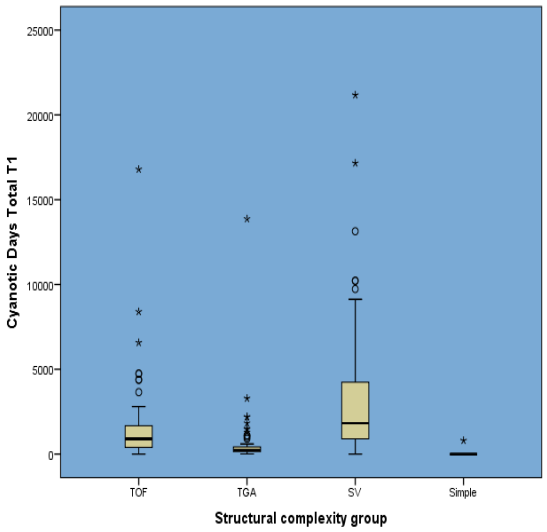


Figure 8.7 Data distribution for number of cyanotic days by complexity group

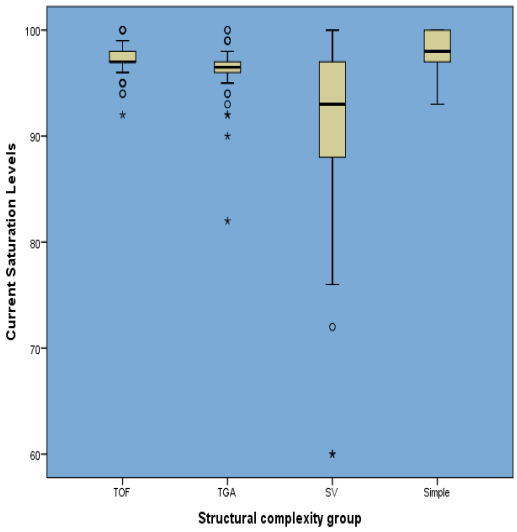


Figure 8.8 Data distribution for current oxygen saturation levels by complexity group

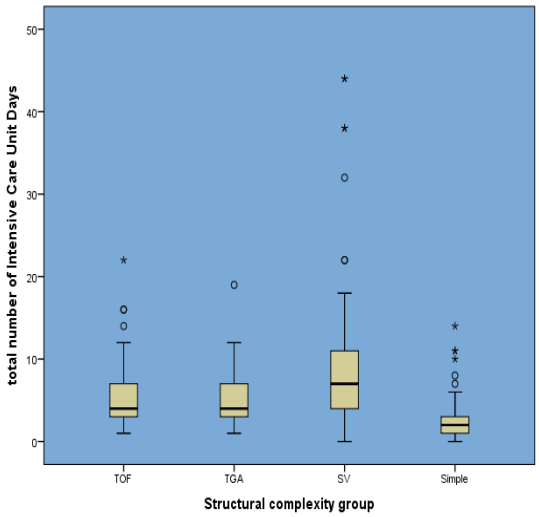


Figure 8.9 Data distribution for days spent in ICU by complexity group

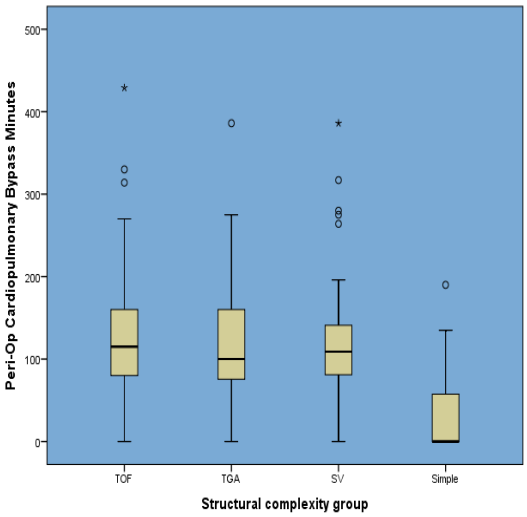


Figure 8.10 Data distribution for minutes on CPB by complexity group

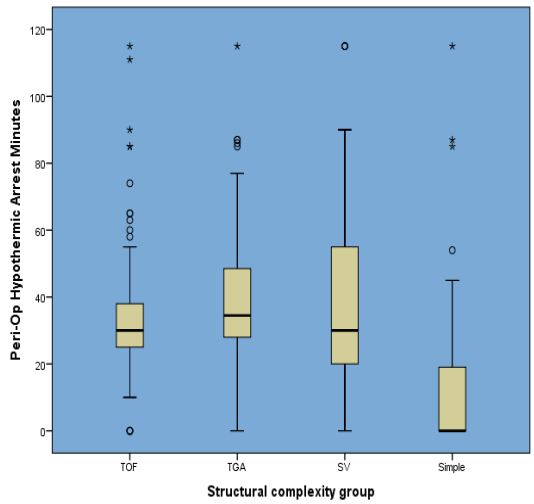


Figure 8.11 Data distribution for minutes under HA by complexity group

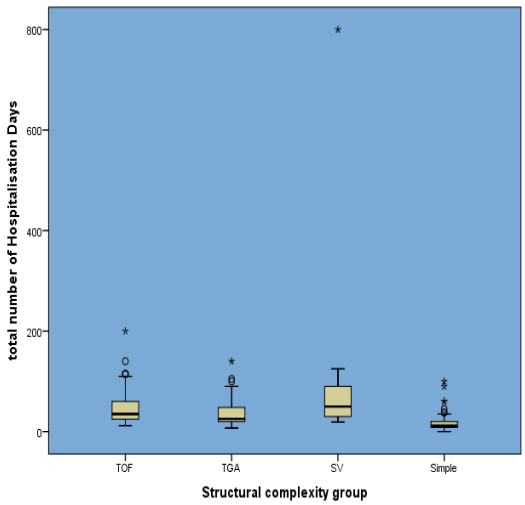


Figure 8.12 Data distribution for number of days in hospital by complexity group

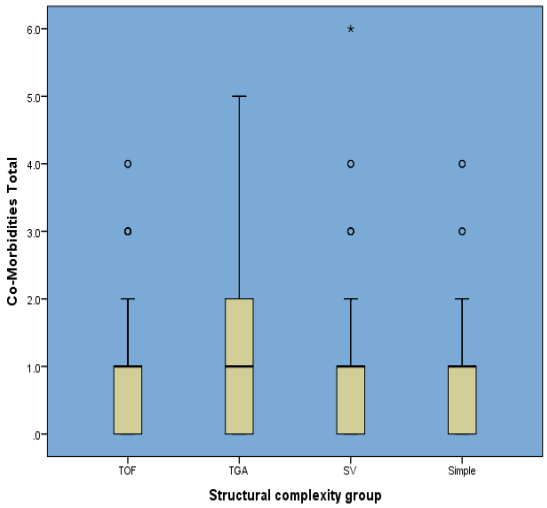


Figure 8.13 Data distribution for number of co-morbidities by complexity group

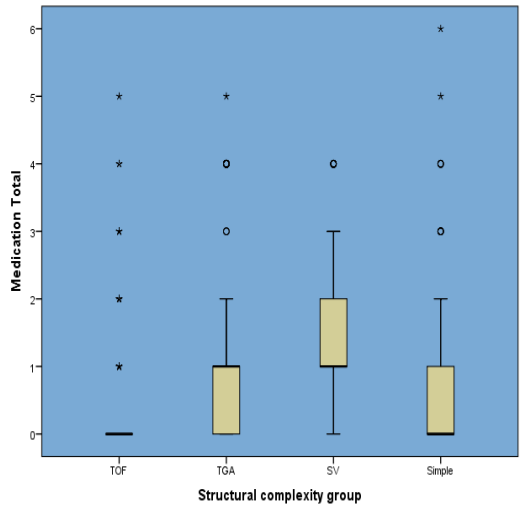


Figure 8.14 Data distribution for number of medications by complexity group

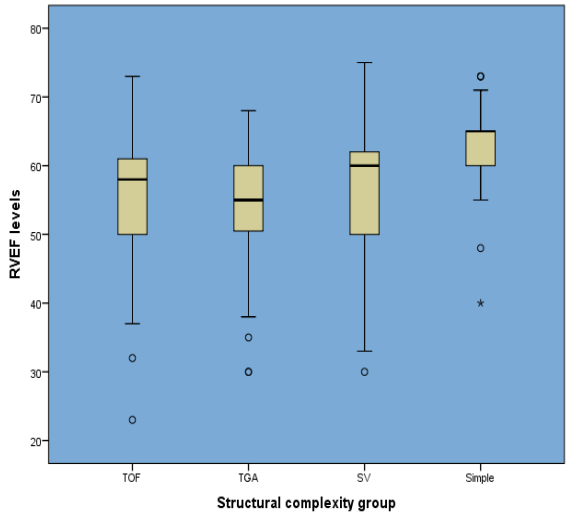


Figure 8.15 Data distribution for the level of RVEF by complexity group

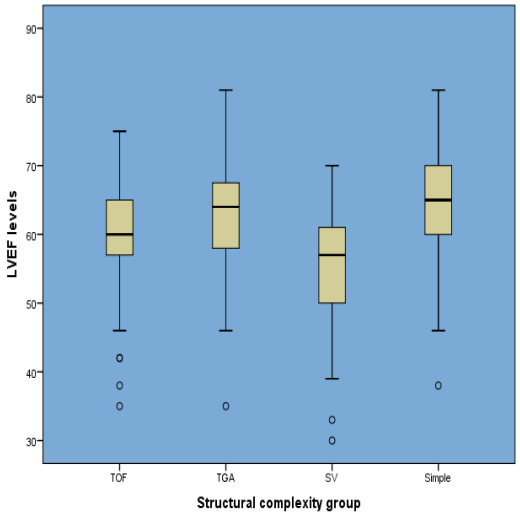


Figure 8.16 Data distribution for the level of LVEF by complexity group

Figures 8.1 to 8.16, illustrate the differences between the groups on clinical variables (See Appendix-P for results). The four complexity groups differed significantly on symptomology related variables for example cyanosis, with the Simple group being significantly different from the ToF, TGA and SV group (Fig 8.7) and current saturation (Fig 8.8) with all groups being significantly different from each other. These differences could be expected given the cyanotic and acyanotic nature of the different structural complexity groups. Furthermore, the groups differed significantly on surgery related variables, including CPB minutes (Figure 8.10), and hypothermic arrest minutes (Figure 8.11) with the Simple group being significantly different to the ToF, TGA and SV groups on both these variables. The simple group consistently had a median score of zero on these surgery related variables, emphasizing the differences in the treatments undertaken for different forms of ACHD. The four groups did not differ significantly on the variable co-morbidities, thus suggesting that most differences were due to the differential diagnosis between groups (Figure 8.13). These figures illustrate the variability and spread of the different clinical characteristics across groups, making them clinically distinct.

Table 8.2 illustrates the significant differences in clinical characteristics across the four structural complexity groups on categorical clinical variables. The values of the Fisher's exact test are reported where one or more cell counts were lower than 5. The four groups differed significantly on the majority of clinical variables with the exception of the New York Health Assessment classification (p=0.118), types of medication taken (beta-blockers (p=0.080) and diuretic (p=0.810) medication), post-operative CNS complications (p=0.011), ventricular dysfunction (p=0.015) and the presence of a pacemaker (p=0.056). Most of the differences found can be expected given the diverse nature of the forms of CHD, for example differences in procedures (number of palliation procedures before surgical repair) and complications (the need to attend heart failure clinics) can be expected given that the less complex forms of CHD generally do not undergo as many procedures nor experience as many complications. Post-operative CNS complication was borderline significant with the Simple group not exhibiting any CNS complications (See Table 8.2).

Table 8.2: Clinical characteristics of the study sample by structural complexity groups (Categorical variables)

Categorical clinical variables N (%)									
	Total sample	**ToF**	**TGA**	**SV**	**Simple**	**x^2**	**Cramer's V (ES)**	**df**	**p-value**
Palliation before repair									
No	153 (49.4)	47 (15.4)	12 (3.9)	10 (3.20)	84 (27.1)	156.41	0.71	3	**<0.001**
Yes	157 (50.6)	34 (11.10)	68 (22.3)	55 (18)	0 (0)				
Post-operative CNS complications									
No	291 (93.9)	76 (24.9)	72 (23.6)	59 (19.0)	84 (27.1)	10.83 [a]	0.16	3	0.011
Yes	19 (6.1)	5 (1.6)	8 (2.6)	6 (1.9)	0 (0)				
Post-operative infection									
No	233 (75.2)	54 (17.7)	56 (18.4)	44 (14.2)	79 (25.5)	22.264	0.266	3	**<0.001**
Yes	77 (24.8)	27 (8.9)	24 (7.9)	21 (6.8)	5 (1.6)				
Post-operative Ventricular dysfunction									
No	282 (91.0)	74 (24.3)	69 (22.6)	56 (18.1)	83 (26.8)	10.302	0.182	3	0.015
Yes	28 (9.0)	7 (2.3)	11 (3.6)	9 (2.9)	1 (0.3)				
Heart failure clinic									
No	255 (82.3)	76 (24.5)	53 (17.1)	43 (13.9)	83 (26.8)	48.794	0.397	3	**<0.001**
Yes	55 (17.7)	5 (1.6)	27 (8.7)	22 (7.1)	1 (0.3)				

Categorical clinical variables N (%)									
	Total sample	**ToF**	**TGA**	**SV**	**Simple**	**x^2**	**Cramer's V (ES)**	**df**	**p-value**
Arrhythmias									
No	228 (73.5)	66 (21.3)	46 (14.8)	39 (12.6)	77 (24.8)	33.518	0.329	3	**<0.001**
Yes	82c (26.5)	15 (4.8)	34 (11)	26 (8.4)	7 (2.3)				
Hypertension									
No	278 (89.7)	80 (25.8)	74 (23.9)	63 (20.3)	61 (19.7)	38.007	0.35	3	**<0.001**
Yes	32 (10.3)	1 (0.3)	6 (1.9)	2 (0.6)	23 (7.4)				
NYHA category									
Class 1	272 (87.7)	70 (22.6)	70 (22.6)	53 (17.1)	79 (25.5)	5.840 [a]	0.122	3	0.118
Class 2	28 (9)	10(3.2)	5 (1.6)	8 (2.6)	5 (1.6)				
Class 3	7 (2.3)	1 (0.3)	4 (1.3)	2 (0.6)	0 (0)				
Class 4	3 (1)	0 (0)	1 (0.3)	2 (0.6)	0 (0)				
Pacemaker									
No	293 (94.5)	81 (26.1)	70 (22.6)	60 (19.4)	82 (26.5)	14.434	0.216	3	0.056
Yes	17 (5.5)	0 (0)	10 (3.2)	5 (1.6)	2 (0.6)				
ACE inhibitors medication									
No	244 (78.7)	74 (23.9)	56 (18.1)	49 (15.8)	65 (21)	11.872	0.196	3	**0.008****

Categorical clinical variables N (%)									
	Total sample	**ToF**	**TGA**	**SV**	**Simple**	**x^2**	**Cramer's V (ES)**	**df**	**p-value**
Yes	66 (21.3)	7 (2.3)	24 (7.7)	16 (5.2)	19 (6.10)				
Diuretic medication									
No	275 (88.7)	73 (23.5)	70 (22.6)	56 (18.1)	76 (24.5)	0.964	0.056	3	0.810
Yes	35 (11.30)	8 (2.6)	10 (3.2)	9 2.9)	8 (2.6)				
Beta-blocker medication									
No	258 (83.2)	74 (23.9)	61 (19.7)	53 (17.1)	70 (22.6)	6.759	0.148	3	0.080
Yes	52 (16.8)	7 (2.3)	19 (6.1)	12 (3.9)	14 (4.5)				
Anti-arrhythmic medication									
No	274 (88.4)	75 (24.2)	69 (22.3)	48 (15.5)	82 (26.5)	22.116	0.267	3	**<0.001**
Yes	36 (11.6)	6 (1.9)	11 (3.5)	17 (5.5)	2 (0.6)				
Anti-coagulant medication									
No	233 (75.2)	71 (22.9)	64 (20.6)	21 (6.8)	77 (24.8)	83.971	0.52	3	**<0.001**
Yes	77 (24.8)	10 (3.2)	16 (5.2)	44 (14.2)	7 (2.3)				

Note- x^2-chi square statistics calculated based on the 4 groups, [a] Fisher's exact chi square value and significance reported, **p<0.01, ES= Effect Size

8.3 Cognitive functioning in ACHD patients compared to normative data and different structural complexity groups

In order to address these research objective two sets of analyses were undertaken. First, the performance of the ACHD patients on each neuropsychological test was compared to normative values both for the total sample (all groups combined) and for each structural complexity group independently. Finally, differences in cognitive functioning between the four structural complexity groups were assessed and presented in Section 8.6.

As discussed in Chapter 7 (section 7.7.1) participants' raw scores (See Table 8.3 below) on the neuropsychological (NP) assessments were converted into standardized z-scores. All the NP scores were calculated using normative data matched by the participant's age, and, where available, educational level (See Appendix-M for further details and sources of the normative data).

Cognitive impairment was defined as a score less than or equal to 1.5 SD below the normative mean score for all the tests; except IQ, for which the criteria for impairment was 1SD below the normative mean score. As discussed in Chapter 7 (section 7.7.1) the nature of a normal data distribution suggests approximately 15% of the sample can be expected to fall 1 SD below the mean and 7% can be expected to fall 1.5 SD below the mean on any test (See Lezak et al, 2012 for a visual representation of the normal distribution).

Table 8.3: Mean (SD) NP raw scores for the sample by structural complexity group

NP test raw score	ToF Mean (SD)	TGA Mean (SD)	SV Mean (SD)	Simple Mean (SD)	Total Sample Mean (SD)
IQ					
WAIS III-Mental Arithmetic	12.20 (4.34)	11.81 (3.97)	12.32 (4.00)	13.34 (4.06)	12.46 (4.13)
WAIS III- Information	15.74 (5.10)	16.50 (5.44)	16.97 (5.96)	17.17 (5.36)	16.58 (5.45)
WAIS III- Digit Symbol	71.84 (15.58)	73.19 (16.17)	71.65 (17.39)	75.65 (15.62)	73.18 (16.14)
WAIS- Estimated Full scale IQ (FSIQ)	95.04 (15.40)	95.26 (15.78)	96.63 (15.67)	100.44 (14.64)	96.89 (15.45)
Executive functioning					
COWA- F	11.86 (3.69)	11.20 (4.4)	12.82 (4.44)	12.17 (4.11)	11.97 (4.19)
COWA –A	9.63 (4.01)	9.91 (4.74)	11.72 (4.23)	10.83 (4.40)	10.47 (4.41)
COWA - S	13.99 (4.58)	14.19 (4.69)	14.83 (5.03)	14.75 (4.47)	14.42 (4.67)
Stroop Colour-Word	111.86 (0.49)	111.70 (1.32)	111.83 (0.52)	111.80 (0.74)	111.8 (0.84)
WCST- Errors	18.54 (8.97)	17.74 (8.31)	17.18 (8.18)	16.32 (8.52)	17.45 (8.52)
WCST-CLR	40.69 (12.45)	41.50 (11.50)	4 2.45 (11.71)	43.76 (11.63)	42.10 (11.83)
WCST- No. Cat	3.06 (1.43)	3.20 (1.45)	3.29 (1.31)	3.65 (1.31)	3.31 (1.39)
WCST-TTC	13.27 (7.59)	13.00 (8.68)	13.63 (8.37)	12.63 (7.83)	13.10 (8.08)
WCST- FTM	0.46 (0.72)	0.39 (0.62)	0.43 (0.81)	0.27 (0.62)	0.38 (0.69)
Attention					
TMT A	32.04 (11.47)	32.54 (11.99)	31.62 (13.26)	31.06 (9.39)	31.81 (11.46)
TMT B	67.15 (25.75)	62.60 (18.92)	65.17 (19.08)	60.74 (25.03)	63.82 (22.65)
SDMT- W	51.37 (10.17)	53.15 (12.02)	53.65 (12.51)	54.11 (10.79)	53.05 (11.34)
SDMT- O	61.90 (12.70)	63.58 (13.93)	65.06 (13.54)	63.57 (14.37)	63.45 (13.64)
Motor function					
GP-D time	72.99 (11.58)	72.44 (13.92)	73.69 (17.86)	69.61 (13.31)	72.08 (14.16)
GP-ND time	79.14 (14.13)	80.71 (21.30)	81.62 (22.46)	78.26 (18.69)	79.83 (19.17)
Memory					
RAVLT trial 1	8.62 (2.06)	8.50 (2.60)	8.97 (2.43)	8.39 (2.29)	8.60 (2.35)

NP test raw score	ToF Mean (SD)	TGA Mean (SD)	SV Mean (SD)	Simple Mean (SD)	Total Sample Mean (SD)
RAVLT trial 2	11.28 (2.48)	10.85 (2.94)	11.88 (2.34)	11.10 (2.80)	11.25 (2.68)
RAVLT trial 3	12.54 (2.37)	12.21 (2.53)	12.09 (2.43)	12.04 (2.26)	12.23 (2.39)
RAVLT trial 4	12.95 (1.69)	12.94 (1.84)	13.03 (1.70)	12.83 (2.29)	12.93 (1.90)
RAVLT trial 5	12.73 (1.73)	12.81 (1.66)	13.11 (1.63)	12.60 (2.00)	12.79 (1.77)
RAVLT list B	7.51 (2.16)	7.26 (2.12)	7.63 (2.31)	7.17 (2.35)	7.38 (2.23)
RAVLT trial 7	11.54 (2.52)	11.88 (2.41)	12.12 (2.39)	11.63 (2.76)	11.77 (2.53)
RAVLT total acquisition	58.12 (6.79)	57.31 (8.48)	59.07 (6.78)	56.95 (8.96)	57.79 (7.87)
Total composite score	-6.63 (10.93)	-7.61 (15.07)	-6.72 (13.55)	-1.75 (10.40)	-5.58 (12.72)

Note-SD- Standard Deviation, TMT= Trail Making Test, COWA= Controlled Oral Word Association test, WAIS= Wechsler Adult intelligence Scale, GP=Grooved Pegboard, WCST-CLR= Wisconsin Card Sorting Test – Conceptual Level Responses, WCST-TTC= Wisconsin Card Sorting Test – Trials to Complete first category, WCST-FTM= WCST- Wisconsin Card Sorting Test -Failure to Maintain Set, WCST-No.Cat = Wisconsin Card Sorting Test – Total number of categories, SDMT-W= Symbol Digit Modalities Test-Written score, SDMT-O= Symbol Digit Modalities Test-Oral score.

For the purposes of this thesis the magnitude of the cognitive impairment was only considered important if over 15% of the sample showed impairment on the IQ test and over 7% on the NP tests. The relative performance of the ACHD group as compared to an age matched normative sample was evaluated on each test, and is presented below, for IQ and the four overarching cognitive domains (executive functioning, attention, memory and motor function). Results for each test are discussed for the total sample followed by the structural complexity groups.

8.3.1 IQ in ACHD patients compared to normative data

8.3.1.1 Total sample

The normative data for comparison of IQ scores was derived from the test manual consisting of scores from healthy participants, aged 16-89 years (Wechsler, 1997). The mean score of the total sample within this study was 96.89 (Figure 8.17), ranging from 53.80 – 137.80. IQ scores

in the total study sample showed that 24% of the sample had an IQ score at least 1 SD below the normative mean of 100, greater than the expected 15% for a normal distribution.

8.3.1.2 Structural complexity groups

The mean score of all four groups were within the 'average' IQ category as classified by Wechsler (IQ= 90-109). Within the different structural complexity groups 22.2% of the ToF group, 23.8% of the TGA group, 20% of the SV group and a 16.7% of the Simple group scored 1 SD below (i.e. IQ <85) the normative mean score (i.e. IQ=100) (See Figure 8.17). In all groups more than 15% of the sample exhibited impairment in IQ.

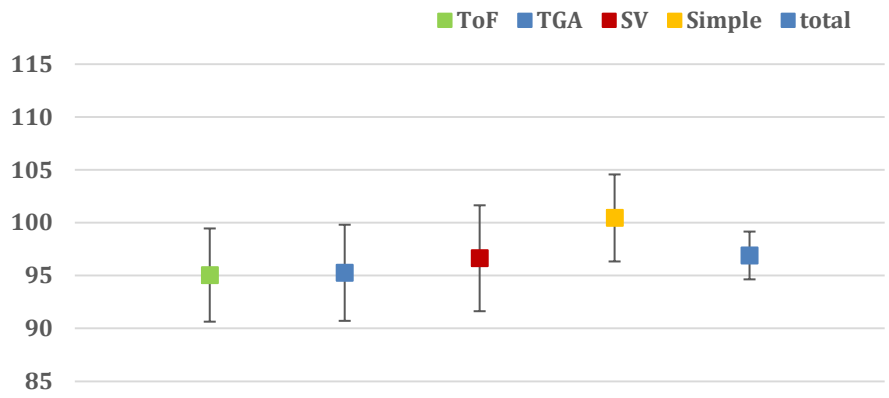


Figure 8.17 Mean full scale IQ scores, with 1SD error bars

8.3.2 Executive functioning in ACHD patients compared to normative data

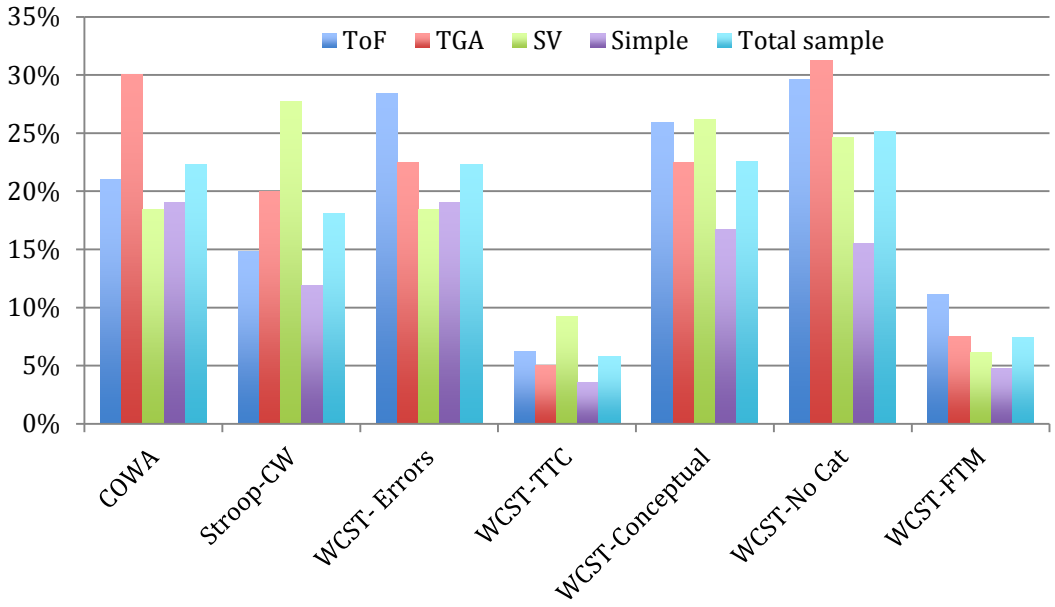
The overarching domain of executive functioning was assessed using three NP tests WCST, COWA and Stroop. The normative data for comparison in the WCST test was acquired from the test manual consisting of scores from 445 healthy participants, aged 18-89 years (Kongs et al, 2000). Normative data for the COWA and the Stroop tests were taken from a study including 1,300 and 156 healthy participants aged 16-95 years and 18-75 years respectively (Tombaugh, Kozak and Rees, 1999; Trenerry et al, 1989).

8.3.2.1 Total sample

The data presented in Figure 8.18 illustrates the total proportion (%) of the sample exhibiting impaired performance (1.5 SD below norms) on tests of executive functioning. The sample exhibited impairments on most of the tests used. More than 7% of the total sample exhibited impairment in executive functions as assessed by the WCST (No. of categories =25%, conceptual level responses= 23% and Errors= 22%). Almost one quarter of the sample exhibited impairment on the number of categories achieved score, which is indicative of frontal lobe dysfunction (Barcelo and Knight, 2002) and is also considered one of the most diagnostically useful scores to detect impairment in executive function (Lezak et al, 2012; Strauss, Sherman, and Spreen, 2006). The only exception was the trials to complete first category score (6%) and the failure to maintain set score (7%), on which participant's demonstrated performance comparable to that expected in a normal distribution. A greater proportion of participants showed impairment on the Stroop test (18%) and the COWA test (22%) than would be expected in a normal distribution (7%).

8.3.2.2 Structural complexity groups

Figure 8.18 showed a large proportion of participants within each group were impaired on the Stroop, COWA and WCST (WCST- No. of categories, errors and conceptual level responses) which assess the ability to formulate concepts and solve problems respectively. It is of note that fewer participants in the SV and Simple groups displayed impairments on the 'failure to maintain set' score, and the ToF, TGA and Simple groups on the 'trials to complete 1st category scores' of the WCST (i.e. < 7% exhibiting impairments) demonstrating performance comparable to that expected in a normal distribution.



Note – COWA= Controlled Oral Word Association test, Stroop-CW= Stroop Colour Word score, WCST = Wisconsin Card Sorting Test, TTC= Trials to complete 1st category, WCST-conceptual= conceptual level responses, WCST No Cat= Number of categories, WCST-FTM= Failure to Maintain Set

Figure 8.18 Proportion (%) of the sample with impairment on tests of executive functioning

8.3.3 Attention in ACHD patients compared to normative data

8.3.3.1 Total sample

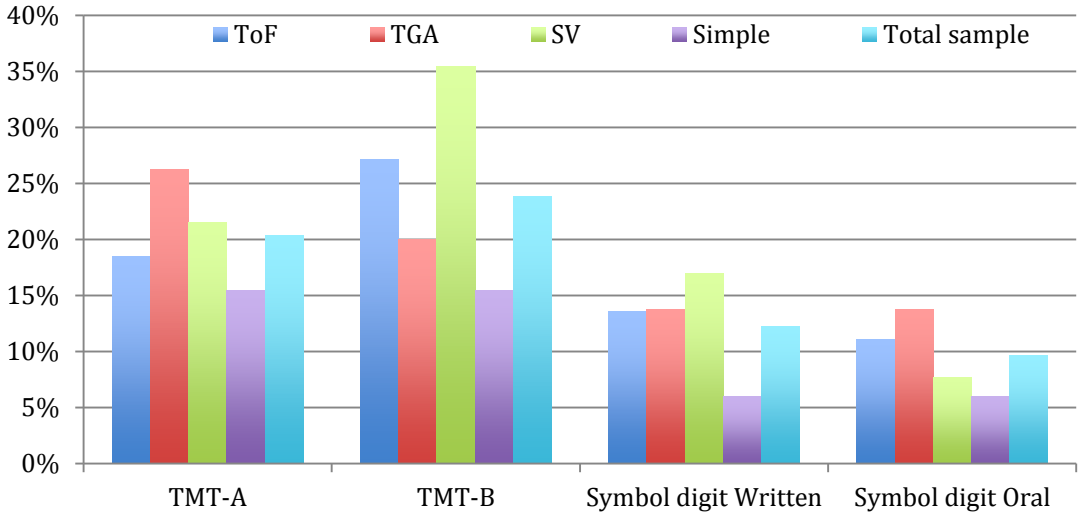
Attention was assessed using three tests, the TMT-A and TMT-B and the SDMT. The normative data for the TMT was derived from a study including a healthy sample (N=911) ranging from 18-89 years of age (Tombaugh, 2004). The SDMT normative data was taken from the test manual, based on 420 healthy individuals ranging from 18-75 years of age (Smith, 1978).

Figure 8.19 illustrates the proportion (%) of the total sample exhibiting impairment on the TMT and SDMT tests. A greater proportion of participants showed impairment on the TMT (part A =20% and B= 24%) than would be expected in a normal distribution (7%). In the SDMT test participants showed an impairment on both the written (10%) and oral (12%) subtest in >7% of

the total sample. SDMT scores falling 1 to 1.5 SD below the norms are considered indicative of a cerebral dysfunction (Smith, 1982).

8.3.3.2 Structural complexity groups

Figure 8.19 illustrates the proportion (%) of each structural complexity group exhibiting impairment on the TMT and SDMT tests; all four groups exhibited an impairment on both part A and B of the test. More than 7% of the sample in each group exhibited impairment, which is greater than can be expected in a normal distribution. Similarly, a considerable proportion in each group exhibited impairment on both parts of the SDMT test. The only exception was the Simple group that showed performance similar to that expected in a normal distribution, with less than 7% of the sample showing impairments on the SDMT scores.



Note – TMT= Trail Making Test

Figure 8.19 Proportion (%) of the sample with impairment on tests of attention

8.3.4 Memory in ACHD patients compared to normative data

8.3.4.1 Total sample

Memory and verbal learning in this study sample was assessed using RAVLT. The normative data for the RAVLT was taken from the test manual including healthy individuals (Schmidt, 1996). A single score was computed from this test; total acquisition. Figure 8.19 illustrates the

proportion of the total sample exhibiting impairment in memory. Within the total sample only a small proportion of participants exhibited impairment in memory and verbal learning (8.7%), only marginally exceeding the 7%, which could be expected in a normal distribution.

8.3.4.2 Structural complexity groups

Although more than 7% of the sample in most complexity group exhibited impairments in memory, the SV group only marginally exceeded (8%) the 7%, which could be expected in a normal distribution. The only exception was the Simple group, which exhibited the smallest proportion of participants with impairments (6%), which is similar to that expected in a normal distribution.

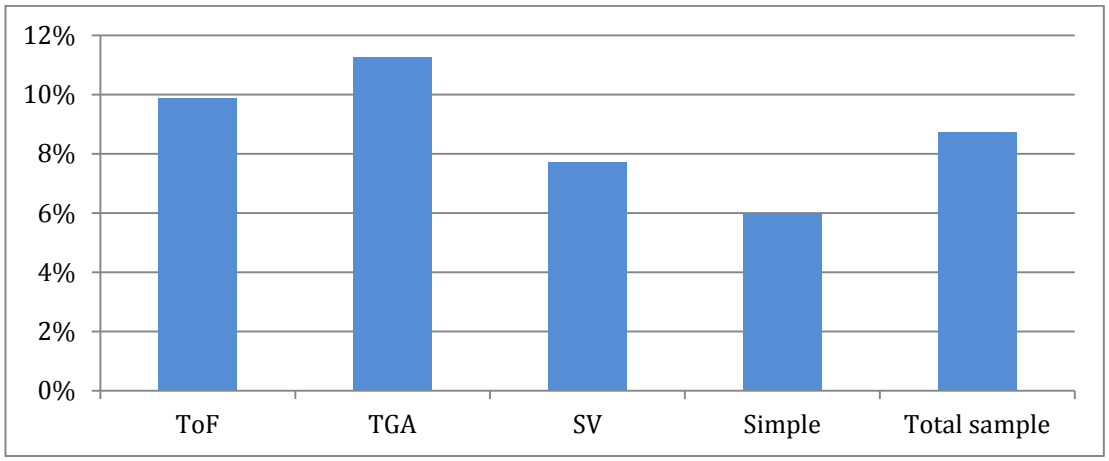


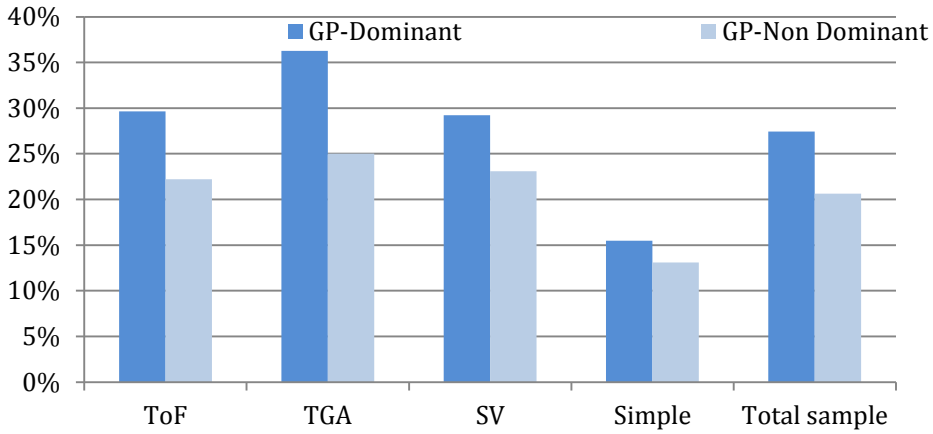
Figure 8.20 Proportion (%) of the sample with impairment on the memory test (RAVLT)

8.3.5 Motor function in ACHD patients compared to normative data

8.3.5.1 Total sample

Motor function and dexterity in this study was assessed using the Grooved Pegboard test. The normative data was taken from the test manual including scores of healthy individuals ranging from 15 to over 60 years of age (Grooved Pegboard user's manual, 2003). Data presented in Figure 8.21 illustrates the proportion (%) of the total sample exhibiting impairment in motor

function (dominant and non- dominant hand time scores). Interestingly the total study sample exhibited more impairment in motor functioning when using their dominant hand (27%) as compared to the non-dominant (21%). More than 7% of the sample, higher than would be expected in the normal population showed impairment on both scores.



Note – GP= Grooved Pegboard

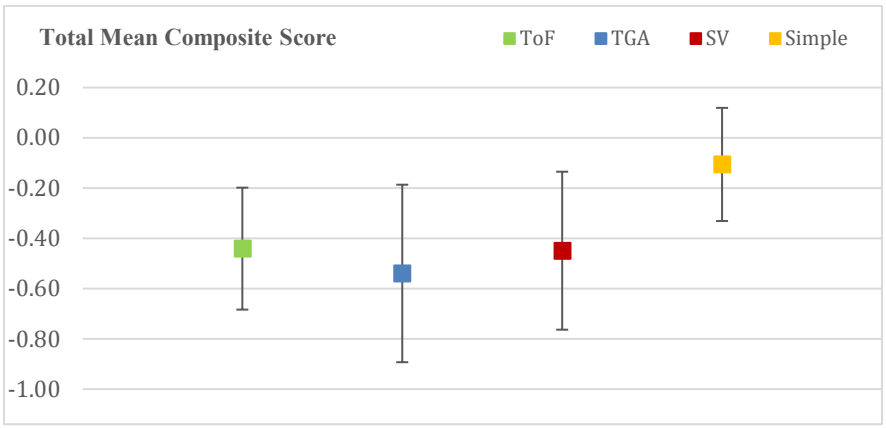
Figure 8.21 Proportion (%) of the sample with impairment on tests of motor functioning

8.3.5.2 Structural complexity groups

A similar pattern was noted across all the four groups, with a higher number of participants exhibiting impairments on the dominant hand in comparison to the non-dominant hand. The TGA group had the highest proportion of participants with impairments on both dominant and non-dominant hands (36% and 25% respectively). The simple group had the lowest proportion of participants with impairments on both the dominant and non-dominant (15% and 13% respectively) scores. All groups showed more than 7% of the sample exhibiting impairment on both tests scores.

8.4 Total mean composite NP score (all NP scores combined) in the total ACHD sample

Along with identifying specific impairments in different cognitive domains a cumulative mean NP score was also computed by summing the z-scores of all the NP indices to obtain a total mean composite score for the NP tests. A total composite score enabled comparison of overall cognitive functioning to be made between the four structural complexity groups (See Figure 8.22). Tests where a higher score demonstrated poorer performance were reverse scored such that in all tests a higher score represented a better performance. As stated in Chapter 7, Section 7.7.1 with regards to the WCST test only a single score (Total number of categories completed) was incorporated in the computation of the composite score given that the test scores were not independent of each other, and could therefore inflate the score.



Note**:** A lower score is indicative of a poorer overall performance on tests of cognitive functioning

Figure 8.22 Mean composite NP z-scores with 1SD error bars

The total sample had a mean composite cognitive score of -0.37. The error bars in Figure 8.22 illustrate the range and spread of scores across the different structural complexity groups, demonstrating the varied levels of cognitive functioning.

Section 8.6 details the analyses assessing statistically significant group differences on the different cognitive domains and the total composite score.

8.5 Corrective measures for multiple cognitive assessments

The previous section (Section 8.3) discussed the proportion of the normal population that can be expected to exhibit impairment on each individual test. However, when using multiple test batteries for assessment additional factors need to be taken into account such as the risk of overestimating the extent of cognitive impairment. As discussed in Chapter 7, there is a widely used approach provided by Ingraham and Aieken, (1996), to account for the use of multiple tests in a cognitive test battery. The authors argue that an inter-correlation among the scores may result in the estimates of the percentage of the population exhibiting impairment being higher than expected, due to the additional variance correlated scores may add. To account for this assumption the correlation among the test scores was examined. Within this study the correlation between tests was not very large (i.e. r=>0.80) and ranged between 0.01- 0.70. One exception was that of the WCST-64 test where the scores were highly correlated (>.8) amongst themselves (See Appendix-Q); therefore only one WCST score was chosen in order to calculate the estimated proportion of the sample that would be likely to show impairment. Nonetheless the results must be interpreted with some caution, as this only provides an estimation of the extent of NP impairments (accounting for number of tests).

Based on the number of test scores and the impairment criteria used in the present study, the estimation provided by Ingraham and Aiken suggests that ~4% of the sample can be expected to exhibit impairment on at least three tests using an impairment criterion of 1.5SD. Therefore, identification of >4% of cases with impairment (>1.5SD) on 3 or more tests could be indicative of the presence of overall cognitive impairment, even after accounting for multiple tests and chance findings.

Table 8.4 (below) shows the proportion of participants scoring 1.5 SD below the norms on at least one and three tests respectively in this study. As is evident, a considerable proportion of participants in each group had scores within the impaired range on at least three tests with the Simple group showing the lowest proportion of participants with impairments. Even after accounting for the 4% of cases that may be attributable to chance, a considerable proportion of participants (ToF= 24.4%, TGA=29.7%, SV=25.2% Simple=7.9%) exhibited impairments on three or more tests.

Table 8.4: Percentage of patients scoring 1.5 SD below the normative mean on at least one and three tests

Structural complexity Groups	Percentage >1.5 SD below the normative mean on at least 1 test score	Percentage >1.5 SD below the normative mean on at least 3 test scores
TOF	64.2	28.4
TGA	75.0	33.7
SV	69.2	29.2
Simple	59.5	11.9

Note: SD=Standard Deviation

8.6 Are there significant differences in cognitive functioning across different structural complexity groups?

Statistically significant differences in cognitive functioning among the four structural complexity groups were investigated using Analysis of Covariance (ANCOVA). It is acknowledged that the majority of the NP test data was non-normally distributed (See Appendix-L), however an ANCOVA (a parametric test) was chosen as it enables controlling for covariates. This was considered important as the covariates may have the potential to influence the outcome/dependent variable (NP test scores). Furthermore there is no non-parametric alternative to the ANCOVA (Pallant, 2007).

8.6.1 Rationale for covariate selection

The potential covariates in the ANCOVAs were years of education and mood (depression and anxiety). These were selected based on previous research suggesting their potential influence on cognitive performance (Lezak et al, 2012). Age was not included as a covariate because participant scores (i.e. the NP test scores used as dependent variables (DV) in this analysis) were already corrected for age when transformed into standardized z-scores, using normative data. The internal consistency reliability estimates (Cronbach α) for each of the mood and psychosocial scales were calculated. The results are presented in Table 8.5 (below). All scales met the criterion for internal reliability satisfactorily whereby, a Cronbach's α of 0.7 and above is generally suggested to be an adequate measure of reliability (Field, 2013).

Table 8.5: Internal reliability of the psychosocial scales and subscales

Measures including sub-scales	**Total no. of items**	**Cronbach α**
PANAS	20	-
Positive Affect (PA)	10	0.905
Negative Affect (NA)	10	0.861
STAI	6	0.809
CESD-10	10	0.851
SF-36	36	-
Physical Component Summary(PCS)	18	0.927
Mental Component Summary (MCS)	18	0.911

Note: PANAS= Positive And Negative Affect Scale, STAI=State and Trait Anxiety Inventory, CESD= Center for epidemiology Depression Scale, SF-36, Short form 36

Prior to entry into the model the association of all potential covariates with each cognitive outcome was assessed using simple (univariate) linear regressions. The significance level applied was $p<0.05$ to avoid exclusion of any potential covariate, which may influence results. Only significant variables ($p<0.05$) were included as covariates in the main analyses (See Table 8.6 below for correlation between covariates and outcome variables). The data presented in Table 8.6 shows a consistent association of education and positive affect with most of the test scores (13/15 and 10/15 respectively).

Further, the correlation between covariates was also assessed for collinearity (correlation between variables) as a significant correlation between two covariates makes one of them statistically redundant, as it would not affect the DV over and above the other covariate. Each ANCOVA was also tested for the assumption of homogeneity of regression slopes, and all analyses met the assumption satisfactorily (suggesting the relationship between the outcome variable and its covariates was similar across all groups). The results of the analyses are presented in Table 8.7 (page no. 181).

Two scores including the TMT-B (attention) and the mean total composite score showed a significant difference between the structural complexity groups. ANCOVA revealed a significant ($p<0.01$) group difference in divided attention as measured by the Trail Making Test (TMT-B), after controlling for years of education ($F(1,303)=5.54$ $p=.019$, Partial $\eta_p^2=.018$) and positive affect ($F(1,303)=9.97$, $p=.002$, Partial ŋ2p=.032) (See table 8.7). The measure of state anxiety (STAI) had no significant association with the outcome ($p= .891$). The adjusted means of the TMT-B score are presented in Figure 8.23.

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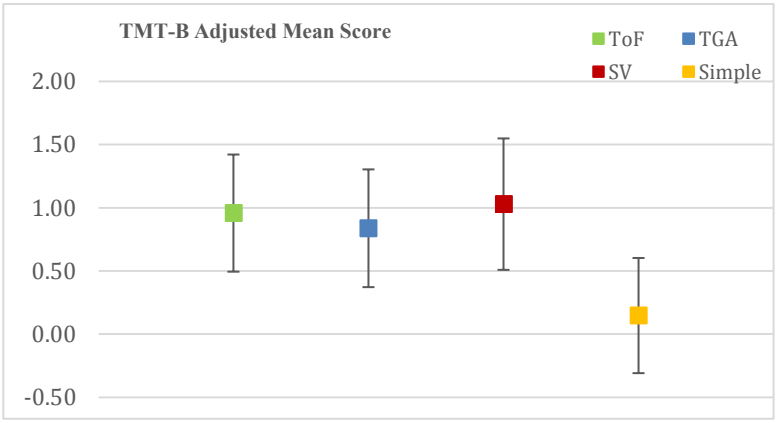


Note: A higher score (i.e. more time taken) is indicative of a poorer performance on the TMT test of divided attention

Figure 8.23 Adjusted mean standardized scores on the TMT-B test with 99% error bars

Table 8.6: Correlation matrix of NP scores and potential covariates (mood and education)

	TMT - A	TMT - B	COWA	Stroop CW	WAIS	GP-D	GP-ND	WCST - Error	WCST - CLR	WCST- No.Cat	WCST -TTC	WCST- FTM	RAVLT	SDMT W	SDMT -O
Edu	-.065	**-.175****	**.286****	**.238****	**.326****	**-.181****	**-.155****	**-.311****	**.294****	**.288****	**-.126***	-.071	**.299****	**.303****	**.257****
PANAS -PA	-.058	**-.217****	**.163****	**.165****	**.168****	**-.158****	**-.141***	**-.113***	.109	.076	-.075	.063	**.172****	**.249****	**.266****
PANAS -NA	-.023	.089	.025	**-.216****	-.099	-.053	-.081	.078	-.074	-.081	**.126***	-.033	-.038	-.086	-.086
STAI	.044	**.124***	-.071	**-.266****	-.091	.055	.059	.108	-.092	-.014	.057	-.104	-.058	-.088	**-.118***
CESD	.011	.073	-.059	**-.183****	**-.116***	.022	-.022	.111	-.103	-.086	**.152****	-.062	-.083	**-.120***	**-.135***

Note: *p<0.05, ** p<0.01 Edu-Education, TMT= Trail Making Test, GP=Grooved Pegboard, WCST-CLR= Wisconsin Card Sorting Test – Conceptual Level Responses, WCST-TTC= Wisconsin Card Sorting Test – Trials to Complete first category, WCST-FTM= WCST- Wisconsin Card Sorting Test -Failure to Maintain Set, SDMT-W= Symbol Digit Modalities Test-Written score, SDMT-O= Symbol Digit Modalities Test-Oral score

Table 8.7 Analysis of covariance for NP test scores

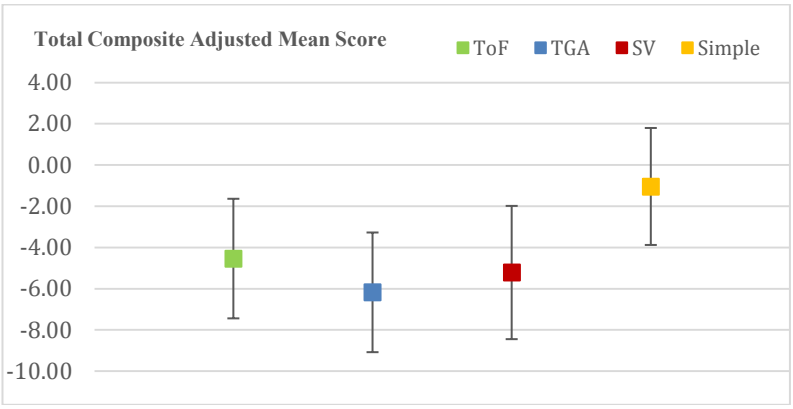
NP variable	Adjusted means for groups				Test statistic for group variable	p- value	Partial η^2p
	ToF	TGA	SV	Simple			
Domain – Attention							
TMT-A	0.634	0.839	0.824	0.42	F(3,306)=1.74	0.157	0.017
TMT B	0.958[a]	0.838[a,b]	1.029[a]	0.147[b]	F(3,303)=5.01	0.002**	0.047
SDMT-O	0.3	0.279	0.463	0.623	F(3,302)=.954	0.415	0.009
SDMT-W	-0.024	-0.03	0.026	0.462	F(3,303)=2.17	0.091	0.021
Domain - Motor function and dexterity							
GP-D	1.103	1.134	1.242	0.503	F(3,304)=3.30	0.021	0.032
GP-ND	0.741	0.929	0.869	0.465	F(3,304)=1.94	0.122	0.019
Domain - Executive functioning							
Stroop-Word	-0.265	-0.499	-0.579	0.085	F(3,301)=3.56	0.015	0.034
COWA	-0.768	-0.855	-0.502	-0.547	F(3,304)=2.19	0.089	0.021
WCST-Error	0.708	0.692	0.621	0.38	F(3,304)=1.56	0.197	0.015
WCST-CLR	-0.666	-0.67	-0.609	-0.349	F(3,305)=1.57	0.195	0.015
WCST-No.Cat	-0.699	-0.668	-0.575	-0.212	F(3,305)=3.49	0.016	0.033
WCST-FTM	-0.765	-1.286	-0.839	-0.758	F(3,247)=1.09	0.354	0.013
WCST-TTC	0.113	0.293	0.51	-0.051	F(3,303)=.945	0.419	0.009
Domain – IQ							
WAIS-III	-0.082	-0.102	0.091	0.114	F(3,299)=1.04	0.375	0.01
Domain – Memory							
RAVLT	0.631	0.38	0.532	0.573	F(3,304)=1.03	0.377	0.01
Total composite NP score							
Total NP score	-4.542[a,b]	-6.18[a]	-5.219[a,b]	-1.044[b]	F(1,303)= 3.99	.002**	.047

Note: significant results (group differences) are reported using superscripts- with same superscripts (letter) indicating lack of a significant group difference); ** p<0.01 TMT= Trail Making Test, GP=Grooved Pegboard, WCST-CLR= Wisconsin Card Sorting Test – Conceptual Level Responses, WCST-TTC= Wisconsin Card Sorting Test – Trials to Complete first category, WCST-No.Cat= Wisconsin Card Sorting Test – Total Number of Categories, WCST-FTM= Wisconsin Card Sorting Test -Failure to Maintain Set, SDMT-W= Symbol Digit Modalities Test-Written score, SDMT-O= Symbol Digit Modalities Test-Oral score, RAVLT= Rey Auditory Verbal Learning Test.

Post-hoc tests (Sidak correction) revealed that the Simple group performed significantly better than the ToF (p= .009) and SV groups (p=. 007) on the TMT-B, however comparison to the TGA group did not reach significance (p= .040). A significant group difference in the mean composite neuropsychological test scores was found after controlling for covariates including education, and affect. The covariates Education: F= (1,303)= 33.29, p=.000, partial η^2p =.099, and positive affect: F (1,303)= 8.68, p=.003, partial η^2p =.028 were also significantly associated with the outcome between the groups.

Post hoc tests (Sidak correction) revealed a significant difference between the TGA and Simple group only (p=. 008) on the mean NP composite score. The adjusted mean scores of the groups are presented in Figure 8.24 below. Post-hoc tests (Sidak correction) revealed that the Simple group performed significantly better than the ToF (p= .009) and SV groups (p=. 007) on the TMT-B, however comparison to the TGA group did not reach significance (p= .040).

A significant group difference in the mean composite neuropsychological test scores was found after controlling for covariates including education, and affect. The covariates Education: F= (1,303)= 33.29, p=.000, partial η^2p =.099, and positive affect: F (1,303)= 8.68, p=.003, partial η^2p =.028 were also significantly associated with the outcome between the groups. Post hoc tests (Sidak correction) revealed a significant difference between the TGA and Simple group only (p=. 008) on the mean NP composite score. The adjusted mean scores of the groups are presented in Figure 8.24.



Note: A lower score is indicative of a poorer performance on the TMT test of divided attention

Figure 8.24 Adjusted mean standardized scores for NP composite score with 99% error bars

Overall the results showed that the prevalence of cognitive impairments in ACHD patients was greater in comparison to that expected in a healthy normal population. Impairments were identified in a range of cognitive domains including attention, executive function and motor function. The domain of memory was the only one that showed performance comparable to a normal healthy population. There were two significant differences in cognitive functioning between the four complexity groups, the TMT-B test of attention and the total composite score.

8.7 Are demographic, clinical and mood factors associated with cognitive performance in ACHD patients?

The associations between demographic, clinical, and mood factors and cognitive functioning in ACHD patients were examined using hierarchical multiple regressions. Two approaches were taken; first the entire cohort was assessed to identify factors associated with cognitive functioning in ACHD irrespective of the specific structural complexity group. Second, each structural complexity group was assessed independently. This was done because the clinically diverse nature of ACHD conditions could lead to different factors being associated with cognitive outcomes across the complexity groups. In addition, certain variables are only applicable to certain groups; for example, cyanosis (i.e. inadequate oxygenation in the blood) is

not relevant in the Simple group as this group includes only acyanotic conditions, which by nature do not involve lack of oxygenation in the blood.

When assessing each structural complexity group independently the sample size for the sub-groups was less than required according to convention for a regression analysis (Rule of thumb is usually ≥100) (Field, 2013). However more recent evidence from Austin and Steyerberg, (2015) states that two subjects per variable in a liner regression is sufficient to provide adequate estimation of regression coefficients, standard errors, and confidence intervals.

Full details of the methodology adopted for this analysis are presented in Chapter 7, Section 7.7.2. The full tables of the regression models and change statistics for the sub-group analyses can be found in Appendix-R. Given the large number of results from the sub-group analyses, a summary of the key factors consistently associated with specific cognitive domains in different structural complexity groups are presented in Tables 8.16-8.19 (page 199). Results presented in these tables are based on the final regression models only.

A univariate screening was conducted using linear regression for each cognitive test (DV) using the demographic, clinical and mood variables (IV) to assess significance before entering into the multivariate analysis. This analysis was conducted for the total sample and repeated for each sub-group individually. Only those variables significant at a $p<0.05$ in the univariate screening were included in the multivariate model (See Appendix-N). The results of this analysis are presented in the following sections.

8.7.1 Demographic, clinical and mood factors associated with IQ

Total sample

Table 8.8 (below) illustrates the regression model for the demographic, clinical and mood factors associated with estimated Full Scale IQ (FSIQ) in the total study sample. The final regression model (F=11.834(15,294), p=<0.001) explained 36% of the total variance in the sample's IQ scores. Years of education achieved and CNS complications after surgery explained unique variance in IQ scores over and above the other clinical and mood factors in the equation. The results showed that lower years of education achieved and the presence of a CNS complication were associated with lower IQ. The addition of mood to the model did not explain any significant additional variance in IQ scores.

Table 8.8: Demographic, clinical and mood factors associated with WAIS-III in the total study sample

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.289	.285	.289	62.440		.000**
	Education (Yrs.)					.521	.000**
	Employment					.088	.071
2		.299	.290	.010	2.136		.120
	Education (Yrs.)					.511	.000**
	Employment					.077	.121
	NYHA					-.029	.579
	HF clinic					-.089	.077
3		.370	.344	.071	4.166		.000**
	Education (Yrs.)					.488	.000**
	Employment					.072	.139
	NYHA					-.055	.299
	HF clinic					-.063	.223
	Interventions total					-.016	.815
	Palliation Before Repair					-.047	.428
	Post-Op CNS Complications					-.204	.000**
	Post-Op Infection					-.073	.154
	Cath lab total					-.007	.895
	Hospital days Q2					-.097	.102
	Hospital days Q3					-.057	.406
	Hospital days Q4					.044	.559
4		.376	.345	.007	1.065		.364
	Education (Yrs.)					.487	.000**
	Employment					.081	.100
	NYHA					-.054	.361
	HF clinic					-.040	.450

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	Interventions total					-.008	.907
	Palliation Before Repair					-.048	.422
	Post-Op CNS Complications					-.210	.000**
	Post-Op Infection					-.072	.157
	Cath lab total					-.007	.898
	Hospital days Q2					-.088	.144
	Hospital days Q3					-.049	.474
	Hospital days Q4					.059	.440
	ACE medication					-.077	.147
	Diuretic medication					.041	.499
	RVEF					.055	.296
5		.400	.360	.023	2.811		.026
	Education (Yrs.)					.464	.000**
	Employment					.038	.451
	NYHA					-.024	.682
	HF clinic					-.051	.334
	Interventions total					-.022	.747
	Palliation Before Repair					-.050	.395
	Post-Op CNS Complications					-.193	.000**
	Post-Op Infection					-.091	.077
	Cath lab total					.002	.973
	Hospital days Q2					-.103	.088
	Hospital days Q3					-.045	.507
	Hospital days Q4					.066	.385
	ACE medication					-.056	.285
	Diuretic medication					.033	.585
	RVEF					.050	.337
	Positive affect (PA)					.140	.019
	Negative affect (NA)					-.015	.823
	Anxiety (STAI)					-.046	.469
	Depression (CESD)					.008	.910

Note: Q= Quartile HF= Heart Failure, ACE= angiotensin-converting-enzyme inhibitors, NYHA=New York Health Association classification, RVEF= Right Ventricular Ejection **p=<0.01

Structural complexity groups

The demographic, clinical and mood factors associated with IQ for each of the individual complexity groups are presented in Tables 8.16-8.19. In the ToF group the simple linear regression showed no significant association between clinical and mood variables with IQ, hence these are not presented in the Table 8.16 (page 199). In the TGA group the final model showed that CPB minutes and years of education significantly explained unique variance in IQ scores; with a positive association between the two variables, suggesting an increased duration

of CPB and higher years of education were associated with higher IQ scores (See Table 8.17). The final model in the regression analysis for the SV group revealed a significant negative association with post-operative CNS complication; suggesting CNS complications after surgery were associated with lower IQ scores (See Table 8.18 on page 203). Furthermore, a positive association between positive affect and years of education with IQ was also noted in the SV group. Lastly, in the simple group none of the variables explained significant unique variance in the IQ (See Table 8.19).

8.7.2 Demographic, clinical and mood factors associated with executive functioning

Executive functioning in this study was measured using the WCST, Stroop (response inhibition) and COWA (verbal fluency) tests. These tests include multiple scores, each of which assesses some aspect of executive functioning. A total of 5 WCST scores were used in this study, these included the WCST- conceptual level responses, total number of errors, total number of categories completed, failure to maintain set and trials to complete first set. The factors associated with each of these test scores will be discussed below; firstly for the total sample and then for each structural complexity group.

8.7.2.1 Wisconsin Card Sorting Test (WCST)

Total sample

Table 8.9 illustrates the regression model for the WCST- Conceptual level responses score. The final model significantly ($F= 6.605(10,299)$, $p=<0.001$) explained 15.4% of the variance in conceptual level responses. In the final step, education and CNS complications continued to explain unique variance in executive functioning over and above the other variables in the equation. Fewer years of education and post-operative CNS complications were associated with impaired conceptual level responses. The mood variables did not explain unique variance in the outcome.

Table 8.9 Demographic, clinical and mood factors associated with WCST Conceptual level responses in the total study sample

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	B	*Sig.*
1		.086	.083	.086	29.139		.000**
	Education (Yrs.)					.294	.000**
2		.162	.146	.076	5.478		.000**
	Education (Yrs.)					.252	.000**
	Palliation before repair					-.049	.426
	Post-op CNS complication					-.222	.000**
	Hospital days Q2					-.055	.410
	Hospital days Q3					-.088	.232
	Hospital days Q4					-.121	.093
3		.181	.154	.019	1.712		.147
	Education (Yrs.)					.244	.000**
	Palliation before repair					-.042	.495
	Post-op CNS complication					-.215	.000**
	Hospital days Q2					-.043	.520
	Hospital days Q3					-.067	.364
	Hospital days Q4					-.057	.459
	Medication total					-.013	.830
	Anti-arrhythmia medication					-.043	.477
	LVEF					.096	.092
	Diuretic medication					-.064	.278

Note: Q= Quartile, LVEF= Left Ventricular Ejection Fraction

The demographic, clinical and mood factors associated with the WCST-error score are presented in Table 8.10 (below). The final model was significant (F=6.467(10,299), p=<0001), and explained 14.9% of the total variance in the number of errors made on the WCST test. The variables education and CNS complications continued to explain significant unique variance in the final model even after the addition of the mood variable (positive affect) thus suggesting that education and post-operative CNS complication explained unique variance in the errors made.

Table 8.10 Demographic clinical and mood factors associated with WCST Error score in the total study sample

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	**B**	*Sig.*
1		.097	.094	.097	32.981		.000**
	Education (Yrs.)					-.311	.000**
2		.161	.142	.064	3.863		.001**
	Education (Yrs.)					-.270	.000**
	Hospital days Q2					.041	.543
	Hospital days Q3					.102	.172
	Hospital days Q4					.099	.187
	Post-op CNS complication					.187	.001**
	Post-op infection					.041	.481
	Palliation before repair					.040	.516
3		.178	.150	.017	2.026		.110
	Education (Yrs.)					-.258	.000**
	Hospital days Q2					.031	.645
	Hospital days Q3					.081	.280
	Hospital days Q4					.040	.615
	Post-op CNS complication					.184	.001**
	Post-op infection					.039	.499
	Palliation before repair					.034	.581
	Medication total					.027	.645
	LVEF					-.100	.076
	Diuretic medication					.068	.249
4		.179	.149	.001	.439		.508
	Education (Yrs.)					-.252	.000**
	Hospital days Q2					.034	.616
	Hospital days Q3					.082	.276
	Hospital days Q4					.037	.637
	Post-op CNS complication					.182	.001**
	Post-op infection					.044	.457
	Palliation before repair					.037	.520
	Medication total					.022	.708
	LVEF					-.098	.081
	Diuretic medication					.067	.255
	Positive affect (PA)					-.036	.508

Note: Q= Quartile, LVEF= Left Ventricular Ejection Fraction, **p=<0.01

The demographic, clinical and mood factors associated with the WCST number of categories score are presented in Table 8.11 (below). The final model (F=3.261(25,284), p=<0.001) explained 15.5% of the total variance in the number of categories achieved. Two variables education and CNS complications continued to explaining unique variance in the score over and above all the other variables in the equation demonstrating that greater years of education was

associated with greater number of categories completed. CNS complications after surgery were associated with fewer categories completed. None of the mood variables explained unique variance in the outcome.

Table 8.11 Demographic clinical and mood factors associated with WCST No. of categories score in the total study sample

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.086	.080	.086	14.514		.000**
	Age					-.058	.298
	Education (Yrs.)					.277	.000**
2		.129	.106	.043	2.472		.024
	Age					-.074	.219
	Education (Yrs.)					.258	.000**
	TOF					-.185	.005**
	TGA					-.156	.032
	SV					-.118	.103
	NYHA					-.034	.556
	HF clinic					-.033	.615
	Arrhythmias					-.056	.392
3		.184	.143	.055	2.828		.007
	Age					-.067	.365
	Education (Yrs.)					.217	.000**
	TOF					-.081	.303
	TGA					-.045	.585
	SV					.028	.766
	NYHA					-.034	.567
	HF clinic					-.024	.710
	Arrhythmias					-.058	.388
	Palliation total					-.079	.279
	Post-op CNS complication					-.188	.000**
	Post-op infection					-.068	.249
	Cath lab total					-.041	.523
	Hospital days Q2					-.038	.604
	Hospital days Q3					-.094	.252
	Hospital days Q4					-.046	.615
4		.192	.142	.008	.948		.418
	Age					-.075	.216
	Education (Yrs.)					.214	.000**
	TOF					.032	.899
	TGA					.090	.725
	SV					.110	.642
	NYHA					-.047	.439
	HF clinic					-.024	.707
	Arrhythmias					-.055	.411
	Palliation total					-.085	.250
	Post-op CNS complication					-.196	.001**
	Post-op infection					-.072	.225
	Cath lab total					-.048	.460

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	Hospital days Q2					-.041	.576
	Hospital days Q3					-.091	.269
	Hospital days Q4					-.039	.665
	Cyanosis days Q2					-.130	.587
	Cyanosis days Q3					-.157	.520
	Cyanosis days Q4					-.047	.848
5		.223	.155	.031	1.614		.131
	Age					-.042	.507
	Education (Yrs.)					.213	.000**
	TOF					.064	.799
	TGA					.105	.681
	SV					.198	.407
	NYHA					-.020	.772
	HF clinic					.011	.873
	Arrhythmias					.003	.971
	Palliation total					-.083	.267
	Post-op CNS complication					-.182	.002**
	Post-op infection					-.070	.239
	Cath lab total					-.035	.593
	Hospital days Q2					-.040	.592
	Hospital days Q3					-.083	.320
	Hospital days Q4					-.011	.907
	Cyanosis days Q2					-.159	.506
	Cyanosis days Q3					-.198	.420
	Cyanosis days Q4					-.077	.754
	Medication total					-.056	.496
	ACE medication					-.038	.590
	Diuretic medication					-.003	.967
	B-Blocker medication					-.061	.355
	Anti-arrhythmia medication					-.050	.445
	RVEF					-.028	.705
	LVEF					.165	.021

Note: Q= Quartile HF= Heart Failure, ACE= angiotensin-converting-enzyme inhibitors, NYHA=New York Health Association classification, RVEF= Right Ventricular Ejection Fraction LVEF= Left Ventricular Ejection Fraction, **p<0.01

Table 8.12 illustrates the regression model for the demographic, clinical and mood factors associated with WCST failure to maintain set scores. The final model was significant; however no individual predictors were significant. The addition of the variables RVEF and LVEF in the final step rendered the total number of repair surgeries non-significant from the previous model. The final model showed no significant unique factors associated with the ability to maintain set. None of the mood variables explained any unique variance in the outcome.

Table 8.12 Demographic clinical and mood factors associated with WCST Failure to maintain set score in the total study sample

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.017	.014	.017	5.478		.020
	NYHA					.132	.020
2		.038	.032	.021	6.563		.001**
	NYHA					.119	.034
	Repair surgery total					.144	.001**
3		.047	.034	.009	1.383		.252
	NYHA					.097	.096
	Repair surgery total					.136	.020
	RVEF					-.038	.590
	LVEF					-.070	.298

Note: NYHA=New York Health Association classification, RVEF= Right Ventricular Ejection Fraction LVEF= Left Ventricular Ejection Fraction, **p=<0.01

The regression model for the WCST trials to complete the first category score is presented in Table 8.13. The final model was significant and explained 12.3% of the total variance in the scores (F=6.758(8,301), p=<0.001). Post-operative CNS complications continued to explain unique variance in the scores over and above all other variables in the equation, demonstrating that a post-operative CNS complication was associated with an increased number of trials taken to complete the first category of the test. None of the other clinical or mood variables explained any unique variance in the outcome. The addition of the mood variables did not explain significant additional unique variance in the model.

Table 8.13 Demographic clinical and mood factors associated with WCST (Trials to complete 1st category) score in the total study sample

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.016	.013	.016	4.955		.027
	Education (Yrs.)					-.126	.027
2		.095	.089	.079	26.877		.000**
	Education (Yrs.)					-.096	.081
	Post-Op CNS complications					.283	.000**
3		.139	.119	.044	3.050		.011
	Education (Yrs.)					-.064	.247
	Post-Op CNS complications					.262	.000**
	Medication total					-.010	.885
	Diuretic medication					.132	.028

	Anti-arrhythmic medication					.042	.487
	Anti-coagulant medication					.066	.348
	LVEF					-.077	.177
4		.148	.123	.010	1.712		0.181
	Education (Yrs.)					-.058	.294
	Post-Op CNS complications					.252	.000**
	Medication total					-.024	.748
	Diuretic medication					.125	.038
	Anti-arrhythmic medication					.056	.364
	Anti-coagulant medication					.064	.358
	LVEF					.072	.208
	Negative affect (NA)					.036	.620
	Depression (CESD)					.073	.321

Note: LVEF= Left Ventricular Ejection Fraction, **p=<0.01

8.7.2.2 Controlled Oral Word Association test (COWA)

The factors associated with executive functioning and verbal fluency as measured by the COWA is presented in Table 8.14.

The final model in the regression analysis for the COWA test was significant, explaining almost 15% of the variance in verbal fluency and executive functioning. The addition of the mood variables (Positive Affect) in the final model did not explain any significant additional unique variance in the outcome. Education and age consistently continued to explain unique variance over the other variables in the equation, with higher years of education and an older age associated with higher scores and better performance. Results demonstrated that no significant unique variance in COWA scores was explained by clinical or mood factors.

Table 8.14 Demographic, clinical and mood factors associated with COWA test in the total study sample

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	β	*Sig.*
1		.135	.130	.135	24.021		.000**
	Age					.236	.000**
	Education (Yrs.)					.333	.000**
2		.151	.134	.016	1.405		.232
	Age					.195	.001**
	Education (Yrs.)					.320	.000**
	Post-op CNS complication					-.083	.125
	Age at repair Q2					.035	.589
	Age at repair Q3					.003	.961
	Age at repair Q4					.108	.123
3		.165	.140	.014	1.700		.167
	Age					.190	.002
	Education (Yrs.)					.323	.000**
	Post-op CNS complication					-.085	.118
	Age at repair Q2					-.080	.333
	Age at repair Q3					-.112	.198
	Age at repair Q4					.009	.916
	Cyanosis days Q2					-.120	.121
	Cyanosis days Q3					.067	.333
	Cyanosis days Q4					.040	.551
4		.176	.149	.011	4.003		.046
	Age					.171	.005**
	Education (Yrs.)					.300	.000**
	Post-op CNS complication					.081	.137
	Age at repair Q2					.092	.267
	Age at repair Q3					.122	.159
	Age at repair Q4					.013	.882
	Cyanosis days Q2					.137	.075
	Cyanosis days Q3					.063	.360
	Cyanosis days Q4					.038	.568
	Positive affect (PA)					.110	.046

Note: Q= Quartile, **p=<0.01

8.7.2.3 Stroop test

The last test of executive function was the Stroop test. The factors associated with executive functioning as measured by the Stroop test (colour-word score) are presented in Table 8.15. The final model was significant and included the addition of the mood variables (F=3.678(19,290),

p=<0.001). The final model collectively explained 17.2% of the variance explained in executive functioning.

The variables education and post-operative CNS complications continued to explain unique variance in the outcome over and above the other variables in the equation, in the final step. The results showed that higher years of education were associated with a higher score demonstrating better performance; while the presence of post-operative CNS complications was associated with lower scores demonstrating poorer performance.

Table 8.15 Demographic, clinical and mood factors associated with Stroop test (Color-Word) in the total study sample

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.075	.069	.075	12.427		.000**
	Education (Yrs.)					.224	.000**
							<0.001
	Employment					.136	.014
2		.111	.096	.036	4.119		.007**
	Education (Yrs.)					.226	.044
	Employment					.147	.007**
	TOF					-.104	.112
	TGA					-.171	.009**
	SV					-.209	.001**
3		.117	.093	.006	.668		.572
	Education (Yrs.)					.220	<0.001
	Employment					.139	.015
	TOF					-.097	.143
	TGA					-.134	.057
	SV					-.176	.010
	Arrhythmias					-.038	.553
	NYHA					-.005	.934
	HF Clinic					-.059	.367
4		.184	.142	.067	3.443		.001**
	Education (Yrs.)					.201	.000**
	Employment					.145	.010
	TOF					-.054	.497
	TGA					-.080	.391
	SV					-.146	.116
	Arrhythmias					-.064	.311
	NYHA					-.038	.534
	HF Clinic					-.054	.404
	Palliation Before Repair					.039	.623

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	Post-Op CNS Complications					-.182	.002**
	Post-Op Infection					-.080	.179
	Post-Op Ventricular dysfunction					-.047	.422
	Hospital days Q2					.020	.792
	Hospital days Q3					-.112	.175
	Hospital days Q4					.096	.291
5		.198	.149	.014	1.754		.156
	Education (Yrs.)					.199	.000**
	Employment					.143	.012
	TOF					-.054	.502
	TGA					-.065	.502
	SV					-.084	.404
	Arrhythmias					-.059	.357
	NYHA					-.027	.664
	HF Clinic					-.053	.415
	Palliation Before Repair					.044	.576
	Post-Op CNS Complications					-.197	.001**
	Post-Op Infection					-.072	.225
	Post-Op Ventricular dysfunction					-.062	.292
	Hospital days Q2					.022	.765
	Hospital days Q3					-.105	.202
	Hospital days Q4					.114	.212
	Current saturation Q2					.019	.754
	Current saturation Q3					-.076	.225
	Current saturation Q4					-.139	.065
6		.198	.146	.000	.000		.990
	Education (Yrs.)					.199	.000**
	Employment					.143	.012
	TOF					-.054	.510
	TGA					-.065	.503
	SV					-.084	.407
	Arrhythmias					-.059	.377
	NYHA					-.027	.665
	HF Clinic					-.053	.418
	Palliation Before Repair					.044	.580
	Post-Op CNS Complications					-.197	.001**
	Post-Op Infection					-.072	.228
	Post-Op Ventricular dysfunction					-.062	.293
	Hospital days Q2					.022	.765
	Hospital days Q3					-.105	.209
	Hospital days Q4					.114	.219
	Current saturation Q2					.019	.755

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	Current saturation Q3					-.076	.226
	Current saturation Q4					-.139	.066
	Medication total					-.001	.990
7		.233	.172	.035	3.273		.012
	Education (Yrs.)					.181	.001**
	Employment					.112	.053
	TOF					-.048	.551
	TGA					-.076	.432
	SV					-.075	.452
	Arrhythmias					-.058	.375
	NYHA					.013	.833
	HF Clinic					-.062	.339
	Palliation Before Repair					.040	.611
	Post-Op CNS Complications					-.168	.004**
	Post-Op Infection					-.084	.157
	Post-Op Ventricular dysfunction					-.065	.267
	Hospital days Q2					.013	.860
	Hospital days Q3					-.108	.190
	Hospital days Q4					.094	.306
	Current saturation Q2					.025	.681
	Current saturation Q3					-.059	.336
	Current saturation Q1					-.119	.111
	Medication total					.021	.742
	Positive affect (PA)					.024	.723
	Negative affect (NA)					-.085	.273
	Anxiety (STAI)					-.159	.026
	Depression (CESD)					.047	.589

Note: Q= Quartile HF= Heart Failure, NYHA=New York Health Association classification, **p=<0.01

Executive functioning

Structural complexity groups

The results of the sub-group regression analyses on measures of executive functioning are presented in Tables 8.16-8.19. Results for the ToF group showed no significant association of clinical or mood factors with measures of executive functioning. Only education was significantly associated with the WCST-error and conceptual level response score (See Table 8.16 on page 201). The TGA group showed a significant negative association of post-operative CNS complications with the WCST-number of categories completed score and the conceptual level responses score. In contrast a significant positive association was noted between post-

operative CNS complications and the WCST- errors and trials to complete 1st category score. Thus suggesting that the presence of CNS complications after a surgical procedure was associated consistently with impaired executive functioning (4/5 scores) (See Table 8.17). None of the demographic, clinical or mood variables were significantly associated with the Stroop test. A significant positive association was noted between negative affect, education and the COWA scores.

A similar pattern was noted on the WCST scores in the SV group, with 3/5 scores showing a significant association of CNS complications post-surgery with reduced executive functioning (See Table 8.18). Additionally, current saturation showed a significant negative association with conceptual level responses; again suggesting its association with reduced executive functioning. None of the other two tests (Stroop & COWA) were associated with any demographic, clinical or mood variables.

Lastly, the Simple group showed a significant positive association between age at repair, and WCST-Conceptual level responses, Number of categories completed, and a negative association with WCST-errors. These results demonstrate that a younger age at repair was associated with reduced executive functioning (WCST scores) (See Table 8.19). The Simple group also exhibited a positive association of anti-coagulant medication and score for trials required to complete the first category suggestive of reduced executive function being associated with taking anti-coagulant medication.

Table 8.16 Demographic, clinical & mood factors associated with cognitive functioning in multiple hierarchical regression analysis for ToF group by cognitive domain (N=81)

Factors associated with cognitive functioning	Attention		Executive functioning						Motor Function	Memory
	TMT-B	SDMT-Written	STROOP	WCST ERROR	WCST CLR	WCST FTM	WCST No Cat	WCST TTC	GP-ND	RAVLT
Model Significance (p-value)	.108	<0.01	<0.001	.003	.060	.018	.140	.105	.027	<0.01
Adjusted R^2	.216	.178	.256	.117	.084	.133	.025	.064	.087	.192
Age	△					▽				
Gender			△			▽		△		
Education	△	▲	△	▲	▲	△				▲
Employment	△									▽
Arrhythmias		▽			▽					
NYHA				▽	▽			▽		
HF Clinic					▽			▽		
Age at repair Q2										
Age at repair Q3										
Age at repair Q4										▲
Palliation total						△				
Palliation before repair						▽				
Post-op CNS complications			▽							
Post-op Ventricular dysfunction			▽					△		
Cyanotic days Q2									△	
Cyanotic days Q3									△	
Cyanotic days Q4									△	
Medication total					△			△		
ACE medication					▽		▽		△	
B-blocker medication								△		
Anti coagulant medication							▽	▽		
LVEF					△					
Positive affect (PA)	△	△	`							

Factors associated with cognitive functioning	Attention		Executive functioning						Motor Function	Memory
	TMT-B	SDMT-Written	STROOP	WCST ERROR	WCST CLR	WCST FTM	WCST No Cat	WCST TTC	GP-ND	RAVLT
Negative affect (NA)			▽							
Anxiety (STAI)			▽			△				
Depression (CESD)			▽							

Note: All results are based on the final model of the hierarchical regression analysis Interpretation Key: ▲Increase in value of IV = significant improvement in cognitive test performance ($p<0.01$), ▼Increase in value of IV = significant decline in cognitive test performance ($p<0.01$) △Increase in value of IV = non-significant improvement in cognitive test performance ($p<0.01$) ▽= Increase in value of IV = non-significant decline in cognitive test performance ($p<0.01$), **blank cells**= not included in the model, NYHA= New York Health Assessment, CNS= Central Nervous System, Q=Quartile, CPB= Cardio Pulmonary Bypass, ACE= Angiotensin-Converting-Enzyme Inhibitor, RVEF= Right Ventricular Ejection Fraction LVEF= Left Ventricular Ejection Fraction.

Table 8.17 Demographic, clinical and mood factors associated with cognitive tests in the multiple hierarchical regression analysis for the TGA group (N=80)

Factors associated with cognitive functioning	**Attention**				**Executive functioning**							**Motor**		**IQ**	**Memory**
	TMT-A	**TMT-B**	**SDMT- W**	**SDMT - O**	**STROOP**	**WCST Error**	**WCST CLR**	**WCST FTM**	**WCST No Cat**	**WCST TTC**	**COWA**	**GP-D**	**GP-ND**	**WAIS**	**RAVLT**
Model Significance (p value)	.010	<0.001	<0.01	<0.001	<0.01	<0.01	<0.001	.004	<0.001	<0.001	<0.001	<0.01	.005	<0.001	<0.001
Adjusted R^2	.116	.279	.286	.276	.207	.204	.205	.109	.257	.200	.263	.175	.174	.510	.273
Employment	△	▲	△	△							△			△	
Education			△	△	△			△	△		▲	△	△	▲	△
Gender															▽
HF Clinic														△	△
Age at repair Q2		▽													
Age at repair Q3		▽													
Age at repair Q4		▽													
Repairs total				▽		▽	▽							▽	
Palliation before repair			▽	▽											▽
CPB minutes Q2	▽			▽	▽									▽	
CPB minutes Q3	△			△	△									▲	
CPB minutes Q4	▽			△	△									▲	
Post-op CNS complications		▼	▽	▽		▼	▼		▼	▼		▽	▽	▽	
Post-op Infections			▽										▽	▽	
Hospital days Q2													▽		
Hospital days Q3													▽		
Hospital days Q4													▽		
Cyanotic days Q2		▽													▽
Cyanotic days Q3		△													▽
Cyanotic days Q4		△													▽
Pacemakers						▽									
ACE medication									▽			▽	▽		
Diuretic medication					▽	▽	▽							△	
Anti coagulant medication														▽	

Factors associated with cognitive functioning	Attention				Executive functioning							Motor		IQ	Memory
	TMT-A	TMT-B	SDMT- W	SDMT - O	STROOP	WCST Error	WCST CLR	WCST FTM	WCST No Cat	WCST TTC	COWA	GP-D	GP-ND	WAIS	RAVLT
RVEF					△	△	△	△	△					△	
LVEF				▲	△	△	△		△						
Positive affect (PA)													△		
Negative affect (NA)			▲							▽	▲				
Anxiety (STAI)															
Depression (CESD)										▽					

Note: All results are based on the final model of the hierarchical regression analysis Interpretation Key: ▲Increase in value of IV = significant improvement in cognitive test performance ($p<0.01$), ▼Increase in value of IV = significant decline in cognitive test performance ($p<0.01$) △Increase in value of IV = non-significant improvement in cognitive test performance ($p<0.01$) ▽= Increase in value of IV = non-significant decline in cognitive test performance ($p<0.01$), **blank cells**= not included in the model, NYHA= New York Health Assessment, CNS= Central Nervous System, Q=Quartile, CPB= Cardio Pulmonary Bypass, ACE= Angiotensin-Converting-Enzyme Inhibitor, RVEF= Right Ventricular Ejection Fraction LVEF= Left Ventricular Ejection Fraction.

Table 8.18: Demographic, clinical and mood factors associated with cognitive tests in the multiple hierarchical regression analysis for the SV group (N=65)

Factors associated with cognitive functioning	**Attention**				**Executive functioning**							**Motor**	**IQ**	**Memory**
	TMT A	**TMT B**	**SDMT W**	**SDMT O**	**COWA**	**WCST Error**	**WCST CLR**	**WCST FTM**	**WCST No Cat**	**WCST TTC**	**STROOP**	**GP-ND**	**WAIS**	**RAVLT**
Model significance (p value)	<0.01	.008	<0.01	<0.01	<0.01	<0.001	<0.001	.005	<0.001	<0.001	.121	.036	<0.001	.004
Adjusted R^2	.203	.091	.279	.115	.218	.369	.434	.132	.347	.287	.090	.053	.530	.281
Age					△									△
Education			△		△	△	△		△				▲	△
Employment			△											
Hypertension						▽	▽							
Palliation before repair									▽				▽	
CPB minutes Q2											△		△	
CPB minutes Q3											△		△	
CPB minutes Q4											△		△	
HA minutes Q2			△											▲
HA minutes Q3			△											△
HA minutes Q4			△											△
Post-op CNS complications					▽	▽	▼		▼	▼			▼	▽
Post-op Infections	▽	▼	▼			▽	▽		▽			▽	▽	
Years since last operation								▽						
Current saturation Q1				▽		△	▽							
Current saturation Q2				▽		▽	▼							
Current saturation Q3				▽		▽	▽							
Pacemakers	▽													
Diuretic medication	▽					▽				▽				
B-blocker medication	▽					▽	▽		▽					
Anti arrhythmia medication										▽				
Anti coagulant medication								△						
Positive affect (PA)					△	△					△		▲	△
Negative affect (NA)			▽	▽										

Factors associated with cognitive functioning	Attention				Executive functioning							Motor	IQ	Memory
	TMT A	TMT B	SDMT W	SDMT O	COWA	WCST Error	WCST CLR	WCST FTM	WCST No Cat	WCST TTC	STROOP	GP-ND	WAIS	RAVLT
Anxiety (STAI)														
Depression (CESD)				▽										

Note: All results are based on the final model of the hierarchical regression analysis. **Interpretation Key:** ▲Increase in value of IV = significant improvement in cognitive test performance ($p<0.01$), ▼Increase in value of IV = significant decline in cognitive test performance ($p<0.01$) △Increase in value of IV = non-significant improvement in cognitive test performance ($p<0.01$) ▽= Increase in value of IV = non-significant decline in cognitive test performance ($p<0.01$), **blank cells**= not included in model, HA= Hypothermic Arrest, Central Nervous System, Q=Quartile

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Table 8.19 Demographic, clinical and mood factors associated with cognitive tests in the multiple hierarchical regression analysis for the Simple group (N=84)

Factors associated with cognitive functioning	**Attention**			**Executive functioning**						**Motor**		**IQ**	**Memory**
	TMT A	**SDMT W**	**SDMT O**	**COWA**	**STROOP**	**WCST Error**	**WCST CLR**	**WCST No Cat**	**WCST TTC**	**GP-D**	**GP-ND**	**WAIS**	**RAVLT**
Model significance (p-value)	<0.01	<0.01	.027	<0.001	<0.01	<0.001	<0.001	<0.001	<0.001	<0.01	<0.001	<0.001	<0.01
Adjusted R^2	.173	.220	.124	.307	.237	.261	.240	.277	.314	.193	.176	.378	.186
Age				△			▽	▽					
Education		△		▲		△	△	△	△			▲	
Employment					△								
Gender										▽			▽
Hypertension						▽	▽						▽
HF Clinic				▽									
NYHA					▽				▽				
Palliation total											▽		
Repairs total			△									△	
Catheter lab total												▽	
Years since last operation											▼		
Age at repair Q2	△	△				△	△	△					
Age at repair Q3	▽	△				▲	▲	▲					
Age at repair Q4	△	△				▽	▽	▽					
CPB minutes Q2													
CPB minutes Q3	△												
CPB minutes Q4	▽												
HA minutes Q2													
HA minutes Q3					▽								
HA minutes Q4					△								
Current saturation Q1									▽				
Current saturation Q2									△				
Current saturation Q3									▽				

Factors associated with cognitive functioning	Attention			Executive functioning						Motor		IQ	Memory
	TMT A	SDMT W	SDMT O	COWA	STROOP	WCST Error	WCST CLR	WCST No Cat	WCST TTC	GP-D	GP-ND	WAIS	RAVLT
Post-op Ventricular dysfunction			△										
ACE medication					▽								▽
Anti arrhythmia medication											▼		
Diuretic medication			▽						△				
Anti coagulant medication									▼				
LVEF				△									
Positive affect (PA)		△	△	△	▽	▽	▽	△		▲		△	△
Negative affect (NA)				△	▽	△	△	▽		△			▽
Anxiety (STAI)	▽	▽	▽	▽	▽							▽	
Depression (CESD)		△		▽	▽	▽	▽	▽	▽			▽	▽

Note: All results are based on the final model of the hierarchical regression analysis. **Interpretation Key:** ▲Increase in value of IV = significant improvement in cognitive test performance ($p<0.01$), ▼Increase in value of IV = significant decline in cognitive test performance ($p<0.01$), △Increase in value of IV = non-significant improvement in cognitive test performance , ▽= Increase in value of IV = non-significant decline in cognitive test performance ($p<0.01$), **blank cells**= not included in the model, NYHA= New York Health Assesment, CNS= Central Nervous System, Q=Quartile, CPB= Cardio Pulmonary Bypass, HA= Hypothermic Arrest, ACE= Angiotensin-Converting-Enzyme Inhibitor, LVEF= Left Ventricular Ejection Fraction

8.7.3 Demographic, clinical and mood factors associated with attention

Attention was examined in this study using three measures; the TMT (Part A and B) and the SDMT (written and oral subtest). Both these tests generate two scores each. Factors associated with each score are discussed below both by total sample followed by the different structural complexity groups.

8.7.3.1 Trail Making Test (TMT)

Total sample

The factors associated with the TMT A and B scores are presented in Table 8.20 and Table 8.21 respectively.

Table 8.20 Demographic and Clinical factors associated with TMT-A scores (Divided attention)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	B	*Sig.*
1		.025	.021	.025	7.753		.000**
	Age					-.157	.006**
2		.056	.044	.031	3.378		.019
	Age					-.152	.007**
	Current saturation Q1					.146	.020
	Current saturation Q2					.007	.911
	Current saturation Q3					-.064	.310
3		.071	.056	.015	5.073		.025*
	Age					-.154	.006**
	Current saturation Q1					.127	.043
	Current saturation Q2					.008	.896
	Current saturation Q3					-.073	.246
	Pacemaker					. 126	.025

Note: Q= Quartile, **p=<0.01,

The final model for the TMT-A was significant (F= 4.676(5,304), p=<0.001), explaining 5.6% of the variance in attention. Age consistently continued to explain unique variance over the other variables in the equation showing a negative association, suggesting that the older participants performed better than younger participants. No clinical or mood variables explained unique variance in attention (on the TMT-A) (See Table 8.20).

Table 8.21 Demographic, clinical and mood factors associated with TMT-B scores

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.116	.108	.116	13.422		.000**
	Age					-.233	.000**
	Education (Yrs.)					-.203	.000**
	Employment					-.176	.001**
2		.146	.126	.029	2.602		.036
	Age					-.207	.000**
	Education (Yrs.)					-.185	.001**
	Employment					-.174	.002**
	NYHA					.054	.347
	TOF					.177	.007**
	TGA					.121	.071
	SV					.142	.035
3		.195	.145	.049	1.607		.096
	Age					-.199	.001**
	Education (Yrs.)					-.162	.004**
	Employment					-.159	.005**
	NYHA					.075	.220
	TOF					.120	.165
	TGA					.083	.398
	SV					.128	.179
	Interventions					.018	.821
	Palliation Before Repair					-.030	.738
	Years Since Last Op					-.073	.267
	Post Op CNS Complications					.127	.024
	Post-Op Infection					.099	.094
	HA arrest Q2					.158	.026
	HA arrest Q3					.064	.402
	HA arrest Q4					.029	.702
	Hospital days Q2					.022	.762
	Hospital days Q3					.019	.829
	Hospital days Q4					-.090	.345
4		.234	.169	.039	2.432		.026
	Age					-.159	.008**
	Education (Yrs.)					.115	.011
	Employment					.107	.011
	NYHA					-.014	.197
	TOF					.095	.417
	TGA					.054	.754
	SV					.057	.432
	Interventions					-.054	.714
	Palliation Before Repair					-.062	.810
	Years Since Last Op					-.078	.276
	Post Op CNS Complications					.122	.023
	Post-Op Infection					.110	.060
	HA arrest Q2					.149	.034

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	HA arrest Q3					.049	.526
	HA arrest Q4					.036	.636
	Hospital days Q2					.013	.860
	Hospital days Q3					.020	.818
	Hospital days Q4					-.098	.304
	Cyanosis days Q2					.074	.756
	Cyanosis days Q3					-.061	.804
	Cyanosis days Q4					-.169	.489
	Current-saturation Q1					-.078	.205
	Current-saturation Q2					-.098	.115
	Current-saturation Q3					.064	.397
5		.252	.184	.019	3.522		.031
	Age					-.132	.029
	Education (Yrs.)					-.116	.041
	Employment					-.112	.054
	NYHA					.058	.345
	TOF					.268	.293
	TGA					.146	.577
	SV					.255	.292
	Interventions					.037	.642
	Palliation Before Repair					-.017	.844
	Years Since Last Op					-.064	.319
	Post-Op CNS Complications					.118	.038
	Post-Op Infection					.124	.034
	HA arrest Q2					.155	.028
	HA arrest Q3					.053	.485
	HA arrest Q4					.041	.585
	Hospital days Q2					.024	.744
	Hospital days Q3					.018	.828
	Hospital days Q4					-.100	.290
	Cyanosis days Q2					.029	.904
	Cyanosis days Q3					-.120	.629
	Cyanosis days Q4					-.225	.359
	Current-saturation Q1					-.079	.199
	Current-saturation Q2					-.110	.076
	Current-saturation Q3					.047	.527
	Positive affect (PA)					-.159	.013
	Anxiety (STAI)					-.020	.755

Note: Q= Quartile, **p=<0.01

The final model for the TMT-B, which included the addition of the mood variables, explained a total of 18.4% of the variance in divided attention (F= 3.625(24,285), p=<0.001). The addition of mood variables rendered the demographic variables (education, age) non-significant. None of the clinical or the mood variables explained any unique variance in the TMT-B scores (See Table 821). In summary no clinical or mood factors explained any unique variance in divided attention and executive functioning as measured by the TMT.

8.7.3.2 Symbol Digit Modalities Test (SDMT)

The demographic, clinical and mood factors associated with attention and complex visual scanning as measured by the oral subtest of the SDMT are presented in Table 8.22 (below). The final model was significant (F= 10.09(3,306), p<0.001) explaining a total of 12.2% of the total variance in attention and complex visual scanning. Education and positive affect explained unique variance in attention over and above the other variables in the equation. None of the clinical variables significantly explained any unique variance in this score.

Table 8.22 Demographic, clinical and mood factors associated with SDMT-O

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.066	.063	.066	21.823		.000**
	Education (Yrs.)					.257	.000**
2		.090	.081	.024	4.023		.019
	Education (Yrs.)					.238	.000**
	Post-op CNS complication					-.130	.022
	Post-op infection					-.058	.303
3		.140	.122	.049	5.800		.001**
	Education (Yrs.)					.195	.000**
	Post-op CNS complication					-.120	.033
	Post-op infection					-.075	.180
	Positive affect (PA)					.248	.000**
	Anxiety (STAI)					.035	.612
	Depression (CESD)					.013	.858

Note -**p=<0.01

Table 8.23 Demographic, clinical and mood factors associated with SDMT –W score

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.126	.120	.126	22.116		.000**
	Education (Yrs.)					.284	.000**
	Employement					.185	.001**
2		.191	.167	.065	3.459		.001**
	Education (Yrs.)					.261	.000**
	Employment					.186	.001**
	Interventions total					.008	.908
	Palliation before repair					-.087	.186
	Post-op CNS complication					-.146	.008**
	Post-op CNS infection					-.127	.027
	Hospital days Q2					-.080	.231
	Hospital days Q3					-.042	.577
	Hospital days Q4					.029	.720
3		.204	.172	.013	1.586		.193
	Education (Yrs.)					.261	.000**
	Employment					.177	.001***
	Interventions total					.014	.845
	Palliation before repair					-.061	.372
	Post-op CNS complication					-.156	.005**
	Post-op CNS infection					-.129	.025
	Hospital days Q2					-.072	.280
	Hospital days Q3					-.030	.689
	Hospital days Q4					.055	.507
	Current saturation Q2					.012	.832
	Current saturation Q3					.006	.923
	Current saturation Q1					-.116	.075
4		.234	.197	.030	5.727		.004**
	Education (Yrs.)					.233	.000**
	Employment					.143	.011
	Interventions total					.017	.806
	Palliation before repair					-.072	.285
	Post-op CNS complication					-.151	.006**
	Post-op CNS infection					-.140	.014
	Hospital days Q2					-.809	.180
	Hospital days Q3					-.030	.686
	Hospital days Q4					.065	.432
	Current saturation Q2					.010	.866
	Current saturation Q3					.013	.822
	Current saturation Q1					-.107	.099
	Positive affect (PA)					.215	.001**
	Depression (CESD)					.079	.227

Note: Q= Quartile, **p=<0.01

Table 8.23 illustrates the factors associated with the written sub-test of the SDMT measuring attention and complex visual scanning. The final model was significant ($F_{(12,297),}$ = 6.342p<0.001) and explained 19.7% of the variance in SDMT written scores. The final model revealed that education, post-operative CNS complication and positive affect explained unique variance in attention. Higher years of education achieved and positive affect was associated with better performance; while the experience of a post-operative CNS complication was associated with impaired performance.

Structural complexity groups

The summary results of the final models for the sub-group analyses related to the domain of attention are presented in Tables 8.16-8.19. Results for the ToF group showed no significant unique association between the demographic, clinical and mood factors with attention as measured by both the TMT. A significant positive association was found between education and SDMT-W score (See Table 8.16). The TGA group showed a significant negative association between employment status and impaired divided attention, with those currently employed performing better on the test. A significant positive association between CNS complications after surgery and impaired divided attention (TMT-B) was also noted. Further, a significant positive association was also noted between the SDMT-O scores and LVEF, suggesting a low ejection fraction was associated with lower scores and impaired attention. In the written subtest the TGA group showed a significant positive association between attention and negative affect suggesting that higher level of negative affect was associated with better performance on the written subtest (See Table 8.17).

The SV group exhibited a significant positive association between post-operative infections with TMT-B scores and a negative association with the SDMT-W scores, suggesting the occurrence of an infection after surgery is associated with impaired attention and complex

visual scanning (See Table 8.18). Lastly, in the Simple group no demographic, clinical and mood variables explained any unique variance in the outcomes (See Table 8.19).

8.7.4 Demographic clinical and mood factors associated with memory performance

Rey Auditory Verbal Learning Test (RAVLT)

Total sample

Demographic, clinical and mood factors associated with memory are presented in Table 8.24. The final regression block was significant (F=14.319(4,305), p=<0.001) explaining 15.9% of the overall variance in memory and verbal learning. The results showed that education and female gender consistently continued to explain unique variance in memory over the other variables in the equation.

Table 8.24 Demographic, clinical and mood factors associated RAVLT (total acquisition) score

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.126	.120	.126	22.166		.000**
	Education (Yrs.)					.269	.000**
	Gender (Males)					-.244	.000**
2		.151	.142	.025	8.828		.003**
	Education (Yrs.)					.273	.000**
	Gender (Males)					-.241	.000**
	Hypertension					-.157	.003**
3		.158	.147	.007	2.686		.102
	Education (Yrs.)					.261	.000**
	Gender (Males)					-.233	.000**
	Hypertension					-.122	.032
	ACE medication					-.094	.102
4		.173	.159	.015	5.333		.022
	Education (Yrs.)					.240	.000**
	Gender (Males)					-.239	.000**
	Hypertension					-.128	.023
	ACE medication					-.078	.175
	Positive affect (PA)					.124	.022

Note: ACE= angiotensin-converting-enzyme inhibitors, **p=<0.01

Structural complexity groups

The final model for the sub-group analysis conducted to identify factors associated with memory across the different groups is presented in Table 8.16-8.19. The ToF group demonstrated a significant positive association between years of education and age at repair with memory, suggesting that fewer years of education and younger age at repair were associated with poorer memory (See Table 8.16). The SV group showed a significant positive association of memory and the minutes the patient spent under hypothermic arrest suggesting that a longer duration of HA was associated with better performance on the memory test (See Table 8.18). None of the variables explained unique variance in memory for the TGA and Simple groups.

8.7.5 Demographic clinical and mood factors associated with motor functioning and dexterity

Grooved Pegboard (GP)

Motor functioning and dexterity in the study sample was measured using the Grooved Pegboard test. The test included two parts: one completed by the participant using their dominant hand and one using the non-dominant hand in that order. The demographic, clinical and mood variables associated with motor function (dominant hand scores) are presented in Table 8.25.

Table 8.25 Demographic, clinical and mood factors associated with GP-D score

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.065	.059	.065	10.724		.000**
	Education (Yrs.)					-.189	.001**
	Gender (Males)					.181	.000**
2		.084	.069	.019	2.110		.099
	Education (Yrs.)					-.186	.001**
	Gender (Males)					.158	.005**
	TOF					.121	.070
	TGA					.126	.061
	SV					.149	.024*
3		.104	.080	.020	2.227		.085
	Education (Yrs.)					-.185	.001**

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
	Gender (Males)					.149	.008**
	TOF					.118	.155
	TGA					.126	.123
	SV					.159	.038
	CPB minutes Q2					.126	.115
	CPB minutes Q3					-.026	.752
	CPB minutes Q4					-.015	.864
4		.116	.083	.012	1.329		.265
	Education (Yrs.)					-.195	.001**
	Gender (Males)					.141	.013
	TOF					-.164	.516
	TGA					-.170	.506
	SV					-.116	.618
	CPB minutes Q2					.119	.142
	CPB minutes Q3					-.034	.683
	CPB minutes Q4					-.024	.780
	Cyanosis days Q2					.314	.206
	Cyanosis days Q3					.239	.342
	Cyanosis days Q4					.336	.176
5		.125	.089	.009	2.946		.087
	Education (Yrs.)					-.183	.001**
	Gender (Males)					.133	.018
	TOF					-.142	.572
	TGA					-.178	.486
	SV					-.108	.640
	CPB minutes Q2					.120	.137
	CPB minutes Q3					-.034	.687
	CPB minutes Q4					-.027	.755
	Cyanosis days Q2					.321	.195
	Cyanosis days Q3					.237	.344
	Cyanosis days Q4					.323	.193
	ACE medication					.097	.087
6		.141	.104	.017	5.734		.017
	Education (Yrs.)					-.158	.005**
	Gender (Males)					.138	.014
	TOF					-.115	.646
	TGA					-.143	.571
	SV					-.089	.699
	CPB minutes Q2					.127	.113
	CPB minutes Q3					-.026	.749
	CPB minutes Q4					-.017	.845
	Cyanosis days Q2					.297	.227
	Cyanosis days Q3					.212	.395
	Cyanosis days Q4					.297	.227
	ACE medication					.083	.145
	Positive affect (PA)					-.133	.017

Note: Q= Quartile, CPB=Cardio Pulmonary Bypass, ACE= angiotensin-converting-enzyme inhibitors, **p=<0.01

Table 8.26 Demographic, clinical and mood factors associated with GP-ND score

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.039	.032	.039	6.171		.002**
	Education (Yrs.)					-.161	.004**
	Gender (Males)					.121	.032
2		.048	.039	.009	2.957		.087
	Education (Yrs.)					-.151	.007**
	Gender (Males)					.113	.044
	HF clinic					.097	.087
3		.069	.054	.021	3.436		.033
	Education (Yrs.)					-.134	.017
	Gender (Males)					.111	.046
	HF clinic					.077	.173
	Post-op CNS complication					.085	.142
	Post-op CNS infection					.101	.083
4		.087	.066	.018	2.966		.053
	Education (Yrs.)					-.121	.033
	Gender (Males)					.103	.064
	HF clinic					.041	.487
	Post-op CNS complication					.085	.140
	Post-op CNS infection					.093	.110
	ACE medication					.137	.030
	Diuretic medication					.008	.896
5		.098	.074	.011	3.728		.054
	Education (Yrs.)					-.103	.073
	Gender (Males)					.107	.054
	HF clinic					.043	.460
	Post-op CNS complication					.077	.176
	Post-op CNS infection					.104	.076
	ACE medication					.126	.045
	Diuretic medication					.002	.975
	Positive affect (PA)					-.109	.054

Note: HF= Heart Failure, ACE= angiotensin-converting-enzyme inhibitors, **p=<0.01

The final model was significant and explained 10.4% of the total variance in motor functioning. The results revealed years of education achieved had a significant negative association with motor functioning, suggesting more years of education was associated with less time taken to complete the task demonstrating better motor functioning. The model for the non-dominant hand is presented in Table 8.26. The final model revealed no significant factors explaining unique variance in motor functioning as assessed by the non-dominant hand (F=4.103(7,302),

P<0.001). In summary, the results of the grooved pegboard test suggest the absence of any clinical or mood factors explaining unique variance in motor function.

Structural complexity groups

The sub-group analyses conducted to identify factors associated with motor functioning and dexterity across the different structural complexity groups are presented in Tables 8.16-8.19. The results showed no significant factors associated with motor functioning in three groups; ToF, TGA and SV. The simple group showed a significant positive association between motor functioning (non-dominant hand) and years since last intervention and anti-arrhythmia medication. These results suggest poorer motor functioning was associated with more years since the last intervention and taking anti-arrhythmia medication. Analyses for the dominant hand showed a negative association of positive affect suggesting that lower positive affect was associated with poorer motor functioning (See Table 8.19).

Distribution of residuals

The distribution of residuals (assumption of homoscedasticity) was checked for each regression analysis. The results showed a slight pattern (funnelling) in the residuals for some variables including the RAVLT and COWA. A plausible explanation for this is the presence of categorical predictor variables that by their nature do not allow the data to be randomly distributed leading to a pattern. Therefore, caution is advised when interpreting findings related to these analyses, as the assumption of homoscedasticity may be violated (See Appendix-S for a graphical representation of this data).

Summary

Overall the results showed a number demographic, clinical and mood factors explaining unique variance in cognitive outcomes of ACHD patients. Education and CNS complications were most consistently associated with the different domains assessed, when the total sample was assessed together. The sub-group analyses showed a considerable amount of variability in the factors associated with cognitive outcomes in each group. The Simple group was the only one showing a significant association between medication taken (anti-arrhythmia and anti-coagulants) and cognitive outcomes. Within the mood variables only positive and negative affect explained unique variance in cognition across all groups, with depression and anxiety not explain any significant variance. Clinical variables largely explained the majority of the variance in cognitive outcomes as compared to demographic and mood variables.

8.8 Cognitive functioning and Quality of Life (QoL)

This section investigates the association between QoL and the composite NP score to assess the impact the overall extent of cognitive functioning has on QoL outcomes for ACHD patients. A univariate analysis was conducted using simple linear regression for each QoL outcome (DV) and the demographic, clinical, mood and composite cognitive functioning measures (IV) to assess significance before entering into the multivariate analysis. Simple linear regressions were chosen over the use of correlation analysis as regression analysis allows the selection of the directionality of the analysis by determining the dependent and independent variables. This analysis was conducted for the total sample and repeated for each sub-group individually. Only those variables significant at a $p<0.05$ in the univariate screening were included in the multivariate model. Similar to the previous set of regression analyses this was done to reduce any redundant predictor variables.

8.8.1 Univariate screening results to identify factors associated with QOL

8.8.1.1 Univariate screening of Mental QoL (MCS)

Total sample

The univariate screening for the total sample showed no significant association of cognitive functioning and MCS. Only demographic (employment status), clinical (total and ACE medication, post-op infection, CPB and HA minutes, cyanosis) and mood (positive and negative affect, anxiety and depression) variables demonstrated a significant association with MCS ($p<0.05$) (See Appendix-O for the full analysis results).

Structural complexity groups

Within the subgroup analyses, factors significantly associated with MCS in the ToF group included demographic (age, employment), clinical (HA minutes, days spent in hospital and in ICU, current saturation, RVEF) and mood (positive and negative affect, anxiety and depression) factors.

The TGA group demonstrated a significant association between mental QoL and gender, total number of medications taken and mood (positive and negative affect, anxiety and depression). No significant association was noted with cognitive functioning.

The SV group showed a significant association between mental QoL and the demographic (age, employment status), clinical (ACE medication and current saturation), and mood (positive and negative affect, anxiety and depression) factors. The ToF, TGA and SV groups showed no significant association between QoL (MCS) and cognitive functioning.

Lastly, the Simple group showed a significant positive univariate association of mental QoL with cognitive functioning and mood (positive and negative affect, anxiety and depression). (See Appendix-O for details on univariate screening).

8.8.1.2 Univariate screening of Physical QoL (PCS)

Total sample

The univariate screening for factors associated with PCS in the total sample showed a significant association with demographic (age, education, employment), clinical (e.g. arrhythmias, age at repair, total interventions, years since last intervention, medication, LVEF, and cyanosis) and mood (positive and negative affect, anxiety, depression) variables. No significant association was noted between PCS and cognitive functioning for the cohort as a whole (See Appendix-O for details).

Structural complexity groups

Within the sub-group analysis, the ToF group demonstrated no significant association between cognitive functioning and physical QoL. A significant association was noted with demographic (employment status) and clinical (e.g. arrhythmias, NYHA, interventions total, current saturation, post-operative infection and days spent in the hospital) variables in the ToF group. The TGA group showed no significant association of physical QoL with cognitive functioning and demographic factors. Only one clinical variable was significant (NYHA) along with mood (positive affect and depression).

In the SV group demographic (gender), clinical (NYHA, days spent in hospital, cyanosis, current saturation) and mood (positive and negative affect and depression) variables were significantly associated with physical QoL. The SV group did not show a significant association between physical QoL with cognitive functioning.

Lastly, the Simple group demonstrated a significant association between physical QoL and demographic (age and education), clinical (e.g. NYHA, age at repair, medications total, days spent in hospital) and mood (positive and negative affect, anxiety, depression) factors. No significant association was noted with cognitive functioning across all complexity sub-groups (Please see Appendix-O for details).

8.8.2 Multivariate regression analysis to identify factors associated with QoL (PCS, MCS) in ACHD patients

The primary aim of this research question was to investigate the association between cognitive functioning and QoL after taking account of the clinical and mood factors. However, given that cognitive functioning was consistently not associated with PCS or MCS in the groups and the total sample, little merit was considered in running multivariate regression models without the key variable of interest i.e. cognition. The only exception was the Simple group on the MCS sub-scale. Therefore, a multivariate regression analysis was only conducted for the Simple group on the MCS sub-scale.

The analysis was conducted using hierarchical multiple regressions (See Figure 7.7 for the order of regression blocks). The results of the analysis for the MCS scale are presented in Table 8.27. The final model was significant ($F=26.162(19,290)$, $p<0.001$) and revealed negative affect and depression explained unique variance in mental QoL. The addition of the cognition variable in the final block did not explain any additional variance in the model.

Table 8.27 Demographic, clinical, mood and cognitive factors associated with mental QoL in the Simple group

Block	Predictor Variables	R^2	Adjusted R^2	ΔR^2	ΔF	β	Sig.
1		.631	.612	.631	33.712		.000**
	Positive affect (PA)					.043	.671
	Negative affect (NA)					-.311	.006**
	Anxiety (STAI)					-.005	.964
	Depression (CESD)					-.494	.000**
2		.631	.607	.000	.015		.904
	Positive affect (PA)					.045	.661
	Negative affect (NA)					-.310	.006**
	Anxiety (STAI)					-.007	.950
	Depression (CESD)					-.496	.000**
	Cognitive functioning					-.010	.904

**p<0.01

Overall the results of the multivariate analysis showed no significant association between cognitive functioning and physical or mental quality of life in any of the complexity groups.

8.9 Summary

The results of the cross-sectional analyses showed the presence of cognitive impairment in the ACHD sample and within structural complexity groups, in comparison to normative data. All domains of cognitive functioning assessed showed some impairment, with the exception of memory, where the performance of the ACHD sample was comparable to normative data. The four groups showed significant differences on divided attention and mean composite cognitive functioning. Several factors (demographic, clinical and mood) explained unique variance in the cognitive domains assessed. The results showed considerable variability in the factors explaining unique variance in cognition across the different groups. No relationship was found between cognitive functioning and QoL. Chapter 9 will discuss the findings in more detail and in the context of the wider literature.

9 CROSS-SECTIONAL STUDY DISCUSSION

9.1 Prologue

This chapter discusses the findings of the cross-sectional study detailed in Chapter 8. The primary aim of this chapter is to understand, interpret and discuss the findings of this study in the context of the existent literature.

9.2 Extent of cognitive impairment in ACHD patients in comparison to normative data and other structural complexity groups

A comprehensive range of cognitive domains were assessed in a group of common ACHD conditions. An impairment criterion (score< 1.5SD below norms) was established to evaluate the relative performance of ACHD patients to that of the normal healthy population. It is considered important to emphasize prior to interpreting results that this study was exploratory in nature and these criteria were not used to diagnose a clinically significant impairment.

9.2.1 The extent of cognitive impairment in the <u>total ACHD sample</u> when compared to normative data

Cognitive functioning in this study was assessed using both a measure of IQ and tests of independent cognitive domains. With regards to the IQ a quarter of the present study sample showed impairment when compared to the normative data. This proportion was larger than the 15% that can be expected to show impairment in the general population. Despite this, the mean performance of the study sample was within the 'average' IQ category as classified by Wechsler (Wechsler et al, 1997).

These results support some other studies, which reported IQ in ACHD to be lower in comparison to normative data (Wernovsky et al, 2000; and Eide et al, 2006). Similar to the present study, while the mean IQ scores of the study sample in these studies were lower in comparison to the normative data mean score, they were still within the normal range as specified by the respective tests. It is of note however that one of these studies included both children and adults (Wernovsky et al, 2000), while the other study included only male participants (Eide et al, 2006). The present study is larger in comparison to the study conducted by Wernovsky and colleagues by over three quarters (86%), and more than double in size of the study conducted by Eide and colleagues (133%), and includes a mixed gender sample that comprises of all adult CHD patients, thus providing more substantial support for the finding that IQ in ACHD patients is impaired in comparison to the normal population. The findings of the present study were contrary to those of other studies which reported IQ in ACHD patients as being comparable to that of the normal population (Utens et al, 1994 and Utens et al, 1998), however as discussed previously the methodological quality of these studies was considerably low in comparison to the present study, thus providing little confidence in these contrary finding.

With regards to specific domains of cognitive functioning, the results of the present study showed that a considerable proportion of the study sample exhibited impairments on a number of cognitive domains, above that which could be expected to fall below the 1.5SD by chance. Impairments were noted in the domains of executive functioning, attention, and motor functioning. The domain of memory was not impaired in this study, with majority of the sample demonstrating memory and verbal learning comparable to that of the normal population. These findings are similar to those reported in the ACHD literature, with studies reporting the presence of impaired executive function and divided attention in ACHD patients (Idorn et al, 2013; Daliento et al, 2005; Franklin et al, 2014). Similar to the present study Daliento and

colleagues also reported only a small proportion of their study sample exhibiting impairment in memory function (<10%) (Daliento et al, 2005). Motor function was not assessed in any of the existing studies within the adult literature.

The largest proportion of participants with impairments was noted on tests that assessed attention (TMT) and executive functioning (WCST, COWA and Stroop) in some capacity. For instance, the TMT while being a test of divided attention, is also known to assess executive functioning given the cognitive flexibility, and ability to shift sets that the nature of the test demands (Arbuthnott and Frank, 2000). Similarly, the WCST being a cognitively complex task also requires the test taker to exercise attention and cognitive flexibility along with the ability to shift sets, and develop and maintain a problem solving strategy. Therefore, overall these findings suggest that patients with ACHD may particularly struggle with problem solving, dealing with novel situations, multitasking and decision making skills.

A significant association has previously been reported between the WCST and TMT-B test in the cognitive literature (Kortte, Horner and Windham, 2002). Within the present study a weak but significant association was noted between TMT-B and 3/5 WCST scores (error, conceptual level response and trials to complete 1st category); thus reinforcing the patterns noted above.

The lack of impairments noted on the memory test is further strengthened by the lack of impairments noted on the WCST failure to maintain set score which only marginally exceeded the >7% criteria. The ability to maintain a set in the WCST largely depends on the working memory of the tests taker; as it requires the participant to remember and retain the strategy applied to complete the sets, while being presented with interference in the form of changing categories (i.e. colour, shape, number). Therefore, these results collectively provide findings to support the view that memory in ACHD patients is not impaired.

9.2.2 Cognitive impairment across structural complexity groups

The following sections discuss the extent of cognitive impairments in the different forms of ACHD, and the differences in cognitive functioning between the four structural complexity groups. However, it must be noted that the paucity of literature (N= 2 studies) assessing independent cognitive domains in different forms of ACHD limits the comparison that can be drawn with the existing evidence**.**

Intelligence Quotient (IQ)

The mean IQ scores of the different structural complexity groups were lower than the age matched normative mean, with the exception of the Simple group which demonstrated IQ scores comparable to norms. Although some proportion of each structural complexity groups (16%-24%) scored 1 SD below the normative data, overall the results showed that each of the structural complexity groups had a mean IQ score within the '*average*' IQ category (IQ= 90-109).

No statistically significant differences between the structural complexity groups were noted on IQ. These results are largely indicative of a good overall cognitive functional status in the ACHD sample when compared to a healthy normal population. Furthermore, the lack of statistically significant differences between groups demonstrates that the IQ between the different levels of structural complexity was comparable, with those with structurally complex conditions performing similar to those with a simpler form of ACHD. These results also suggest that the complexity of the ACHD condition does not play a role in determining the IQ in this study sample. However, the findings of this study are contrary to those of Utens et al, (1998), who reported lower IQ in patients with structurally complex forms of CHD (TGA), when compared to those with less structurally complex forms (ASD, VSD).

Executive functioning

Each of the structural complexity groups (ToF, TGA SV and Simple) exhibited some level of impairment in executive functioning, across the different tests used to assess this domain. The different complexity groups had impairments in different areas of executive functioning including problem solving (ToF exhibited highest proportion of participants with deficits), verbal fluency (TGA exhibited highest proportion of participants with deficits), response inhibition and cognitive flexibility (SV exhibited highest proportion of participants with deficits). The simple group consistently had the lowest proportion of participants with impairments across the different tests of executive functioning. These results demonstrated the variability in impairment within the same domain, highlighting the importance of assessing the different areas of this broad domain, among patients with different levels of structural complexity.

The finding of the large proportion of ToF patients with impairments in problem solving (executive function) noted in this study can be compared to the study of ToF patients reported by Daliento et al, (2005). These authors also reported that a large proportion of their ToF sample exhibited impairment in executive function, problem solving, and planning strategies (as measured by the Verbal fluency test, Ravens test, Tower of London test) (Daliento et al, 2005).Within the present study however the ToF groups did not report the largest proportion of patients with impairments on the measure of verbal fluency (COWA) suggesting that the similarities across the studies were mainly limited to the problem solving aspect of this broad domain. These results show that ToF patients struggle with problem solving, planning and processing information. Executive functioning is one of the key domains of cognitive functioning, which is essential for an individual to be able to function independently, work, and

be able to think and solve problems. The high proportion of impairments noted in this domain highlights the challenges faced by ToF patients in these areas.

No statistically significant differences in executive functioning were identified between the structural complexity groups in the present study. This finding could be explained by the fact that all the structural complexity groups exhibited impairment in some aspect of executive functioning as measured across different tests. Consequently, despite the more structurally complex conditions (e.g. TGA and SV) showing a greater proportion of participants with impairments when compared to the 'Simple' group, these differences were however not statistically significant. These findings suggest that the structural complexity of the condition does not seem to play a significant role in determining the level of executive function impairment.

Attention

With regards to the domain of attention more structurally complex forms of CHD such as ToF, TGA and SV had a higher proportion of participants with impairments, across the different measures used, in comparison to the Simple group. The SV group consistently showed the highest proportion of participants with impairments in attention.

Interestingly more participants in the TGA group had impairment on the TMT-A subtest than the TMT-B in comparison to the other groups. This is at odds with what one might expect, given that the TMT-B is a more cognitively challenging task which requires the test taker to exercise multiple skills simultaneously including, divided attention, cognitive flexibility, and executive control, and therefore more likely to identify impairments in attention. A potential explanation for this finding may be the order of the assessment. Given that the TMT-A is presented before TMT-B, there may be some practice effect due to familiarization to the test

format; however, this pattern of findings was not noted across the different structural complexity groups.

An alternative interpretation could be that the TGA group experienced more difficulty in cognitive processing speed and visual numerical scanning as measured by TMT-A in comparison to divided attention, cognitive flexibility and executive control as measured by Part B, when compared to the other groups. This notion is further supported by their performance on the WCST test of executive functioning, which showed that the TGA group almost consistently (4/5 subscales) had a smaller proportion of participants with executive function impairments compared to the ToF group.

With regards to the comparison between structural complexity groups on the measures of attention, TMT-B scores significantly differed between the four groups, with a small to medium effect size. The post-hoc analyses did not show any significant differences between the TGA and Simple groups, but the Simple group did perform significantly better than the ToF and SV groups. These findings suggest that ToF and SV patients experience more impairment in attention when compared to the TGA and the Simple group. The findings of this study corroborated those of Franklin et al, (2014) who reported significantly more impairments in attention in patients with structurally complex forms of CHD (ToF, SV) as compared to the Simple forms (ASD, VSD) using a computerized battery of NP tests- the CNS Vital Signs (CNS-VS) and the Bethesda Conference guidelines to define structural complexity groups (Gualtieri and Johnson, 2006). While these results provide some indication of the differences in cognitive functioning among the different levels of structural complexity; the use of a wider range of measures to assess attention would allow drawing fuller conclusions, as drawing conclusions based on a single test is difficult.

Memory

With regards to the domain of memory the ACHD sample in this study did not show impairments. The performance of the sample was similar to that expected in the normal population. These results are again similar to those of Daliento et al, (2005) who also reported only a small proportion of ToF patients exhibiting impairment in memory (<10%). No statistically significant differences in memory were identified between the structural complexity groups in the present study, showing comparable memory function across different levels of structural complexity.

Motor functioning

Impairments in motor function were observed within the present study, particularly in the more structurally complex forms of CHD. The TGA group in particular had the highest proportion of participants with impairments on both hands while the Simple group had the lowest proportion. A consistent pattern was noted across the four groups, with a greater proportion of participants in each group exhibiting impairments on the task involving the dominant hand in comparison to the non-dominant hand. This finding could be considered contrary to expectation, as one might expect participants to do better when using their dominant hand; however, it is also not entirely unusual for an individual to score lower when using the dominant hand (Lezak et al, 2012).

Some authors have suggested the role of 'transfer of training' that may occur between the hands; whereby the first hand used (usually the dominant hand is assessed first) would improve the performance on the other hand. This transfer of training or familiarization with the test format may explain the better performance noted on the non-dominant hand across the study sample. Therefore, this finding may not necessarily be associated with CHD or be indicative of a cognitive impairment, although understanding the underlying mechanisms of handedness is

outside the scope of this study. Similar to the domains of executive functioning, and memory the structural complexity groups showed no significant differences in motor functioning.

Mean total composite cognitive functioning score

The overall cognitive functioning for the total sample indicated poorer overall cognitive performance for the ACHD group as a whole. The TGA group demonstrated the poorest overall cognitive performance, while the Simple group had the highest mean composite score. These findings indicate, to some extent, that the more structurally complex forms of CHD overall experienced more cognitive impairments in comparison to the less complex forms, potentially suggesting some association between structural complexity and cognitive outcomes. Post hoc tests showed a significant difference between the TGA and the Simple groups.

Individual Cognitive tests and Structural Group Differences

When the total percentage of individuals who were performing 1.5 SD below the mean was calculated the ACHD sample in the present study exhibited impairments across a wide range of cognitive tests compared to age matched normative data. The proportion of participants performing 1.5 SD below the mean by structural complexity groups showed that the more structurally complex forms such as ToF, TGA and SV consistently had a greater proportion of participants with impairments when compared to the less complex forms of ACHD such as ASD and VSD.

However, when inspecting these differences statistically, only the domain of attention (1 test) showed significant differences between the SV, ToF and the Simple group. Furthermore, significant group differences were noted between the TGA and Simple groups on the total composite cognitive score. As discussed earlier findings of the present study are similar to Franklin et al, (2014) who assessed motor function, attention, memory and executive function in

ACHD patients (Gualtieri and Johnson, 2006) and reported that the more structurally complex groups performed worse on all measures of the CNSVS when compared to the simple groups. Further significant differences in complex attention, cognitive flexibility and overall executive functioning between the groups were reported. The authors concluded that the more complex conditions (e.g. TGA, SV, and other cyanotic conditions) performed significantly poorer on measures of attention and executive functioning, as is also the case within the present study. Similarly, Utens et al, (1998) also reported impaired cognitive functioning (impaired IQ) in patients with more complex forms of CHD such as TGA when compared to those with simpler forms such as VSD and ASD.

Overall the existing literature on cognitive functioning in ACHD and the results of the present study indicate an association between more structurally complex conditions and impaired cognitive functioning across domains. One explanation for this could be that the more structurally complex conditions are characterized by cyanosis; given that cyanosis can lead to the lack of oxygen supply to the body including the brain it can have detrimental effects such as cognitive impairment. Within the present study the more structurally complex conditions like SV and TGA which showed the highest proportion of participants with impairments were cyanotic and had the longest duration of cyanosis and the lowest levels of blood oxygen saturation levels in comparison to the other structural complexity groups, thus suggesting the potential role of cyanosis in causing cognitive impairment.

Furthermore, patients with more structurally complex conditions (TGA, SV, ToF) are generally more likely to undergo multiple procedures and interventions, when compared to the less complex counterparts (ASD, VSD) as was the case in this study. As discussed earlier these multiple procedures may increase their risk of surgery related brain injury and neurological complications.

This raises the question of whether it is the symptoms and complexity of the condition, the sequale of the treatments, or a combination of the two, that explain variance in these domains of cognitive functioning.

9.3 Demographic, clinical and mood factors associated with cognitive functioning in ACHD

Another objective of the cross-sectional study was to identify factors that may potentially have the ability to influence and/or impact cognitive functioning in ACHD. The data in the present study was subjected to a twofold investigation with the aim of identifying unique factors (clinical, demographic and psychosocial) associated with cognitive functioning both for the total study sample (all complexity groups combined) and the independent structural complexity groups.

9.3.1 Demographic, clinical and mood factors associated with cognitive functioning in the total ACHD sample (all groups combined)

The results of the present study showed that post-operative CNS complications and fewer years of education were consistently associated with poorer cognitive functioning across the domains of attention, executive functioning and IQ in patients with ACHD.

Although cardiac surgery and treatments for CHD have advanced and led to an increase in survival rates, these techniques often lead to other additional complications. The deleterious effect of surgery is well reported in the cardiac literature; with studies reporting central nervous system complications post surgery (Newman et al, 2006). These complications can result in damage to the brain, and may manifest in a number of ways including cognitive impairment

(Arrowsmith et al, 2000). Within the present study, postoperative CNS complications were associated with lower IQ and impairment attention and executive functioning.

Given that the assessment of CNS complications was dichotomous (i.e. yes / no) the information about the exact nature or kind of the CNS complications was unavailable within this study, making it difficult to draw conclusions about the particular type of complications, only that CNS complications post surgery does appear to influence overall cognitive functioning in ACHD. In some ways this could be expected as the most common CNS postoperative complication post cardiac surgery appears to be impairment in cognitive functioning and what this study demonstrates is that these impairments appear to persist into adulthood. Future studies may benefit from assessing these different kinds of CNS complications post surgery separately, to identify their independent influence on cognitive function.

The association between fewer years of education and lower levels of cognitive functioning found in this study is consonant with this general literature, (Lezak et al, 2012). This gives support to the validity of the results of the study. The on-going need for treatment, surgical procedures and repeated hospitalization in CHD has an impact on education through a reduced attendance at school (Wray and Sensky, 2001). It does however remains unclear on the data presented here whether poor cognitive functioning impacts educational attainment and/or whether poor academic performance is due missing school as a result of the heart condition. These interruptions in the formative years cumulatively may affect the academic performance in this patient group (Razzaghi, Oster and Reefhuis, 2015). Further research is warranted in order to examine this relationship.

Higher levels of positive affect were associated with better performance on the test of attention (SDMT) reflecting findings elsewhere in the literature, which report improved cognitive

functioning with increased positive affect (Dreisbach and Goschke, 2004; Dhinakaran et al, 2013). Within the cognitive literature the role of increased dopamine levels in the brain as a result of positive affect has been used to explain better performance in cognitive outcomes such as working memory and executive attention (Ashby and Isen, 1999).

In line with the general literature on gender, male ACHD patients exhibited poorer working memory in comparison to female patients (Knox et al, 2007). The differences in memory function have been attributed to men and women using different neural networks when exercising working memory (Hill, Laird and Robinson, 2014). Greater cerebral blood flow in the left temporal pole has been associated with better immediate and delayed recall in a verbal memory task among women but not men (Ragland et al, 2000). While the findings of the present study reflect those in the literature, understanding these underlying mechanism in ACHD remain outside the scope of this study.

Overall the findings in the total study sample emphasize the deleterious impact of post-operative CNS complications on long-term cognitive outcomes in ACHD. The results also demonstrated in line with the existing literature the role of demographic factors such as education and gender in influencing cognitive functioning in ACHD.

9.3.2 Demographic, clinical and mood factors associated with cognitive functioning in different structural complexity groups

Given the wide range of sub-group analyses conducted within this study, only the most common and consistent factors associated with cognitive functioning across all of the cognitive domains, are discussed for each structural complexity group independently- ToF, TGA, SV and Simple.

In the case of the ToF group only younger age at the time of surgical repair was associated with poorer memory. Performing surgery at a very young age may make the patient more vulnerable to embolization, hypoxia and brain damage due to the immature and frail development of the brain at that early stage, leading to long-term complications such as cognitive impairment (Newburger and Bellinger, 2006). Surgical treatment (complete repair or palliation) for children with ToF in the first year of their lives is the basis of therapy in this patient group (Monaco and Williams, 2012; Lee, Kwak and Lee, 2014). Age at repair for CHD has also been found to be associated with increased cerebral and neurological damage (Trittenwein et al, 2003), along with impairments in cognitive domains and lower IQ (DeMaso et al, 2010; Chira and Ciotlaus, 2013). The results of this study demonstrate that these associations appear to persist into adulthood, thus highlighting the implications that clinical decisions made early in the patient's life can have in the long-term.

In the TGA group clinical factors including the duration of CPB, post-operative CNS complications, LVEF were associated with cognitive functioning. Interestingly, a longer duration of CPB was associated with higher IQ in this group. This is at odds with some of the existing literature that reports an increased duration of CPB being associated with deleterious effects on cognitive functioning in adults (Newman et al, 2001). However other studies report no association between CPB and cognitive functioning (Tan and Amoako, 2013). One could hypothesize that the longer duration of CPB (total minutes across lifespan) may have led to an improvement in symptoms such as cyanosis, low oxygen saturation levels as a result of the surgical treatment, in turn leading to improved cognitive function. These findings suggest that the increased interventions may have resulted in improvements in functioning and reduced the impact of the heart condition on cognition.

Post-operative CNS complications and lower levels of LVEF in TGA were associated with impaired executive function and attention, respectively. Both the association of CNS complications after a surgical procedure (Arrowsmith et al, 2000) and the association of ejection fraction (EF) with reduced cognitive functioning in coronary artery disease have been reported in the cardiac literature (Gottesman et al, 2009). LVEF has also been associated with brain injury and found to be a significant predictor of worse scores on neuropsychological tests in heart failure patients (Jefferson et al, 2011; Vogels et al, 2007; Nussbaum, Allender and Copeland, 1995; Almeida and Tamai, 2001). One suggested mechanism of this association is cerebral perfusion homeostasis (the stability, or the lack of, in cerebral blood flow) caused by lower levels of LVEF (Jefferson et al, 2011). Further research is needed to understand these relationships specifically in this group of patients.

Lastly, mood was associated with cognitive functioning in the TGA group. Higher levels of negative affect were associated with better performance on tests of executive functioning and attention in the TGA group. This association between increased negative affect and better executive functioning has previously been reported in the cognitive literature (Mitchell and Phillips, 2007). Mitchell and Phillips explain the association between mood and executive functioning using the mood-as-information theory, which proposes that a positive mood is likely to result in heuristic processing, and negative mood in analytic processing (Mitchell and Phillips, 2007). One possible explanation for improved executive functioning when experiencing negative affect may be that, when an individual experiences negative mood it may potentially signal a problem or challenge in the environment which may motivate the individual to carry out information processing and problem solving and in turn improving the underlying executive function (Mitchell and Phillips, 2007; Park and Banaji, 2000).

The positive association between improved attention and negative affect in the TGA group is contrary to the findings of the total study sample, which showed a positive association between positive affect and attention (on both SDMT written and oral) as discussed above in Section 9.3.1. Furthermore, this finding is also contrary to existing literature, which shows poorer cognitive function in those with higher negative affect (Payne and Schnapp, 2014). Given the complex relationship between mood and cognition much more work is needed to establish and understand the mechanisms underlying these relationships in patients with ACHD.

In the case of the SV group, clinical factors were associated with impaired IQ, and executive functioning. These included the presence of post-operative CNS complications and infections, current blood oxygen saturation level and the time spent under Hypothermic Arrest (HA minutes). As mentioned above CNS complications due to surgical procedures can have long-term neurological and cognitive implications (Arrowsmith et al, 2000).

Several of the findings within the SV group were contrary to expectation. Firstly, lower current levels of blood oxygen saturation (i.e. the most recent blood oxygen saturation level at time of assessment) were associated with more conceptual level responses on the WCST, showing better performance on the test of executive functioning. This finding appears unusual given that lower blood oxygen saturation levels (chronic hypoxia and hypoxic spells) are characteristic of cyanotic CHD and are often known to cause cognitive impairment and brain damage (Bass et al, 2004). Within the present study the SV group had the lowest mean oxygen saturation levels compared to the other complexity groups. However, the mean oxygen saturation levels of the SV group were 93% (range 60-100%), which is not below the normal threshold and is a relatively acceptable oxygen saturation level, which may not lead to detrimental effects. This may help explain the lack of a negative association between the two variables, however the positive association noted within this study remains elusive and warrants further investigation.

Furthermore, a number of measures were used to assess executive function, however no patterns in the findings were observed to support this association. Alternatively, these findings could suggest the role of additional unaccounted for confounding variables that were either not included or identified in this analysis.

Secondly, longer duration of HA was associated with better performance on the memory and learning test in SV patients. This finding is contrary to existing evidence, which reports a negative association between increased duration of HA, and cognitive functioning (Ziganshin and Elefteriades, 2013; Wypij et al, 2003). However other studies have reported that HA duration ranging from 14-40 minutes might not adversely affect cognitive function post-cardiac surgery in adults (Uysal et al, 2012). It has been reported that patients can usually tolerate 30 minutes of HA without significant neurological impairment (Conolly, Arrowsmith and Klein, 2010). The HA duration in the present study ranged from 28-34.5 minutes with the median duration of the SV group being 30 minutes. Hence it could be speculated, that the mean duration of the HA in this study may not have been long enough to result in a deleterious effect on cognitive function. While these studies explain the lack of a negative association between the variables, the positive association noted in this study remains unexplained and warrants further investigation.

With regards to the Simple group factors associated with cognitive functioning included current medication (anti-coagulant/anti-arrhythmia), age at repair and years since the last operation. The simple group was the only group in which the use of medication was associated with impaired cognitive functioning. Anti-coagulant medication is often used in some forms of ACHD and other heart conditions, to control symptoms of Atrial Fibrillation (AF) (Walsh and Cecchin, 2007). Poor anticoagulation control in patients with AF has been associated with impaired cognitive functioning and a faster rate of cognitive decline (Van Deelen et al, 2005; Flaker et al,

2010; Wozakowska-Kapton et al, 2009 Thacker et al, 2013). The association between anti-coagulation medication and impaired cognitive functioning in the present study could reflect the association between AF and impaired cognition. However, given that AF was not assessed as part of the present study this relationship cannot be directly assessed and further research is warranted specifically within the ACHD population.

Similar to the ToF group, the Simple group also showed a significant association between younger age at repair and impaired cognitive functioning (executive control). As discussed above, the vulnerability of younger patients due to the immature development of their brain may put them at an increased risk of embolization, hypoxia and brain damage when undergoing cardiac surgery, causing long-term complications such as cognitive impairment (Newburger and Bellinger, 2006).

Longer time (years) since the last surgery was associated with poorer motor function in the Simple group. Although these findings appear contrary to expectation given that one would expect to see more cognitive impairment immediately after surgery. However, given that these groups of patients are generally operated very early on in life when their brains are weaker and fragile, these procedures may cause permanent damage in the form of cognitive impairments, which may then persist or remain stable over a period of time, potentially resulting in the observed relationship.

Similar findings have been reported in patients undergoing coronary artery bypass surgery, with cognitive impairment persisting up to 5 years after cardiac surgery (Stygall et al, 2003). Alternatively, it could be speculated that longer duration since surgery is indicative of a younger age at the time of repair, which as discussed above can impact cognitive outcomes (Newburger and Bellinger, 2006). However, more work and longitudinal examination is required to make

conclusive judgments, as the cross-sectional nature of this data does not allow the determination of causality.

Summary

Overall the results of these analyses demonstrate that a wide range of clinical, demographic and mood related factors have the potential to influence cognitive functioning. Amongst all the variables, clinical factors were more frequently associated with cognitive outcomes than demographic or mood factors. Within the clinical variables post-operative CNS complications was a key explanatory variable across the different domains assessed, both by total sample and in independent groups. Given that CNS complications may reflect cognitive problems; it is not surprising to see that these are predictive in this study. However, it does suggest that at least some of the cognitive difficulties in this patient group do persist into adulthood.

The two-fold analyses demonstrated considerable variability in factors associated with cognitive functions across the different structural complexity groups. This confirms the diverse nature of CHD and the role that different structural complexities and their associated treatments may play in the evolution of cognitive impairments in adulthood.

9.4 Cognitive functioning and QoL in ACHD patients

The results of the univariate screening conducted to identify the association between cognitive functioning and QoL showed no significant association between cognitive functioning and physical QoL in either the total sample, or the four structural complexity groups. Similarly, the total study sample showed no significant association between cognitive functioning and mental QoL. When the structural complexity groups were assessed individually a significant univariate linear association was noted with cognitive functioning showing a positive association with mental QoL in the Simple group alone.

Within the multivariate analysis, reduced mental QoL in the Simple group was associated with higher levels of depression and negative affect, but no unique variance in the outcome was explained by cognitive functioning. These results demonstrate that the effect of cognitive functioning on mental QoL might have been obscured with the addition of other variables such as mood, which explained more unique variance in mental QoL.

It is possible that the QoL measure (SF-36) used in the present study was not sufficiently sensitive to detect any relationship with cognition. Alternatively, it is possible that this group of patients do not present with extremes of cognitive impairment which may be sufficient to find a relationship to QoL. However, contrary to the findings of the present study Idorn et al, (2013) reported a significant negative association between cognitive speed and poorer physical and mental QoL as measured by the SF-36. However, this study only included patients diagnosed with SV, thus limiting the generalizability of the findings.

Future studies may benefit from conducting a more in-depth exploration of the association between QoL and cognitive functioning, perhaps using a wider range of both generic and disease specific measures of QoL, to be able to evaluate the aspects of QoL important to this patient group (See chapter 15 for a more detailed discussion on the subject).

The strengths, limitations and implications of this study are discussed in detail in Chapter 15 (Final overall discussion) and the following chapters present the background, methodology and results of the follow-up study conducted.

10 STABILITY AND LONGITUDINAL ASSESMENT OF COGNITIVE FUNCTIONING IN ACHD

10.1 Prologue

Following a discussion of the concept of longitudinal cognitive research this chapter examines the stability of cognitive functioning in ACHD. Finally, it presents the methodological challenges associated with the longitudinal assessment of cognitive functioning; the different technique commonly used to assess change in cognitive functioning; and discusses how these informed the techniques applied within this study.

10.2 Stability of cognitive functioning in the normal adult population

Cognition is dynamic and may be subject to change, even in the absence of any pathophysiology. Age is one of the dominant factors driving change in cognition. Studies have reported that different domains of cognitive functioning have a differential pattern of change over time. While domains such as verbal and numerical ability are associated with little age-associated decline, other domains of cognitive functioning such as memory, processing speed and executive function tend to show more age related decline (Deary et al, 2009). It has been reported that these declines in cognitive functioning can begin as early as the middle age (i.e. thirties) or sometimes even sooner (Park and Reuter-Lorenz, 2009).

Considerable individual variability has been reported in the degree to which declines are noted across individuals that are within "normal cognitive ageing". Assessing the stability of cognitive function can be done to investigate age related changes in cognitive functioning i.e. 'cognitive

ageing'. Alternatively changes in cognitive functioning can also be assessed over shorter periods of time, to investigate the level of within individual variability in cognitive functioning, which may be driven by factors other than ageing. The objective of the present study was to investigate the short-term stability of cognitive function as opposed to cognitive ageing.

Cognitive functioning has the ability to influence different areas of an individual's life for instance their ability to work, earn a living, maintain meaningful relationships, self-care and overall wellbeing. Assessing the stability (or lack of) of cognitive functioning is critical given that these mental abilities and functions are essential to an individual's ability to live, sustain independently and lead fulfilling lives, and decline in these functions can have wide spread implications.

10.3 Longitudinal assessment of cognitive functioning in adult congenital heart disease

The existing literature showed a lack of longitudinal studies assessing the stability of cognitive functioning in ACHD patients; the available longitudinal evidence only focused on the paediatric population (Snookes et al, 2010; Griffin, Elkin and Smith, 2003). A systematic review of studies assessing cognitive and motor outcomes in children with CHD, reported limited number of longitudinal studies assessing cognitive functioning (N=8). Furthermore, the authors emphasized the importance of a well-designed longitudinal study as a potentially valuable basis for research aimed at identifying techniques to decrease the incidence of brain injury and its long-term impact such as cognitive impairments (Snookes et al, 2010).

Bellinger and Newburger, (2016), assessed a group of TGA patients longitudinally and conducted neurodevelopmental and cognitive assessments between the ages of one and sixteen. The authors reported that this group of patients consistently demonstrated neurodevelopmental and cognitive impairment over the years. Furthermore, the patients experienced increasing

cognitive impairment with age, perhaps due to the growing cognitive demands placed on them with advanced education and more complex situations (Bellinger and Newburger, 2016). These results showed the presence of persistent cognitive impairment in children with CHD over time and demonstrated the importance of continually assessing cognitive functioning in TGA patients and CHD patients in general. Although these longitudinal studies showed the persistence and development of cognitive impairment as these groups of patient's grow older, given that cognitive functioning is still in its developmental stages in childhood the stability of cognition cannot be assessed.

There is a lack of studies assessing stability of cognitive functioning in adult CHD patients. This lack of longitudinal evidence limits the understanding of the long-term trajectory i.e. stability and/or decline of cognitive functioning in patients with ACHD. Furthermore, it also limits the understanding of whether cognitive stability in the different structural complexity groups varies over time.

More longitudinal research assessing cognitive changes in ACHD will enable a better understanding of the stability of cognitive functioning in the ACHD population along with identifying predictors of any change in these functions. Information about the modifiable factors (if any) impacting the long term cognitive outcomes in these group of patients will not only enable the development of protective strategies but also help provide age appropriate support and interventions where necessary in the adult population. Given the rise in the number of ACHD patients due to increased survival rates, understanding the long-term trajectory of cognitive outcomes is important, as evidence from longitudinal studies could have implications for clinical management of this patient group.

10.4 The concept and rationale for longitudinal assessment of cognitive functioning

Longitudinal cognitive assessments involve examining the same set of individuals on more than one occasion, using the same or similar measures. The length of time between these consecutive assessments varies greatly in studies and relates both to pragmatics (e.g. funding) and to the question being asked (i.e. whether there is an expected rapid disease progression e.g. dementia). Longitudinal assessments can be done for a number of different reasons including i) assessing individual performance on different cognitive domains over time in order to identify any changes, positive and/or negative, associated with age, e.g. early detection of mild cognitive impairment (MCI) and dementia; ii) to investigate the impact of different treatments and therapeutic techniques on cognitive outcomes, thus enabling the assessment of long-term treatment related benefits and/or complications (Griva et al, 2006; Newman et al, 2001); iii) to assess the cognitive stability or decline over time in long term neurological disorders such as aphasia and Parkinson's disease (Starkstein et al, 1992); iv) to assess the stability of cognitive functioning in long-term chronic conditions that are known to have an impact on the patients cognitive outcomes for instance CHD. In relation to the last category, individuals with ACHD may show greater variability in their cognitive performance when assessed at different time points in comparison to the normal population. This is the question that is addressed in this follow-up study.

10.5 Methodological considerations of conducting longitudinal cognitive testing

With longitudinal cognitive testing the phenomenon of 'practice effect' may occur, which is described as an improvement in a test takers score from one assessment to the other and is characteristic of nearly all longitudinal cognitive assessments (Bartels et al, 2010; Goldberg et al, 2015). Several factors could be considered important in explaining the practice induced effects of repeated testing, for instance increased familiarity with the test and what the testing procedure involves, test sophistication, which is the test takers improved knowledge of how to

respond advantageously to a test given their prior experience of solving the problem/task and improvement of an underlying function as a result of practice, may all contribute to the practice induced effects (Erickson, 1972; Bartels et al, 2010). The time frame between the two assessments can also be a contributing factor to the extent of practice effects. A shorter duration is more likely to facilitate practice effects, as the test taker is more likely to remember the test and the strategy applied upon reassessment. Evidence shows that practice effects may persist for as long as two years after the initial assessment (Lezak et al, 2012). The presence of practice effects makes it difficult to establish a distinction between a 'real change' and change due to prior exposure to the test being administered.

Within the cognitive literature the use of an alternate form of a test is recommended when conducting longitudinal cognitive assessments to address the issue of practice effects. The rationale behind the use of alternate forms is to measure the underlying cognitive function in question, using a different measure with subtle changes, which assesses the same function to provide comparable results to those of the original measures. The alternate form is believed to help reduce the presence of any practice effects that may be present due to familiarity with the original test utilized. However alternate forms are not available for all tests of cognitive functioning and in the absence of one, examiners generally repeat the same measure on different time points. When using an alternate form, it is essential to check if the reliability and validity of the measure has been assessed in comparison to the original form, in order to ensure that it assesses the same function. Therefore, alternate forms must match the original measures in terms of style, number of items, type of content and the method of administration (Groth-Marnat, 2009).

However, the use of alternate test versions may not eradicate the problems of repeated testing entirely (Lezak et al, 2012). While the use of alternate forms enable changing the content of the

test, the examinee may have adapted or learned the overall style and format of the test administered, making it easier to complete upon reassessment. A good example of this would be the WCST test of executive functioning, which requires the test taker to identify a pattern and strategy in order to be able to solve the task by matching a set of cards to 4 key cards using three principles i.e. by colour, form and number (See Chapter 7 for details). While one may attempt to change the colour or the shape of the test symbols, the fundamental concept of matching them to the key cards using the three principles needs to remain the same, in order for the two test forms to be comparable. Thus making it relatively easy for the test taker to replicate the strategy previously applied, given that the 'novelty' of the test may be lost upon reassessment, due to familiarization with the test and its execution (Groth-Marnat, 2009).

Lastly, it is important to note that while practice effects can be considered an interference when interpreting test results, they could also reflect some level of cognitive ability. For example, the ability of an individual to learn and remember a strategy previously applied, and to re-apply it upon re-assessment in itself indicates some cognitive skills.

Another common challenge associated with repeated testing is that of 'regression to the mean'. This statistical phenomenon implies that extreme scores (i.e. towards the upper or lower end of the range of scores) at first assessment are statistically more likely to show a significant change upon reassessment, and appear closer to the mean/norm in a repeated measures design when compared to those with a moderate score at the first assessment (Barnett, Van Der Pols and Dobson, 2005). The presence of regression to the mean complicates the measurement of change over time as it can make a natural variation in repeated data look like a real change, and can therefore affect the true magnitude of change observed (Barnett, Van Der Pols and Dobson, 2005). For instance, if the regression to the mean is not taken into account an improvement in a test score over time may be interpreted as an improvement in the underlying cognitive domain,

while in fact it may simply be a result of regression to the mean. One way of dealing with this issue is the use of residualized change scores, as these scores control for baseline variance (See Section 10.6 for description of change scores) (Levine et al, 2007).

10.6 Measurement of change in cognitive functioning over time

In order to assess change in performance (i.e. improvement or decline in cognitive functioning) it is important to be able to reliably quantify the difference between the first (Time 1) and second (Time 2) assessment scores, while controlling for the influence of confounding factors that may be responsible for the change observed. There are several ways to detect a statistically significant change in cognitive functioning over time but each technique has its own advantages and disadvantages. Some of the common methods used to assess change in cognitive functioning are discussed below.

One technique is the use of simple change (delta) scores, which assess change in cognitive functioning simply by calculating the difference between the scores on the first and second assessment. Another technique is the use of Reliable Change Index (RCI) scores, which are derived by calculating the difference between the T1 and T2 scores, and dividing this value by the standard error of the difference of the test scores, to obtain a standardized score (See Figure 10.1). A modified version of the RCI, RCI_{PE} has been developed in order to control for practice-induced effects (Chelune et al, 1993). Calculating the RCI_{PE} involves calculating the difference between the discrepancy of test scores (T1 and T2) and the discrepancy of the mean from the control group (M1 and M2), divided by the standard error of the difference (See formula below).

An alternative method commonly adopted is the use of residualized change scores. This approach utilizes a regression equation by regressing T1 scores onto T2 scores resulting in a

standardized change score (derived from the two scores of each participant). These residualized change scores are adjusted for baseline variance, by removing the correlation between the two scores (Prochaska et al, 2008).

Formula used to calculate the Reliable Change Index (RCI) and RCI_{PE}

$$RCI = (T_2 - T_1) \div S_{diff}$$

$$RCI_{PE} = (T_2 - T_1) - (M_2 - M_1) \div SED$$

T_2= time two scores
T_1= time one scores
$M_{1=}$ control group mean at time one
$M_{2=}$ control group mean at time two
S_{diff}= Standard Error of difference between two test scores
SED= Standard Error of the Difference

* Formula adopted from Jacobson and Truax, (1991) and Duff, (2012)

There are advantages and disadvantages to each of the methods discussed above. Although mathematically straightforward and easy to execute, the simple (delta) change score has been criticized for its over simplicity and measurement error (difference in actual value versus value obtained by the measure/technique used) in comparison to other techniques. As all measurements contain some degree of error (i.e. not perfect reliability), any change score calculated by subtracting T1 scores from T2 scores would contain error from both time points (Llabre et al, 1991). Further the use of unstandardized scores such as simple change scores may restrict comparison across different measures, if they use a different unit of measurement, for instance timed tests versus vocabulary tests (Russell, 2000). Lastly the simple scores do not take into account other statistical challenges such as regression to the mean, which may affect the true magnitude of change observed.

While the RCI_{PE} method is often used to assess significant change in cognitive functioning while controlling for practice effects, it is limited by certain methodological challenges. The RCI_{PE} method assumes that the change in an individual test score equals the mean score of the normative group, which makes the presumption that the degree of change in the measure over time is equal across different groups (i.e. subjects and control group), therefore not allowing for differential practice effects across individuals. Given that the level of cognitive functioning in certain patient groups such as ACHD may not be the same as the normative group, assuming that the degree of change due to practice effects over time will be the same, may lead to an incorrect estimation of change.

Calculating residualized change scores is a regression based technique, which takes into account the association between the two scores (T1 and T2) and removes any correlation between them, thereby controlling for the problem of regression to the mean (Van Der Elst et al, 2008). Additionally, the resultant score is standardized in nature, which allows different measures to be compared directly irrespective of the original test score metrics (Strauss, Sherman and Spreen, 2006).

Given the nature of the data in this study and the non-normally distributed nature of some of the NP test scores, the use of the regression approach (residualized change score) was considered the most appropriate (See Chapter 12 for details of the methodology).

11 INTRODUCTION TO THE FOLLOW-UP STUDY AND AIMS AND OBJECTIVES

11.1 Summary of the background chapter and rationale for research

The objective of this section of the thesis was to assess the stability of cognitive functions in ACHD patients, and to establish if the impairments noted in the cross-sectional study remained stable, improved, or declined over time.

It also aimed to assess if the stability of cognitive functioning varied across different structural complexity groups over time. Furthermore, predictors of the observed change in cognitive functioning were also identified in order to better understand the factors that may have the ability to influence changes in cognitive functioning.

Lastly, this study also aimed to compare the stability and/or change in cognitive functioning in the ACHD sample to that of the normal healthy population in order to establish if the stability of cognitive functioning was different within this patient population.

11.2 Research questions and objectives of the follow-up study

Research question 1: Does cognitive functioning in ACHD patients change over time?

Specific objectives related to the research question 1 included:

- To assess the stability of cognitive functioning in ACHD patients
- To investigate differences in cognitive functioning between the complexity groups

- To investigate if the level of cognitive functioning changed differentially in the different structural complexity groups over time
- To compare the stability of cognitive functioning in ACHD patients to that of a normal healthy population.

Research question 2: **What factors predict change in cognitive functioning in patients with ACHD?**

Specific objectives related to the research question 2 included:

- To identify clinical, mood, and demographic predictors of change in cognitive functioning in ACHD patients.

11.3 Hypotheses

No specific hypotheses were formulated for the purpose of this study, as these investigations were exploratory in nature.

12 FOLLOW-UP STUDY METHODOLOGY

12.1 Prologue

This chapter presents the methodology adopted for the follow-up study. It is divided into the following sections; first, the study design and procedures are detailed; followed by a description of the measures utilized; and lastly the statistical strategy adopted for data analysis is explained for each research objective.

12.2 Study design and setting

This study adopted a within-subject repeated measures design, and followed-up a subset of the sample from the cross-sectional study. Participants with complete NP data in the cross-sectional study were invited to participate in the follow-up study, in order to investigate the stability of their cognitive functioning over time. It was conducted at the Heart Hospital, London (University College London Hospitals NHS Foundation Trust). The NRES Committee London – Bentham and the University College Hospital Ethical Committee granted an extension on the ethical approval obtained for the cross-sectional study (Study Ref. No- 08/HO715/105).

12.3 Participants and Sampling procedures

12.3.1 Sample size calculation

A sample size calculation was conducted using G-Power software (Faul et al, 2007), for a study including four groups, to detect a significant change in cognitive functioning over time (using repeated measures ANOVA and/or Multilevel Modelling). Based on repeated measures sample size calculations, 55 participants in each group were needed (α=0.05, β=0.80, r= 0.90) to be able to detect a significant change in cognitive functioning.

12.3.2 Inclusion and exclusion criteria

In addition to the inclusion and exclusion criteria established for the cross-sectional study, additional criteria were used for the follow-up study. Participants were eligible if i) they had complete cross-sectional NP data, and ii) their cross-sectional assessment must have been completed at least a year and a half prior to the follow-up assessment. This was done to try and minimize the influence of practice effects and to try and recruit as many potential participants as possible within the study time-frame. In addition, participants were excluded if they had recently (within last 6 months) undergone a surgical procedure; this was done, as the use of anesthetics during the surgical procedure could have resulted in cognitive changes which may have obscured the impact of ACHD on cognitive outcomes.

12.3.3 Study sample and recruitment procedure

All eligible participants included in the cross-sectional study (N=310) were sent a letter inviting them to take part in the follow-up study, along with an information sheet detailing the study procedures and an interest form to indicate his or her willingness to participate in the study (see Appendix-T for information sheet). Two weeks were allowed for patients to consider participation before a reminder letter was sent. For patients who agreed to participate, a week before their prescheduled hospital outpatient appointment (OPA) a reminder telephone call was made, to confirm the study appointment. Following the assessment all participants were sent a letter thanking them for taking part.

A total of 210 (68% of total cross-sectional study sample) patients indicated an interest in participating in the follow-up study. Of these, 153 (73%) consenting participants completed the follow-up assessment, resulting in 49% of the cross-sectional study sample being followed-up (See Figure 12.1 below for recruitment details). There were an equal number of participants in

the TGA and SV group and a similar proportion of participants in the ToF and Simple group (TGA= 35 (22.88%), SV=35 (22.88%), ToF= 42 (27.45%), Simple=41 (26.79%). The remaining participants could not be recruited due to time constraints of the research project.

12.3.4 Data collection

Patients who indicated an interest in participation were assessed on the day of their regular OPA. The purpose of the study was explained to each participant using the information sheet prior to signing an informed consent form; data was gathered only after written consent was obtained. Participants were given a signed copy of the consent form for their records (See Appendix-U).

All the assessments were conducted at the Heart Hospital London and prior to the participants' OPA, where possible, in order to avoid fatigue having an impact on the participants' performance. Demographic information was collected at the start of the session followed by administration of the NP test battery and the self-report questionnaires assessing mood. This sequence of assessment was consistent across all study participants; and each participant was given an optional break of 5 minutes between the NP assessment and completion of the questionnaires.

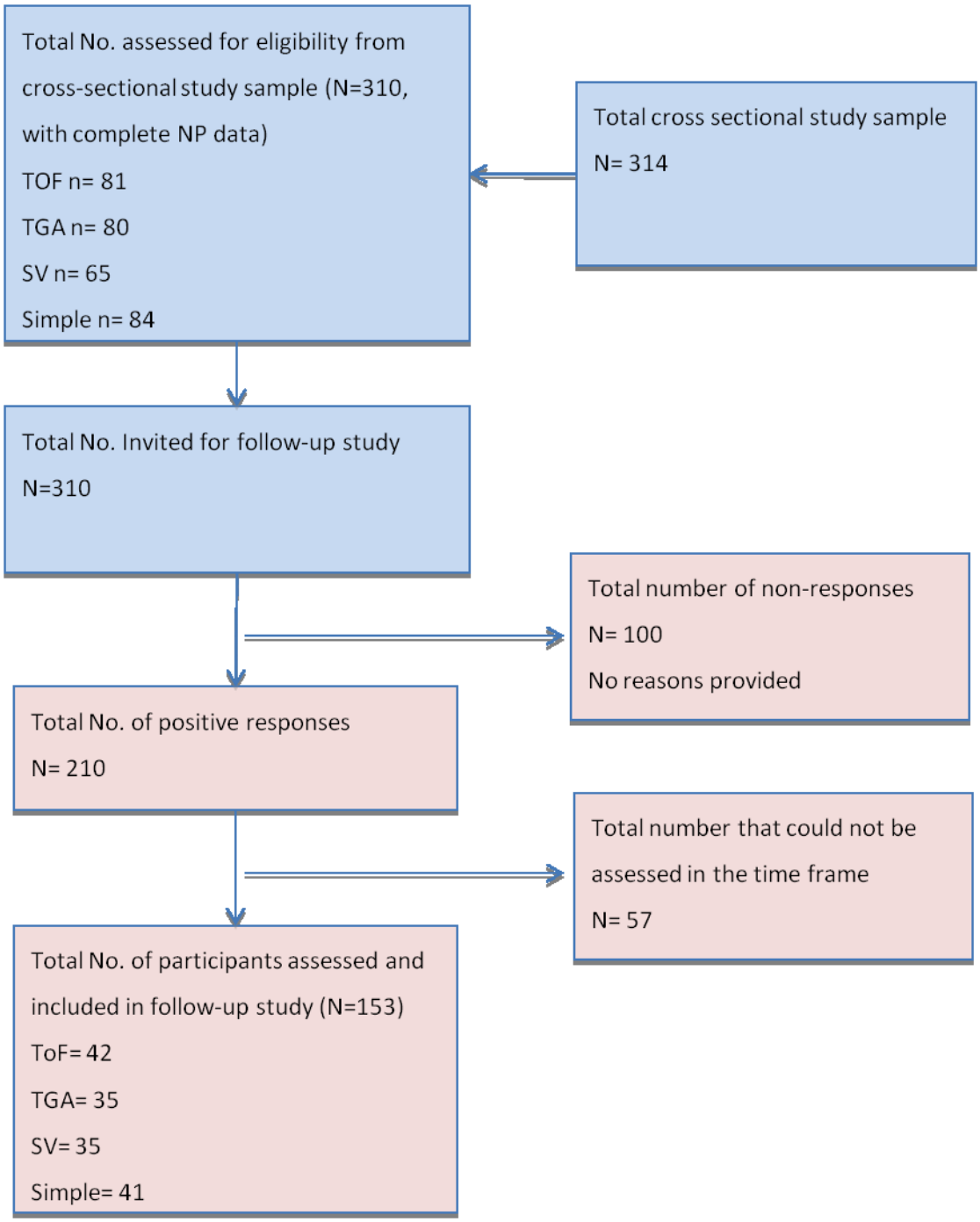


Figure 12.1: Flow chart of the follow-up study recruitment procedure

12.4 Measures utilized in the follow-up study

12.4.1 Neuropsychological (NP) measures

The NP test battery used in the cross-sectional study was re-administered to each participant at follow-up. To control for practice effects, alternate versions of the NP tests were used where available (TMT, SDMT, COWA, and RAVLT) (See Table 12.1 for details). Tests with no appropriate alternate versions were re-administered using the original test utilized in the cross-sectional study (WCST-64, Stroop test and Grooved pegboard). Details of all the tests, including the alternate versions of the NP tests where used, are presented in Table 12.1 below.

The IQ test (WAIS-III) was the only test that was not re-administered at follow-up. Intelligence as a construct has been reported as being stable over time, with tests producing similar scores upon reassessment (Moffitt et al, 1993; Canivez and Watkins, 2001). The NP test administration procedures including the order of assessment, consenting procedures and the test-taking environment were consistent with those in the cross-sectional study (See Chapter 7, Section 7.5.1 for details).

12.4.1.1 Scoring procedures used for NP tests

All NP tests were scored using the same scoring procedures utilized in the cross-sectional study (i.e. z-scores). Normative data used in the cross sectional study was utilized again for the purpose of comparison to the normal population, in the follow-up study. This was done as normative data for the alternate test versions were not available. Furthermore, this allowed consistency of the normative data used for the purposes of comparing the performance over time.

Table 12.1Description of the NP test battery and alternate NP tests used at follow-up

Tests utilized*	Domain assessed	Alternate form	Alternate form/ test-retest reliability	Description of the alternate form, in comparison to the original measures
Alternate version of Trail Making Test (TMT) (Franzen, Paul and Iverson, 1996)	Divided attention	✓	Part C, r= 0.70 Part D, r= 0.78	Two alternate versions are used, one for each part of the test. TMT-C is used to replace TMT-A and TMT-D to replace TMT-B. Both the alternate forms have the same relative positions of the circles with inverted label sequences compared to the original. The test administration and scoring procedure remain the same as the cross-sectional study.
Alternate version of Controlled Oral Word Association Test (COWA) (Dikmen et al, 1999)	Executive function	✓	r= 0.72	The alternate version includes three new letters B, D and T, which replace the original letters, F, A and S. The test administration and scoring procedure remain the same as the cross-sectional study.
Stroop neuropsychological screening test (Trenerry et al, 1989)	Executive function	X	r=0.90	N/A
Grooved Pegboard (GP) (Matthews & Klove, 1964; Wang et al, 2011)	Motor function	X	Dominant-r=0.91 Non-dominant-r=0.85	N/A
Wisconsin Card Sorting Test -64 (WCST-64) (Kongs et al, 2000)	Executive function	X	N/A	N/A
Alternate version of Symbol Digit Modalities Test (SDMT) (Hinton-Bayre and Geffen, 2005)	Attention	✓	r= 0.74	The symbols in the alternate version are different to the original form; but the mirrored symbol pairings are maintained to ensure comparability. The response array is matched to the original form to ensure the same level of visual scanning is required. The test administration and scoring procedure remain the same as the cross-sectional study.
Alternate version of Rey Auditory Verbal Learning Test (RAVLT) (Lezak, 1983)	Memory and learning	✓	RAVLT total acquisition, r= 0.60-0.77 (across trials)	In the alternate version the original list of words is replaced by a new list and a new distracter list. The test administration and scoring procedure remain the same as the cross-sectional study.

*Please see Appendix-V for the complete NP test battery (follow-up study), N/A- Not Applicable

12.4.2 Measures of mood

Along with the NP tests, measures of mood were also re-administered at follow-up. This decision was made for two reasons: i) to be able to control for mood as a covariate in subsequent analyses, and ii) to be able to investigate if a change in mood state was a predictor of change in cognitive functioning.

A total of three self-report questionnaires were re-administered at follow-up, i) The Positive and Negative Affect Scale (PANAS) (Watson, Clark and Tellegen, 1988), ii) Spielberger State Anxiety Inventory-6 (STAI-6) (Marteau and Bekker, 1992) and iii) Centre for Epidemiological studies Short Depression Scale (CESD-10) (Andresen et al, 1994). Standard scoring procedures were used to score all the questionnaires (See Section 7.3.6 for details and Appendix-I for copy of questionnaires).

12.4.3 Demographic details

Demographic information was collected from each participant using a standard self-report form. Information gathered included: age, marital status, living status, total years of education and employment status. Demographic variables such as ethnicity and gender were considered constant and not recorded again; information regarding these variables was obtained from the cross-sectional study database.

12.4.4 Clinical measures

The clinical history of the participants was not recorded again at follow-up; the data gathered in the cross-sectional study was utilized for the purpose of analyses. Only information regarding any additional interventions, surgical procedures and/or changes in medication that patients may have undergone in the time between the two assessments was recorded. This was done to enable the assessment of any influence these factors may have had on cognition.

12.5 Statistical Analysis

This section details the statistical strategy applied to assess the aims and objectives of the follow-up study. Details of the preliminary analyses (missing data, data distribution) and the main analysis (Multilevel Modelling - MLM) are presented below. All analyses were conducted using IBM SPSS (Version 21).

12.5.1 Missing data analysis

After checking the data entered into SPSS for any inconsistencies, such as manual data entry errors (and correcting where necessary through checking of the paper data collection forms), a missing values analysis was conducted; both at item level and scale level (Field, 2009). The patterns of missing data that emerged included:

- Individual items missing within sub-scales of self-report psychosocial questionnaires
- Entire sub-scales missing within a single administration of a questionnaire

No NP data was found to be missing in the follow-up study, and the overall proportion of missing data was under 5%. The exact proportion of missing data on each variable is presented in Appendix-W. A decision to carry out an imputation was made for three reasons: i) in order to be able to obtain a complete data set, ii) to minimize the loss of sample size, and iii) to avoid different sample sizes across analyses. Imputation procedures were conducted for data missing at scale level, and one imputation was performed using SPSS 21.0. Multiple Imputation procedures were conducted on the basis of the predictive mean matching (PMM) (Please see Chapter 7 for details). As discussed in Chapter 7, some neuropsychological tests scores were not applicable to all participants, for example the WCST-64 - failure to maintain set score, which can only be calculated if the participant has completed at least 2 categories and attempted a third. Therefore for those that did not complete adequate categories the score was considered

not applicable and labelled as 888. As these scores were not applicable as opposed to missing they were not subject to imputation. The imputed dataset was used for all further analyses.

12.5.2 Differences between responders and non-responders

A sensitivity analysis was conducted to assess whether there were any differences between patients that participated in the follow-up study and those that did not. T-tests and Pearson's chi square tests were performed to compare characteristics of patients who had only completed the cross-sectional assessment and those that completed both the cross-sectional and follow-up assessment, on all variables including clinical, mood, demographic and NP scores. Furthermore, an analysis of variance (ANOVA) was conducted to investigate if the test-retest interval differed significantly between the structural complexity groups in the follow-up study.

12.5.3 Distribution of variables

The data distribution of each variable was examined to assess the normality of the data points. This was done visually using histograms, and statistically, by performing the Kolmogorov-Smirnov test, for which a statistical significance level of $p < 0.001$ was used to detect non-normality (See Appendix-X). When conducting statistical analysis non-normally distributed data is generally transformed using mathematical formulas to obtain a normal distribution. The data in the follow-up study was not transformed for two reasons: i) to maintain comparability with the cross-sectional data, which was not transformed and ii), because data transformations can hinder the interpretation of the results, by changing the nature of the data (Osborne, 2005).

12.5.4 A note on the level of statistical significance

A significance level of $p<0.01$ was used, unless stated otherwise. This was done to avoid the risk of obtaining a false-positive result i.e. rejecting the null hypothesis when it is in fact true (Type 1 error), due to the large number of tests performed. Furthermore, post hoc tests were employed to adjust for multiple testing where necessary. The main effects in the study were

only considered significant at $p<0.01$. A less conservative significance level of $p<0.05$ was adopted when identifying potential covariates and conducting univariate screening to identify predictor variables for a hierarchical regression analyses. This was done in order to reduce the risk of removing any potential predictor variables based on stringent significance levels.

12.6 Statistical analyses adopted for each research objective

This section details the statistical analyses adopted in order to address each of the research objectives in the follow-up study.

12.6.1 Stability of cognitive functioning in ACHD patients

To assess change in cognitive functioning over time, Multilevel Modelling (MLM) was utilized for each NP outcome variable (Marques and Hamilton, 2014). MLM was the preferred method as, in comparison to more traditional methods such as repeated measures ANOVA: i) it allows the hierarchical structure of the data to be considered, by accounting for the non- independence of scores given on the same test/questionnaire by the same participant at multiple time points, i.e. data points are more similar within individuals over time than they are between individuals (Cartwright, Traviss and Blance, 2012); and ii) it has the ability to include all collected data points despite missing data. The application of MLM approaches are increasingly being recommended in designs where the data has been collected from individuals on more than one occasion, as multilevel models imply that scores are clustered within each individual (Queńe and Van den Bergh, 2004).

Recommendations for dealing with repeated measures data using SPSS software have been provided by Heck and colleagues (2014). These recommendations were used to guide the analysis within this study. In preliminary steps to prepare the data for analysis, the data was restructured (into a 2- level dataset) to recognize its hierarchical nature. This resulted in a vertical arrangement of the data points, with each participant having two rows of observed

scores, with each row representing one time point (See Figure 12.2 for a conceptual visual representation of the data structure) (Heck, Thomas and Tabata, 2014). The specifics of the MLM analysis are presented in the following sections - Section 12.6.1.1 discusses the preliminary MLM analysis (assumption testing) and Section 12.6.1.2 details the main MLM analysis (assessing the main effect of time, group and 'time x group' interaction on each NP score).

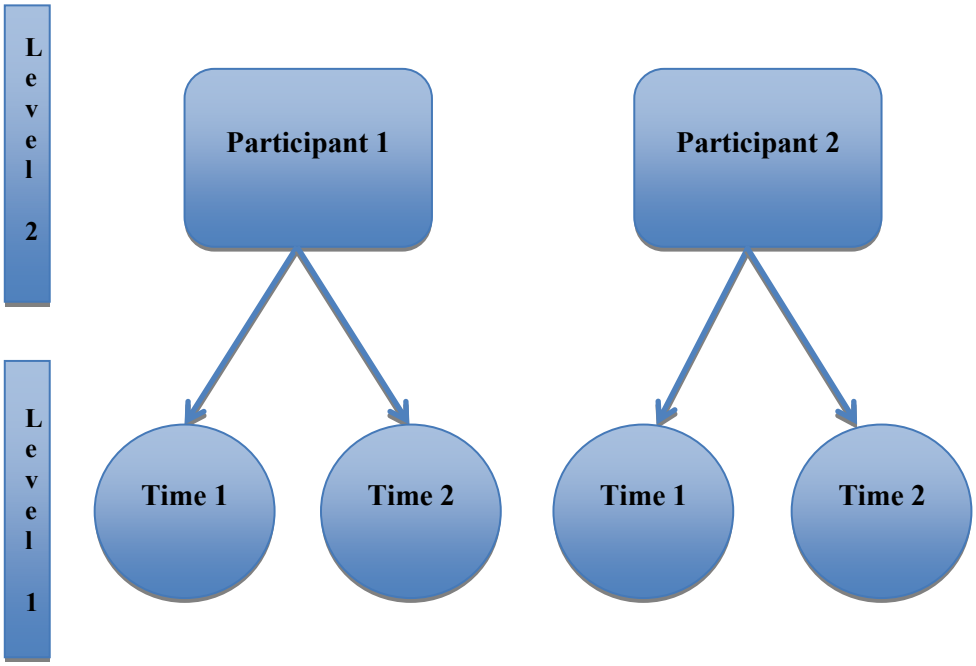


Figure 12.2**:** A conceptual visual representation of the MLM hierarchical data structure

12.6.1.1 Preliminary MLM analysis

Prior to running the MLM analysis, in order to check the assumption that scores within each participant were highly correlated an initial MLM analysis was run for each NP outcome, which included no predictors and a scaled identity covariance type for both levels one and two in order to calculate the Interclass Correlation (ICC). ICC estimates the amount of variance in the outcome that can be explained by the between-subject variance. A higher ICC suggests that scores within a participant are more similar than between participants, therefore violating the assumption of independence (Heck, Thomas and Tabata, 2014). This statistic indicates whether

the higher-level grouping has an impact on the estimates in a way that makes MLM suitable for the data analysis. A cut-off score of 0.05 was used as a criterion with an ICC smaller than this suggesting little advantage in conducting MLM (Heck, Thomas and Tabata, 2014). If an outcome variable in this test achieved ICC>0.05, MLM was performed in its main analyses. Alternatively, if this ICC>0.05 was not achieved more traditional methods such as repeated measures ANOVA would be implemented.

12.6.1.2 Main MLM analysis

Each NP score was used as the dependent variable (DV) in the main MLM analysis, with the participants' years of education, and mood used as covariates. No new potential covariates were identified in the follow-up analyses; this maintained consistency and comparability between the cross-sectional and follow-up analyses. Covariates were selected based on a significant association with the DV ($p<0.05$).

A covariance structure representing the relationship between repeated measures needs to be specified for the data in the MLM analysis. SPSS provides a range of covariance structures suitable for repeated measures data including, i) unstructured, ii) diagonal variance, and iii) first-order autoregressive structure (AR1). An AR1 structure was chosen theoretically to model the correlation structure of within participant effects for these analyses, as scores at adjacent time points of each DV were likely to be correlated and are not assumed to be heterogeneous or unpredictable within each participant. The AR1 parameter takes into account the correlation between repeated measures (Field, 2009). A Restricted Estimate Maximum Likelihood (REML) method was used as a parameter for estimating a model, as opposed to the Maximum likelihood method, as REML is recommended for smaller sample sizes (Bryk and Raudenbush, 1992).

The main effect of time (a difference in scores between the two assessments), group (a difference between the groups irrespective of time-points) and time x group interaction

(difference in the pattern of means between the 4 groups across time points or change in the means of the groups across time) was assessed using adjusted mean scores. If the main effect for the group or the time x group interaction was found to be significant, pairwise comparisons were performed on the adjusted mean scores. The pairwise comparison allows comparing all possible time point combinations whilst controlling for family wise error rates (i.e. the inflated error from conducting several statistical tests on the same data), by correcting the level of significance for each test so that the overall Type 1 error rate across comparisons remains at 0.05 (Field, 2009). To measure the standardized effect size of the fixed effect of time, partial eta squared (η_p^2) was calculated (Lakens, 2013), and were interpreted using Cohen's criteria whereby 0.01 is a small effect, 0.06 is a moderate effect and 0.14 is a large effect (Cohen, 1988).

12.6.1.3 Graphical representation of the data

In addition to the MLM analysis, three additional graphs of the repeated measures were plotted to enable a visual representation of the data. This was done i) to enable assessing the stability of NP scores over time across the different complexity groups, and ii) to enable determining if the observed change was of a clinically significant magnitude (i.e. did the sample change from being impaired to non-impaired and vice versa over time), and iii) how stability in the study sample compared to the normal population. While MLM analyses utilized the entire study sample (i.e. those with and without data at both time-points) as MLM accounts for missing data, the graphs only represent the participants that have data for both time points. The three graphs and their interpretations are detailed below:

- Error bar plots (of means and their 95% Confidence Intervals - CI) were plotted for each structural complexity group and the total sample for both time-points. These were utilised to evaluate the relative mean performance of each group and the total sample in comparison to the normative mean score – which was set at the 0 i.e. representing no

standard deviation difference from the norms (indicated by a blue line in the figures). This helped evaluate if the groups declined/improved over time and if the group mean was different to the normative mean (i.e. the 95% CI do not cross the normative mean).

- Box-plots to evaluate the spread and variability of the data across the two time-points for each group were plotted. This helped identify differential variability of the data across time one and time two, within and between the groups. The whiskers in the graphs help see the shift in scores over time across the different groups, and indicate where the largest and smallest non-outlier scores are.
- Scatter plots to evaluate the correlations between time one and time two scores (i.e. test-retest correlation) for each group were plotted to assess stability of scores over time. They showed the best line of fit and the regression slopes for each group, which indicate the magnitude of the correlation between scores across time points. A higher correlation shows that scores at both time points were related and moved in a similar direction.

Test-retest reliability

The test-retest reliability of scores within this study sample was also compared to existing literature, on test-retest correlation from normal healthy adults, to compare the stability of cognitive functioning in the ACHD sample relative to that of a normal healthy population. Test re-test reliability refers to the temporal stability of a test from one assessment to the other when giving the same test to the same individual after a period of time; and the correlation between these two scores on the same test is in effect the test-retest reliability of the measure (Drost, 2011).

When considering the test-retest reliability across measures some limitations must be considered. One such limitation is the time interval between the first and second assessment. It has been reported that a very short duration may affect the retest results as participants may

remember their responses, causing memory to influence the results. On the contrary when the time frame between assessments is too long 'maturation' may occur (Drost, 2011). Drost, (2011) defines 'maturation' as the changes in the respondents or the subject factors that occur over time and cause a change in the measurement across time. The premise of the argument is that respondents could be exposed to things and confounders, which may affect or change their perception or underlying function in turn affecting the test-retest reliabilities. Therefore, when drawing comparisons across different samples, the time interval between assessments must be carefully considered.

Generally, a test-retest correlation of ≥ 0.7 is considered good (Field, 2009), however within the present study a slightly less stringent test-retest reliability coefficient of ≥0.6 was considered acceptable, given that the mean time between assessments was relatively large at 3.3 years, compared to the 1 month/1 year intervals commonly used by authors (of the measures used) for assessing test-retest reliability in the literature.

12.6.2 Identifying predictors of change in cognitive functioning

Another objective of the follow-up study was to assess if changes in cognitive functioning could be predicted by clinical and demographic factors and/or changes in mood state over time. Residualized change scores were calculated for each of the NP scores and the mood variables. There are several methods that can be utilized to calculate change scores, as discussed in Chapter 10 (See Section 10.6 for details). Residualized change scores were utilized for the purpose of this study; these change scores were then used for all further analyses.

In order to identify the demographic, clinical and mood related variables that predict change in cognitive functioning, hierarchical multiple regressions were performed. First, a univariate screening of all predictor variables was performed, by conducting a simple linear regression between each IV (cross-sectional demographic and clinical variables and mood change scores)

and DV (NP change scores). Only significant variables ($p<0.05$) in the univariate screening were included in the multivariate analysis, in order to reduce the number of redundant predictors from the model.

The order of the regression blocks and testing of all the related parametric assumptions (e.g. collinearity and multi collinearity) were kept consistent to those in the cross-sectional study analysis. The order of the regression blocks included i) demographics, ii) structural complexity, iii) procedural and surgical variables, iv) cyanosis/current saturation, v) current health/medication and vi) mood (See Chapter 7 -Section 7.7.2 for details and rationale of analysis). Lastly the regression analyses to identify predictors of change were only conducted for test scores that demonstrated a significant difference over time within the MLM analysis, as the other scores showed no significant difference over time.

The results of the follow-up study are presented in the next chapter – Chapter 13.

13 FOLLOW-UP STUDY RESULTS

13.1 Prologue

The primary aim of this chapter is to present the results of the follow-up study with each section of the chapter addressing the research questions presented in Chapter 11. It presents a description of the demographic and clinical characteristics of the study sample, followed by the results of the preliminary analyses conducted. Then the results of the multilevel modelling (MLM) analyses assessing change in cognitive functioning over time are discussed. Lastly the demographic, clinical and psychosocial predictors of cognitive change are presented.

13.2 Sample description (demographic and clinical characteristics) at follow-up

The follow-up study sample included 153 participants (49% of the cross-sectional study sample), with a median age of 35 years. The demographic characteristics of the sample are presented in Table 13.1 below. A very small proportion of participants had an additional surgical intervention between the two assessments (N=4; 2 participants from the SV group and 2 from the TGA group). Given the small proportion of participants with additional interventions, these variables were not included in any further analyses. Clinical history recorded in the cross-sectional study was utilized for all analyses pertaining to clinical variables.

13.3 Differences between responders and non-responders

There were no statistically significant differences noted between the responders and non-responders on any of the clinical, demographic or NP variables (See Appendix-Y).

13.4 Distribution of variables

The frequency distribution for each of the variables assessed was examined to evaluate normality. This was done visually by using histograms, and statistically, by performing the Kolmogorov-Smirnov test to detect non-normality (significance level of $p < 0.001$; See Appendix-X). The majority of the variables were non-normally distributed (i.e. Kolmogorov Smirnov statistic $p<0.001$), with the exception of positive affect, both the SDMT written and oral subtest scores, and the COWA test scores, which were normally distributed.

Table 13.1 Demographic characteristics of the follow-up study sample

Demographic variables		**N (%) or Median & interquartile range**
Gender	Males	84 (54.9%)
	Females	69 (45.1%)
Living status	Cohabiting (living with parent, spouse or friend)	130 (86.7%)
	Living alone (living independently on their own)	20 (13.3%)
Employment status	Employed/ Student/in training	125 (83.33%)
	Unemployed/ retired/ unable to work	25 (16.66%)
Occupational level*[a]	Managerial/ Professional	38 (25.3%)
	Intermediate	25 (23.3%)
	Lower	47 (31.3%)
	Never worked/unemployed	30 (20.0%)
Marital status	Married	105 (70.0%)
	Unmarried / Divorced/ Single	45 (30.0%)
Ethnicity	British (white)	134 (87.59%)
	Others	19 (12.41%)
Age	Age (Median, interquartile range)	35.00 (29.5 – 42.5)
Education	Years of education (Median, interquartile range)	13.00 (11-16)

*[a] = The National Statistics Socio-economic Classification (NS-SEC rebased on the SOC2010) (Rose and Pevalin, 2010)

13.5 Are there changes in cognitive functioning over time in ACHD patients?

The following sections detail the results of the MLM analysis conducted to investigate changes in cognitive functioning in ACHD patients over time [range of time since the cross-sectional assessment= 1.7 – 4.6 years, Mean (SD)= 3.36(0.67)]. ANCOVA analysis indicated that the time-interval between the cross-sectional and follow-up assessments was not significantly different between diagnostic groups [$f_{(3,149)}= 1.21$, $p= .307$]. The MLM results are presented

separately for each cognitive domain: executive functioning, attention, motor function and memory.

13.5.1 Changes in executive function over time

The results of the MLM analysis pertaining to the domain of executive functioning are presented in Table 13.2. The only test of executive functioning that showed a significant difference between time-points was the COWA, with a significant main effect for time ($F_{(1,165.74)}$=14.04, $p<0.001$). The mean difference across the two time points showed a gain in the scores (i.e. more words correctly recited) from time one (mean= -0.663; SE= .054) to time two (mean= -0.459; SE= .054), demonstrating an improvement in the scores upon re-assessment, with a medium effect size (η_p^2=0.07).

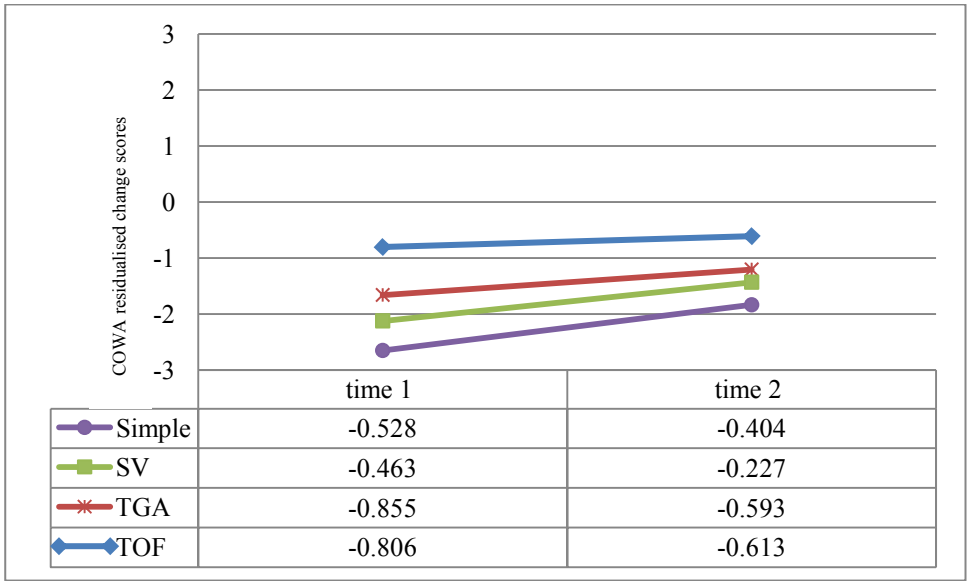
The main effect of group was not significant, demonstrating no differences in the test performance of the structural complexity groups, irrespective of time. Furthermore, the time x group interaction did not reach significance, thus demonstrating i) no difference in the pattern of means between the four groups at each time-point and ii) no differential change in the means of the groups across time. The adjusted means of the four groups on the COWA test at the two time-points are presented below in Figure 13.1.

The main effect of time on the Stroop test (p=0.799) and the WCST test scores; error (p=0.131), conceptual level (p=0.751), number of categories (p=0.400), trials to complete first category (p= 0.828), and failure to maintain set (p=0.189) were non-significant showing no difference in performance over time on these tests of executive functioning. Similarly, the main effect of groups was non-significant (all $p>0.01$) showing no differences in the test performance of the four structural complexity groups (irrespective of time). The time x group interaction term did not show any significant effects across all tests of executive function.

Table 13.2 MLM results (main and interaction effects) across groups on the measures of executive functioning

Measure	Effect of time	Effect size η_p^2	Effect of groups	Effect size η_p^2	Time X group interaction	Effect size η_p^2
COWA	$F_{1,165.74}$=14.04,p=**<0.001****	0.078	$F_{3,327.61}$= 2.41,p=. 066	0.021	$F_{3,166.72}$= 0.307, p=. 820	0.005
STROOP W	$F_{1,158.24}$= .065,p=. 799	0.001	$F_{3,318.60}$= 3.34,p=. 019	0.030	$F_{3,155.13}$= 0.60, p=. 615	0.011
WCST- Error	$F_{1,193.69}$=2.30,p=. 131	0.011	$F_{3,317.59}$= 1.41,p=. 237	0.011	$F_{3,194.11}$= 1.36, p=. 256	0.020
WCST- Conceptual level response	$F_{1,188.54}$=0.10,p=. 751	0.001	$F_{3,317.72}$= 1.58,p=. 193	0.014	$F_{3,188.24}$= 1.24, p=. 297	0.019
WCST- No of categories	$F_{1,190.13}$= .711,p=. 400	0.003	$F_{3,325.32}$= 2.22,p=. 086	0.020	$F_{3,190.11}$= 1.49, p=. 217	0.022
WCST- Trials to complete 1st category	$F_{1,287.13}$= .047,p=. 828	0.000	$F_{3,324.05}$= .875,p=. 454	0.008	$F_{3,287.15}$= 0.185, p=. 907	0.001
WCST- Failure to maintain set	$F_{1,250.86}$= 1.73,p=. 189	0.006	$F_{3,270.83}$= 1.12,p=. 338	0.012	$F_{3,250.45}$= 1.38, p=. 249	0.016

Note- WCST= Wisconsin Card Sorting Test, COWA= Controlled Oral Word Association test, **=p<0.01, η^2p- eta squared (0.01=small, 0.06=medium, 0.14=large)



	time 1	time 2
Simple	-0.528	-0.404
SV	-0.463	-0.227
TGA	-0.855	-0.593
TOF	-0.806	-0.613

Figure 13.1 Graphical representation of change in COWA scores

As discussed in Chapter 12, in order to visually explore the results of the MLM analysis, and assess the stability of scores over time, where a significant main effect of time was observed, additional graphs of the data were plotted. The graphs associated with the COWA scores are presented below (figures 13.2 to 13.4).

Figure 13.2 shows the mean score of the total sample below the normative mean (set at zero) on both time 1 and time 2, with the 95% CI not crossing the normative mean. Within the different groups, all complexity groups showed mean scores below the normative mean score, with the 95% CI not crossing the normative mean at time 1. At time 2, the ToF, TGA and Simple group did not cross the normative mean suggesting that the mean score of these groups was below the norms at both time points; the SV group showed mean scores closest to the normative mean, with the 95% CI crossing the normative mean at time 2, indicating that this group may not be significantly different to the normal population. In all groups time 2 means were greater than time 1 means, reflecting the main effect of time in the MLM analysis, suggesting an improvement in scores over time

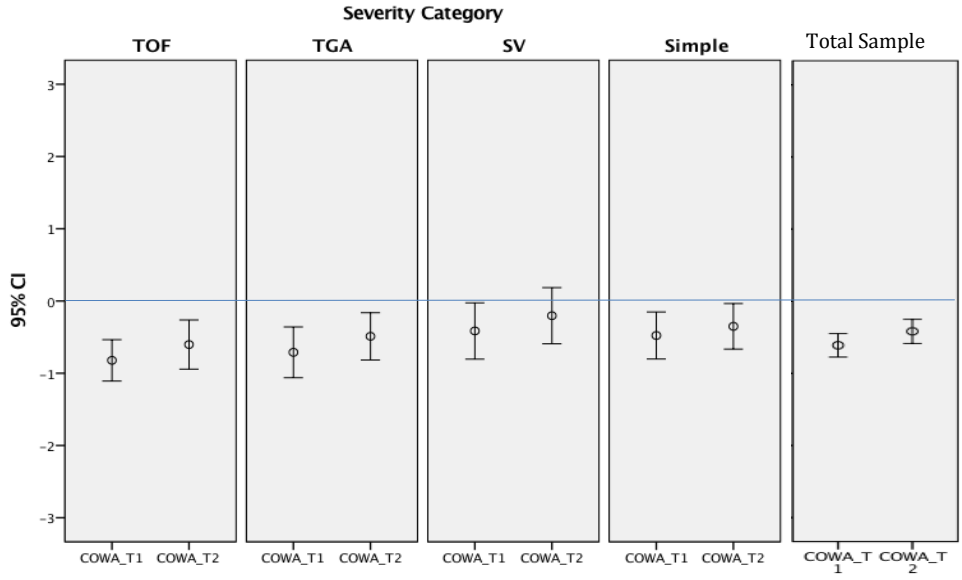


Figure 13.2 Error bar plot (Means and 95% CI) for COWA Time 1 and Time 2 scores

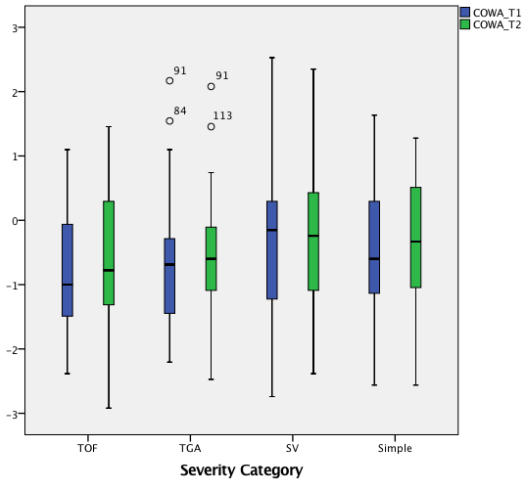


Figure 13.3: Variability of the COWA scores at both time points (Box plot)

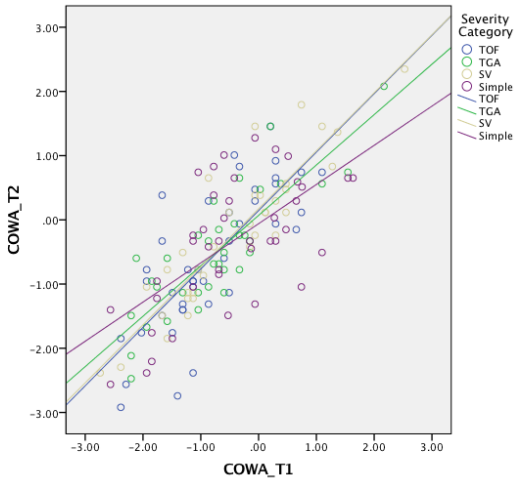


Figure 13.4 Correlation between T1 and T2 COWA (Scatter plot)

Figure 13.3 shows the median scores for the groups are relatively similar across time 1 and time 2; with the IQR also relatively similar and overlapping between time points per group. The TGA group showed similar spread, but a shift to higher scores at time 2 with a higher median; the SV and Simple groups showed slightly less spread at time 2 than time 1, but their scores were in similar ranges; in comparison the TOF group showed a greater spread of scores at time two, and a slight shift to higher scores.

The scatter plot in Figure 13.4 shows the lines of best fit for each group, demonstrating the correlations between the time one and time two scores (i.e. the regression slopes for each group). The time 1-time 2 correlations for each group are similar in direction (ToF r=0.76, TGA r=0.84, SV r=0.90 and Simple r=0.63), with the test –retest correlation in the Simple group being the smallest in comparison to the other groups, which suggests lower stability of scores over time in this group. All four groups performed in a similar manner over time, with those scoring low at time one scoring low at time two and vice versa.

When compared to published test-retest reliability data in healthy adults (r=0.72, 12 month interval), all complexity groups showed comparable or higher test-retest correlation indicating similar stability of scores over time in comparison to the normal population (Dikmen et al, 1999). (See Table 13.3 for test-retest correlation comparisons on all tests across the complexity groups, total sample and normal population data).

13.5.2 Changes in attention over time

Table 13.4 **(**below**)** presents the MLM results for the tests of attention (TMT and SDMT). With regards to the TMT the main effect of time was significant with a large effect size (η_p^2 =0.15) for the TMT-A score ($F_{1, 206.2}$=38.05, p=<0.001), with time two scores (mean=0.103, SE=0.073) being lower than time one (mean=0.676, SE=0.096) scores (i.e. less time taken for completion) demonstrating an improvement in performance over time. The main effect of the structural complexity groups (p=0.017), and the time x group interaction (p=0.027) did not show an overall significant effect; thus demonstrating i) no difference in the pattern of means between the four groups at each time-point and ii) no differential change in the means of the groups across time. The adjusted means of the four structural complexity groups on TMT-A are presented in Figure 13.5.

Table 13.3 Test retest correlation (reliability) on tests that showed a significant change over time across different structural complexity groups and the total sample in comparison to the normal population data

NP Tests	TRT ToF group	TRT TGA group	TRT SV group	TRT SIMPLE group	TRT Total sample	TRT normal population[b]	T1 T2 interval for normal population
COWA	.76	.84	.90	.63	.78	.72	12 months
TMT-A	.39[a]	.27[a]	.84	.61	.60	.79	12 months
SDMT-O	.83	.80	.89	.37[a]	.73	.76	1 month
GP-D	.60	.82	.77	.29[a]	.65	.86	12 months
GP-ND	.57[a]	.19[a]	.60	.76	.47[a]	.86	12 months
RAVLT	.38[a]	.48[a]	.67	.47[a]	.48[a]	.60	12 months

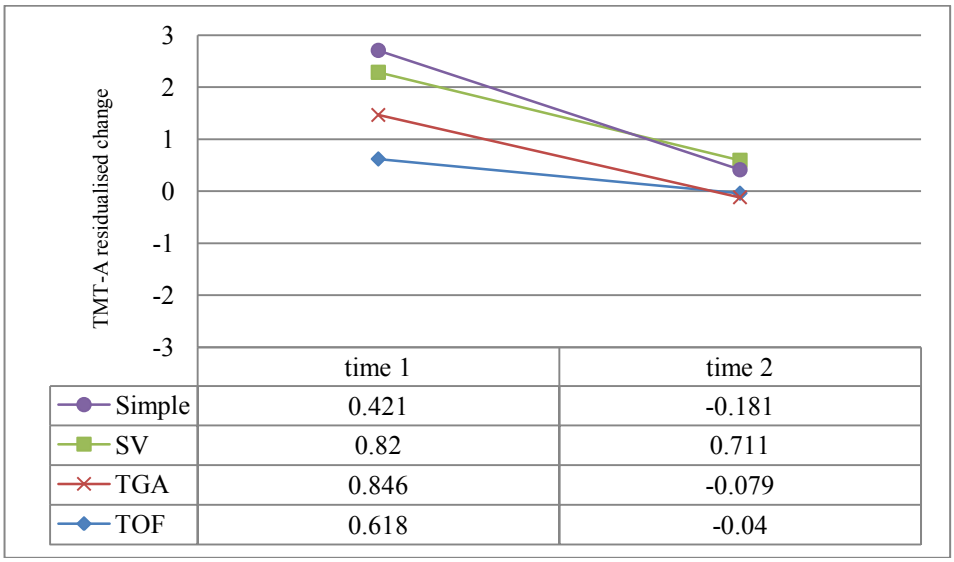
Note: TRT- Test Re-test; [a] test-retest correlation below the ≥0.6 criteria applied within this study; [b] the mean test-retest interval for the total sample was 3.3 years

Table 13.4 Results of the MLM analysis (main and interaction effects) across groups on measures of attention

Measure	Effect of time	Effect size η_p^2	Effect of groups	Effect size η_p^2	Time X group interaction	Effect size η_p^2
TMT-A	$F_{1,206.2}$=38.05,p=**<0.001****	0.155	$F_{3,338.16}$=3.45, p=. 017	0.033	$F_{3,201.86}$=3.13, p=. 027	0.044
TMT-B	$F_{1,208.1}$= .826,p=. 365	0.003	$F_{3,296.11}$= 4.46,p=**.004****	0.043	$F_{3,208.44}$=1.16, p=. 323	0.016
SDMT-Written	$F_{1,173.08}$=6.77,p= 0.01	0.037	$F_{3,327.35}$= 2.98,p=. 032	0.026	$F_{3,170.74}$=2.01, p=. 114	0.034
SDMT- Oral	$F_{1,170.05}$=12.88,p= **<0.001****	0.070	$F_{3,329.45}$= 1.18,p=. 342	0.011	$F_{3,167.69}$=0.19, p=. 903	0.003

Note - TMT= Trail Making Test, SDMT= Symbol Digit Modalities Test, **=p<0.01, η^2p- eta squared (0.01=small, 0.06=medium, 0.14=large)

TMT-B scores did not significantly differ between the two assessments, with the main effect of time being non-significant (p=.365). The main effect of the structural complexity groups (irrespective of time-points) was significant ($F_{3,296.11}$= 4.46,p=.004), demonstrating a difference between groups on the TMT-B score. Pairwise comparison indicated a significant difference (p=0.003) between the SV group (mean=1.229, SE=.200) and the Simple group (mean=0.272, SE=.180); but no other significant group differences were identified with the ToF (mean=.814, SE=.181) and TGA (mean=.898, SE=.191) groups. Furthermore the time x group interaction was not significant (p=0.323); thus demonstrating i) no difference in the pattern of means between the four groups at each time-point and ii) no differential change in the means of the groups across time.



	time 1	time 2
Simple	0.421	-0.181
SV	0.82	0.711
TGA	0.846	-0.079
TOF	0.618	-0.04

Figure 13.5 Graphical representation of change in TMT-A scores

The additional graphs plotted to visually explore the results of the MLM analysis and assess the stability of TMT-A scores are presented below (figures 13.6 to 13.8).

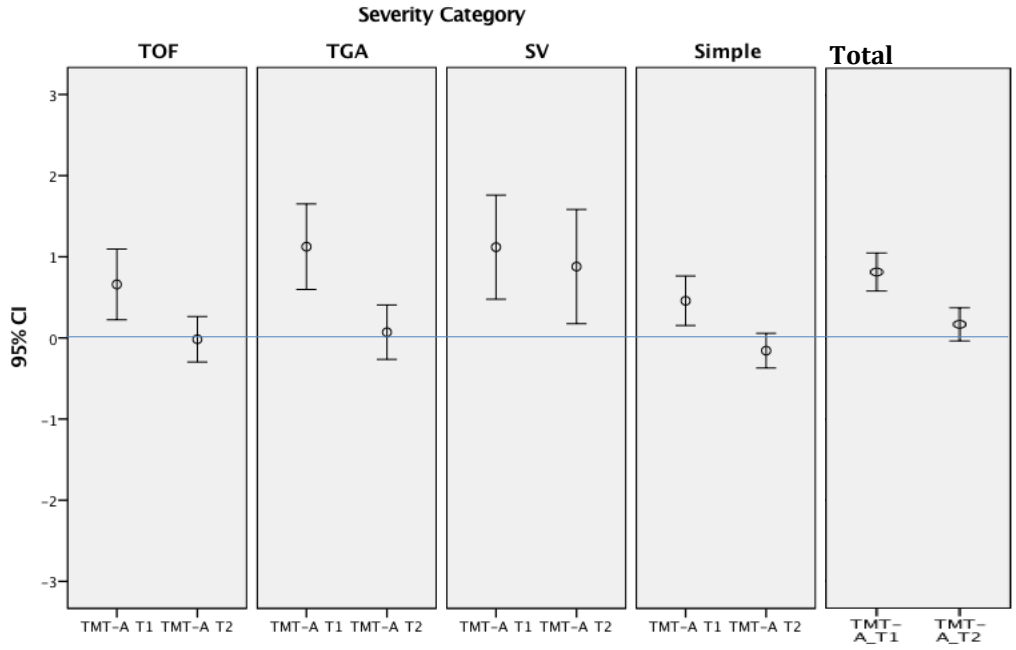


Figure 13.6 Error bar plot (Means and 95% CI) for TMT-A T1 and T2 scores

In Figure 13.6 the total sample showed TMT-A scores above the normative mean score (i.e. it did not cross the normative mean, with 95%CI), thus suggesting poorer performance with longer time taken to complete task, in comparison to normative data at time 1. However, at time 2 the scores of the total sample decreased and the 95% CI crossed the normative mean score, suggesting that scores at time 2 could be similar to the normative data.

With regards to the different complexity groups the ToF, TGA, SV and Simple groups scored above the normative mean at time one on the TMT-A score, with 95% CI (i.e. poorer performance with more time taken to complete task). While all the groups showed a decline in mean scores at T2, only the 95% CI of the TOF, TGA and Simple groups crossed the mean of the normative group, suggesting that their performance was similar to that of the normative mean at time 2, demonstrating an improvement in scores. The SV group continued to perform below the normative group at both time points.

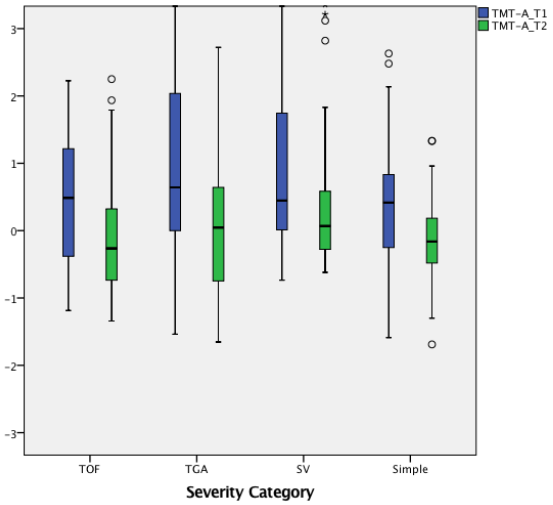


Figure 13.7: Variability of the TMT-A scores at both time points (Box plot)

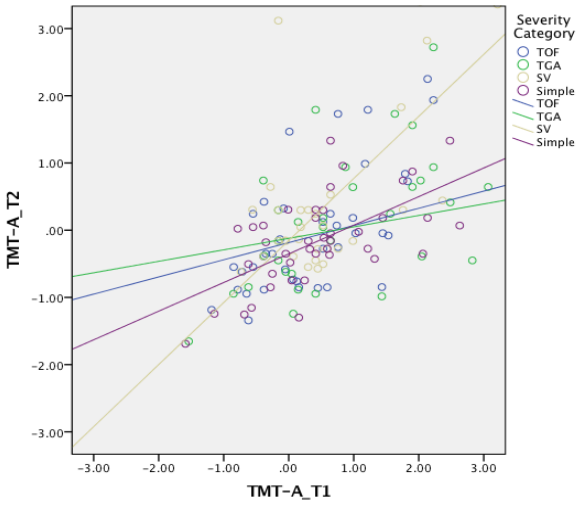


Figure 13.8 Correlation between T1 and T2 TMT-A scores (Scatter plot)

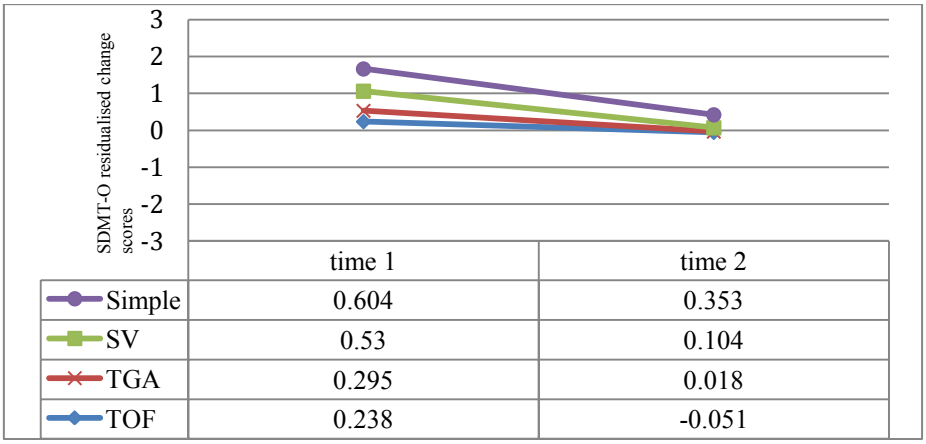
In Figure 13.7 the median scores are lower at time 2 for all the groups; with the IQR's overlapping between time points per group, but with a relative shift to lower scores at time 2. All the groups showed a slightly smaller spread, a shift to lower scores and a lower median at time 2.

Figure 13.8 shows the lines of best fit for each group and demonstrates that correlations between the time 1 and time 2 scores (i.e. the regression slopes for each group) are in a similar direction for the ToF, TGA and simple group, but the regression slope for the SV group shows a larger correlation between time 1 and time 2 scores (r=0.84) in comparison to the other groups (ToF r=0.39, TGA r=0.27, Simple r=0.61). These indicate that the scores for this group are highly correlated between time-points, than those for the other groups. The ToF and TGA group showed low test-retest correlations suggesting poor stability of scores over time, with scores at both time-points being considerably different.

When compared to published test-retest reliability data in healthy adults (r=0.79, 12 month interval), the Simple and SV group's test-retest correlations indicated similar stability of scores over time (See Table 13.3 on page 277). On the contrary the ToF and TGA groups showed a

considerably lower test re-test correlation demonstrating less stability of scores in comparison to the normal population (Dikmen et al, 1999).

The results of the MLM analysis for the SDMT test of attention and complex visual scanning is also presented in Table 13.4. The results showed that the main effect of time was not significant for the written subtest of the SDMT demonstrating no significant difference between scores over time ($F_{1,173.08}$=6.77, p= 0.01). The main effect for the structural complexity groups was also non-significant demonstrating no differences in the test performance of the groups (p= 0.032) (irrespective of time-points). Lastly, the time x group interaction term (p=0.114) was also not significant, demonstrating i) no difference in the pattern of means between the four groups at each time-point and ii) no differential change in the means of the groups across time.



	time 1	time 2
Simple	0.604	0.353
SV	0.53	0.104
TGA	0.295	0.018
TOF	0.238	-0.051

Figure 13.9: Graphical representation of change in SDMT-O scores

The oral subtest of the SDMT showed a significant main effect of time ($F_{1, 170.05}$=12.88, p<0.001) with a significant decrease in the scores (fewer numbers correctly recited**)** from time one (mean= 0.417; SE= 0.084) to time two (mean= 0.106; SE= 0.103) demonstrating a decline in performance over time. Similar to the written subtest, the main effect of groups (p=0.342) and the time x group interaction (p=0.903) was not significant. The adjusted means of the four structural complexity groups on SDMT-O are presented in Figure 13.9.

The additional graphs plotted to visually explore the results of the MLM analysis and assess the stability of scores, for the SDMT-O score are presented below (Figures 13.10 to 13.12).

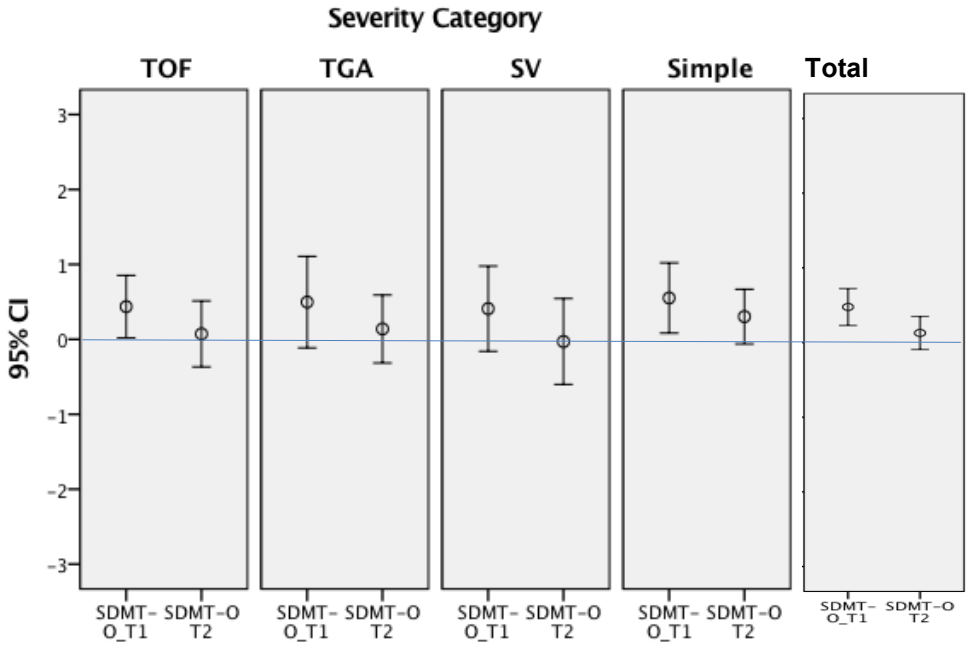


Figure 13.10 Error bar plot (Means and 95% CI) for SDMT-O T1 and T2 scores

In Figure 13.10 the total sample showed SDMT-O scores above the normative mean score at time 1, but the 95% CI crossed the normative mean at time 2, showing a decline in scores over time, indicating poorer performance at time 2. With regard to the different complexity groups all but the Simple group scored similar to the normative mean at both time points, (95% CI crossing normative mean). However, all three groups demonstrated a decline in scores at time 2, with all 4 groups moving closer to the normative mean.

Figure 13.11 shows the median scores for all groups are lower at time 2; with the IQR's showing a relative shift to lower scores. The ToF group showed a larger spread of scores, at

time 2 than time 1; the TGA, SV and simple groups showed smaller spread at time 2 than time 1, showing less variability than the ToF group.

In Figure 13.12 the lines of best fit for each group showed the test-retest correlations between the time 1 and time 2 scores (i.e. the regression slopes for each group). The time 1- time 2 correlations for the ToF (r=0.83), TGA (r=0.80) and SV (r=0.89) groups were similar, but the Simple group showed a much smaller correlation between time 1 and time 2 scores in comparison (r=0.37), thus showing poorer stability of scores, with the scores for this group not being similar over time, in comparison to the other groups.

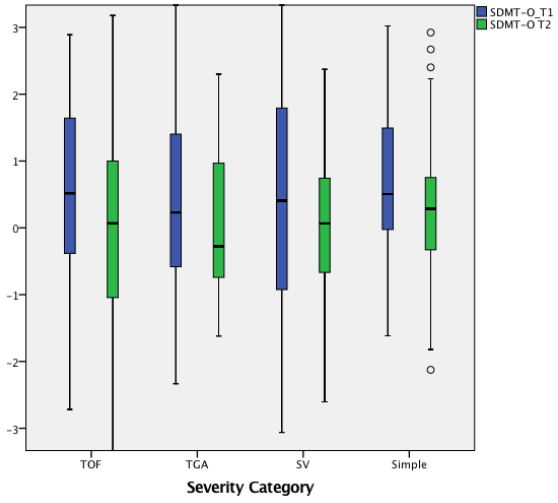


Figure 13.11: Variability of the SDMT-O scores at both time points (Box plot)

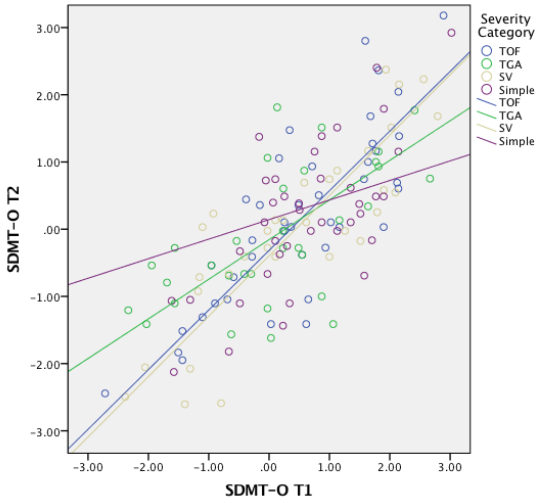


Figure 13.12 Correlation between T1 and T2 SDMT-O scores (Scatter plot)

When compared to published test-retest reliability data in healthy adults (r=0.76, 1-month interval), the ToF, TGA and SV group showed good SDMT-O test-retest correlations indicating better or similar stability of scores over time in comparison to the healthy population (Smith, 1982). The Simple group, however, showed a considerably lower test-retest correlation indicating less stability of scores in comparison to the normal population (See Table 13.3).

13.5.3 Changes in motor functioning and dexterity over time

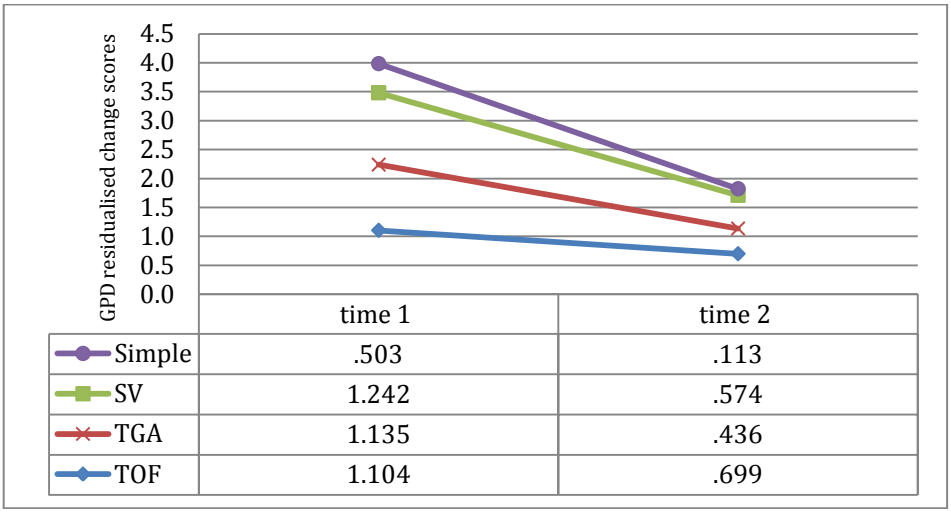
The MLM analysis for the Grooved Pegboard test of motor function and dexterity are presented in Table 13.5. With regards to the performance on the dominant hand score, the main effect of time was significant with a significant difference in the GP-Dominant hand score between the two time-points ($F_{1,187.84}$=22.23, p=<0.001). The mean difference indicated an improvement in performance with less time taken to complete the task from time one (mean= 0.996; SE=0.098) to time two (mean= 0.456; SE=0.125) with a medium effect size (η_p^2=0.10).

Table 13.5 Results of the MLM analysis (main and interaction effects) across groups on the measures of motor functioning over time

Measure	Effect of time	Effect size η_p^2	Effect of groups	Effect size η_p^2	Time X group interaction	Effect size η_p^2
GP-D	$F_{1,187.84}$=22.23, p=**<0.001****	0.105	$F_{3,335.81}$= 2.28, p=. 078	0.006	$F_{3,187.82}$= 0.52, p=. 667	0.008
GP-ND	$F_{1,234.61}$=7.44, p=**.007****	0.031	$F_{3,331.11}$=1.97, p=.118	0.017	$F_{3,234.87}$= 0.259, p=. 855	0.003

Note - GP= Grooved Pegboard, *=<0.05, **=p<0.01 η^2p- eta squared (0.01=small, 0.06=medium, 0.14=large)

The main effect for the structural complexity groups was non-significant (p= 0.078) with no differences between the groups (irrespective of time point). The interaction term between the time and structural complexity group was also non-significant (p=0.667); thus demonstrating i) no difference in the pattern of means between the four groups and ii) no differential change in the means of the groups across time. The adjusted means of the four structural complexity groups on GP-Dominant hand scores are presented in Figure 13.13.



	time 1	time 2
Simple	.503	.113
SV	1.242	.574
TGA	1.135	.436
TOF	1.104	.699

Figure 13.13 Graphical representation of change in GP-D scores

The additional graphs plotted to visually explore the results of the MLM analysis and assess the stability of scores, for the GP-Dominant hand are presented below in Figures 13.14 to 13.16.

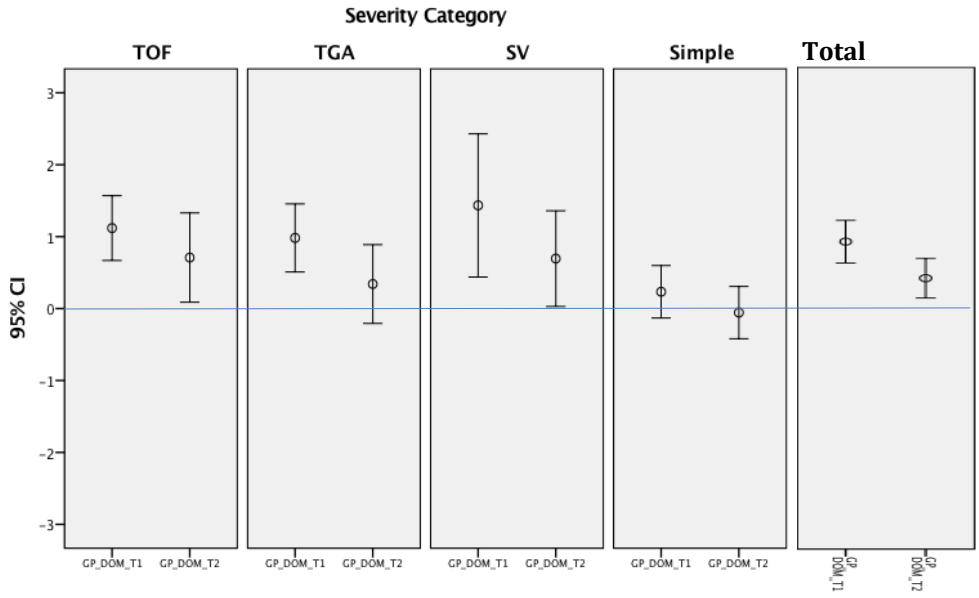


Figure 13.14 Error bar plot (Means and 95% CI) for GP-D T1 and T2 scores

In Figure 13.14 the total sample showed GP-Dominant hand scores above the normative mean score at time 1 (i.e. it did not cross the normative mean, with 95%CI), thus suggesting poorer performance, longer time taken to complete task, in comparison to normative data. At time 2 the scores of the total sample decreased but still remained above the normative data.

With regards to the different complexity groups the ToF and SV groups scored above the normative mean at both time points on the GP-Dominant hand score. The Simple and TGA groups showed the 95% CI of their means crossed the normative mean score at time 2; thus suggesting that their performance was similar to that of the norms. All groups showed a decrease in scores over time, with scores moving closer to the normative mean score suggesting improvement over time in all groups. These results are consistent with the results of the MLM analysis, which showed an improvement in scores over time, consistent in all groups.

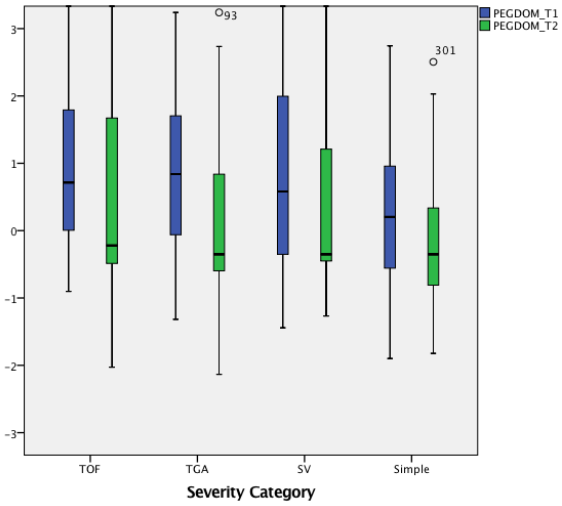


Figure 13.15: Variability of GP-D scores at both time points (Box plot)

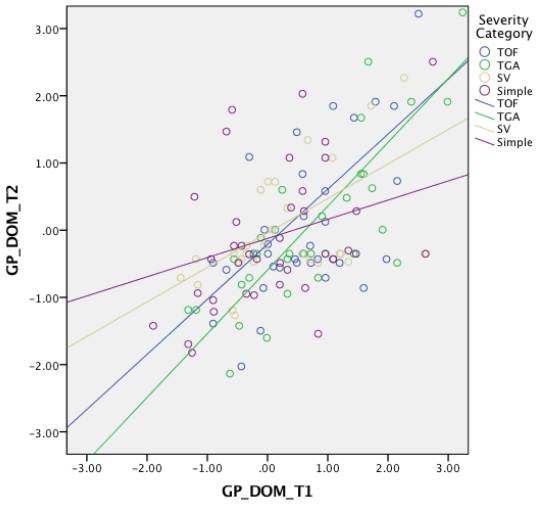


Figure 13.16 Correlation between T1 and T2 GP-D scores (Scatter plot)

In Figure 13.15 the median scores are lower at time 2 for all the groups; with the IQR's overlapping between time points per group, but with a relative shift to lower scores at time 2.

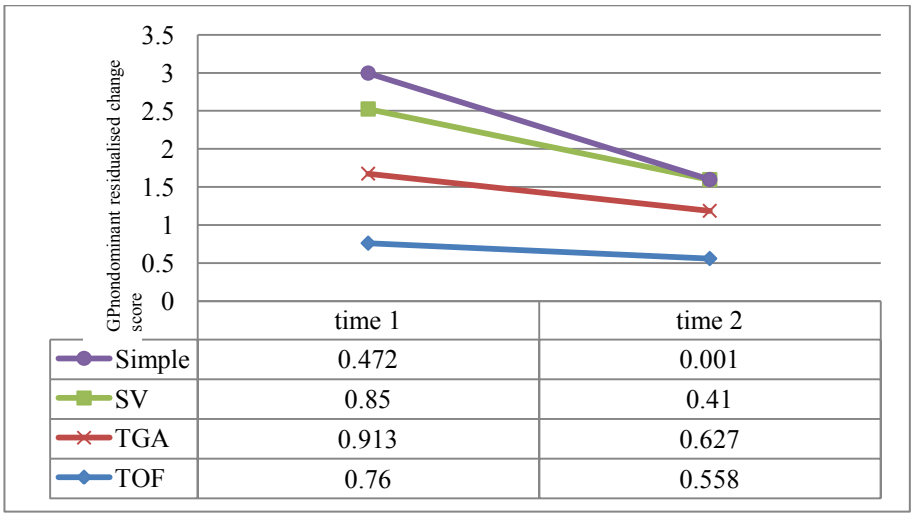
The TGA group showed similar spread, but a shift to lower scores and a lower median in time 2; the SV and simple groups showed slightly less spread at time 2 than time 1, and a shift to lower scores; in comparison the TOF group showed a greater spread of scores at time 2, but still a shift to lower scores.

In Figure 13.16 shows lines of best fit for each group, demonstrating correlations between time 1 and time 2 scores (i.e. the regression slopes for each group) which are in a similar direction for the ToF, TGA and SV group (ToF r= 0.60, TGA r=0.82, SV r=0.77), in comparison the regression slope for the Simple group shows a smaller correlation (r=0.29) indicating that the scores for this group are less similar between time 1 and time 2, than those for the other groups, indicating poorer stability of scores over time.

When compared to published test-retest reliability data in healthy adults (r=0.86, 12-month interval), the ToF, TGA and SV group showed comparable test-retest correlations indicating similar stability of scores over time when compared to a healthy normal population. On the contrary the Simple group showed a much lower correlation demonstrating less stability of scores in comparison to the normal population (Dikmen et al, 1999) (See Table 13.3).

Similar to the dominant hand score the GP-Non-Dominant hand scores showed a significant main effect of time, demonstrating a difference in scores between the two assessments ($F_{1, 234.61}$=7.44, p= 0.007). The mean comparison showed a decrease in the time taken to complete the task from time one (mean= 0.749; SE=0.089) to time two (mean= 0.399, SE=0.122), again demonstrating an improvement in performance over time. The main effect of the structural complexity groups (irrespective of time points) was not significant (p= 0.118), showing no differences in the performance of the groups (irrespective of time point).

Furthermore, the time x group interaction term was also non-significant (p=0.855); thus demonstrating i) no difference in the pattern of means between the four groups and ii) no differential change in the means of the groups across time. The adjusted means for the GP-Non-Dominant hand score is presented in Figure 13.17, showing the change in the scores from assessment one to assessment two in the four structural complexity groups.



	time 1	time 2
Simple	0.472	0.001
SV	0.85	0.41
TGA	0.913	0.627
TOF	0.76	0.558

Figure 13.17: Graphical representation of change in GP-ND scores

The additional graphs plotted to visually explore the results of the MLM analysis and assess the stability of scores, for the GP-Non-Dominant hand are presented below (figures 13.18 to 13.20). In Figure 13.18 the total sample showed GP-Non-Dominant hand scores above the normative mean score, i.e. it did not cross the normative mean on time 1 and time 2, with 95% CI, thus suggesting poorer performance (i.e. longer time taken to complete task) in comparison to norms. However at time 2 the scores of the total sample decreased and were much closer to the normative mean (but still the 95% CI did not cross the normative mean).

With regards to the different complexity groups the ToF group scored above the normative mean at both time points, (95% CI not cross 0). The TGA, SV and Simple groups crossed the normative mean at time 2, suggesting that their performance at time 2 may not be significantly

different to the normative data. Overall the mean scores of all four groups reduced over time, moving closer to the normative mean suggesting improvement over time in all groups. These results are consistent with the results of the MLM analysis, which showed an improvement in scores over time in the total sample.

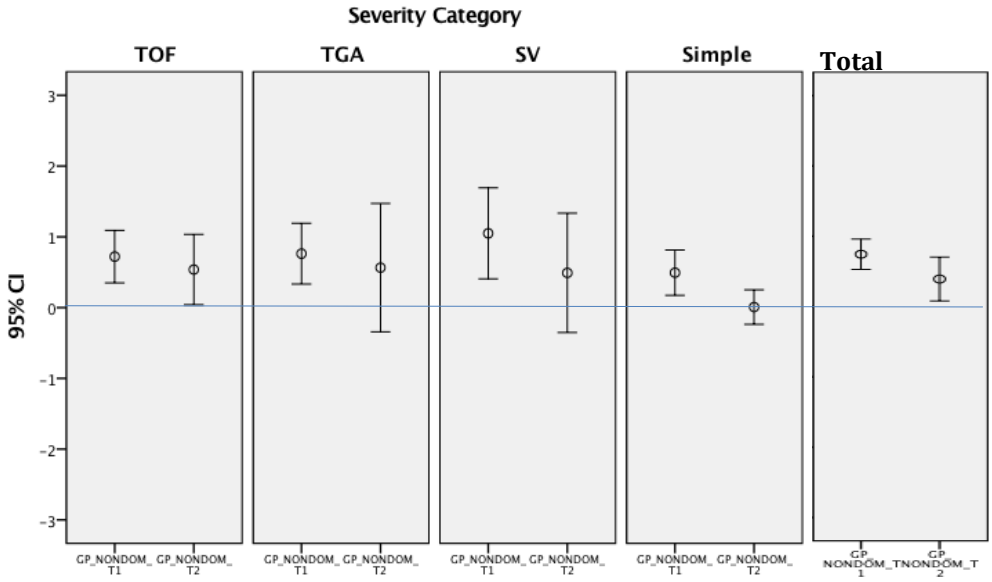


Figure 13.18 Error bar plot (Means and 95% CI) for GP-ND T1 and T2 scores

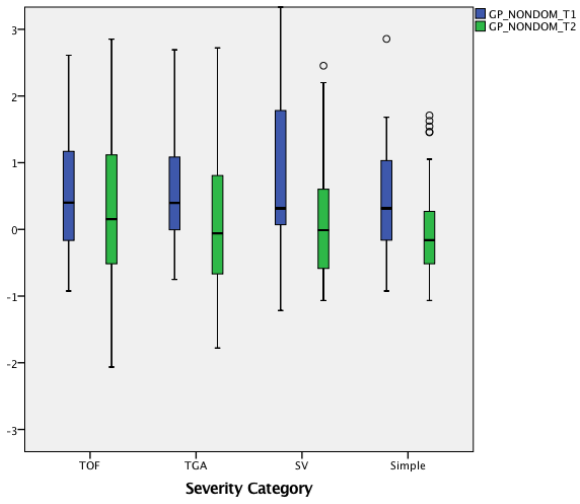


Figure 13.19: Variability of the GP-ND scores at both time points (Box plot)

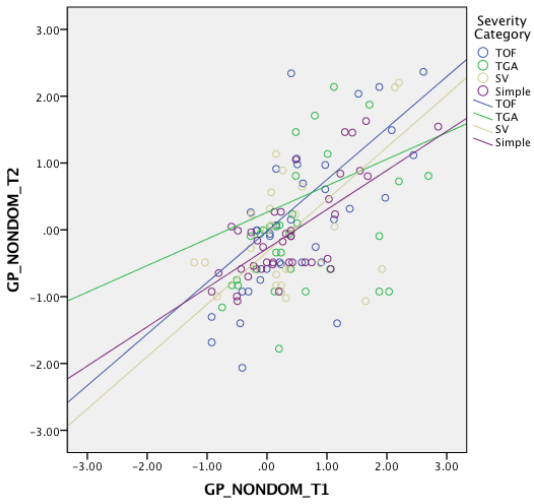


Figure 13.20 Correlation between T1 and T2 GP-ND scores (Scatter plot)

In Figure 13.19 all groups showed lower median scores at time 2; with the IQR's overlapping between time points per group, and with a relative shift to lower scores at time 2. The ToF and TGA groups showed a greater spread, but a shift to lower scores and a lower median at time 2; the SV and simple groups showed less spread at time 2 than time 1, and a shift to lower scores and a lower median.

In Figure 13.14 shows lines of best fit for each group, which demonstrate that correlations between the time 1 and time 2 scores (i.e. the regression slopes for each group) are in a similar direction for the ToF, SV and Simple group (ToF r=0.57, SV r= 0.60, Simple r=0.76); while the TGA group shows a much smaller correlation (r=0.19), indicating that the scores for this group are less similar between time 1 and time 2, thus indicating poorer stability of scores over time in comparison to the other structural complexity groups.

When compared to published GP-Non-Dominant hand test-retest reliability data in healthy adults (r=0.86, 12-month interval) the total sample showed a slightly lower test-retest correlation in comparison. With regards to the different complexity group the ToF, SV and Simple groups showed a comparable test-retest correlation; demonstrating similar stability of scores in comparison to the normal population (Dikmen et al, 1999). The TGA group showed a considerably lower test-retest correlation with scores showing very little stability over time, which may explain why the test-retest reliability of the total sample may have been pulled down (See Table 13.3).

13.5.4 Changes in memory function over time

Table 13.6 presents the results of the MLM analysis for the RAVLT test of memory function. There was a significant difference in the scores on the RAVLT test over time with the main effect of time being significant ($F_{1, 210.26}$=63.42, p= 0.001), with a large effect size (η_p^2= 0.23).

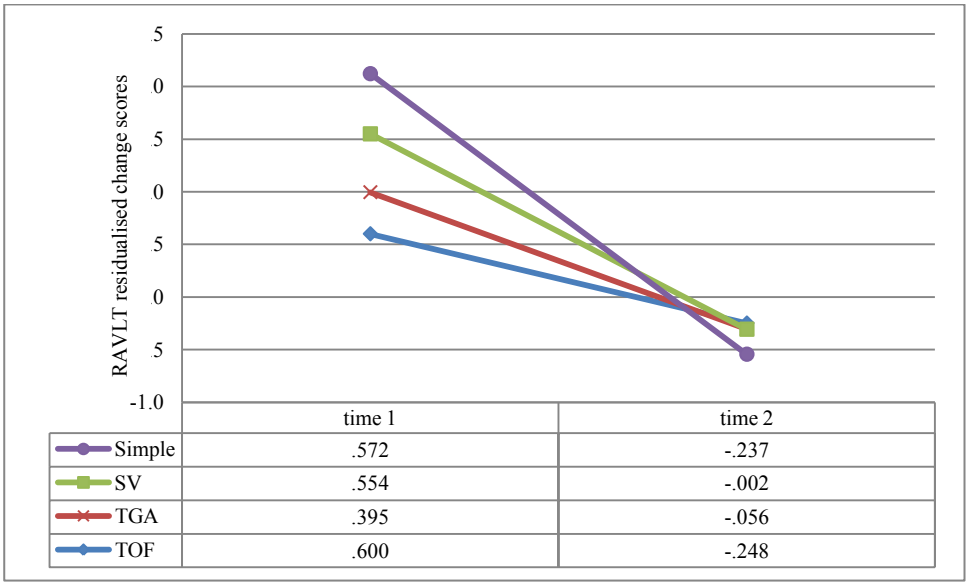
The mean difference showed a decline in performance over time, with fewer words correctly recalled from time one (mean=0.530; SE= 0.061) to time two (mean= -0.136; SE= 0.082). The main effect of the groups was not significant (p= .907), showing the absence of differences between the groups on memory (irrespective of time-points).

Table 13.6 Results of the MLM analysis (main and interaction effects) across groups on the measures of memory

Measure	Effect of time	Effect size η_p^2	Effect of groups	Effect size η_p^2	Time X group interaction	Effect size η_p^2
RAVLT	$F_{1,210.26}$=63.42, p=**<0.001****	0.23	$F_{3,330.88}$= .184, p=. 907	0.001	$F_{3,214.24}$= 1.33, p=. 263	0.016

Note – RAVLT= Rey Auditory Verbal Learning Test, *p<0.05 **p<0.01 η^2p- eta squared (0.01=small, 0.06=medium, 0.14=large)

Figure 13.21 illustrates the adjusted means for the four structural complexity groups on the RAVLT over the two time points. Although the figure shows crossing lines, indicating some interaction between the groups, the interaction term for time x category was non-significant (p= 0.263); thus demonstrating i) no difference in the pattern of means between the four groups and ii) no differential change in the means of the groups across time.



	time 1	time 2
Simple	.572	-.237
SV	.554	-.002
TGA	.395	-.056
TOF	.600	-.248

Figure 13.21 Graphical representation of change in RAVLT scores

The additional graphs plotted to visually explore the results of the MLM analysis and assess the stability of RAVLT scores is presented below (figures 13.22 to 13.24).

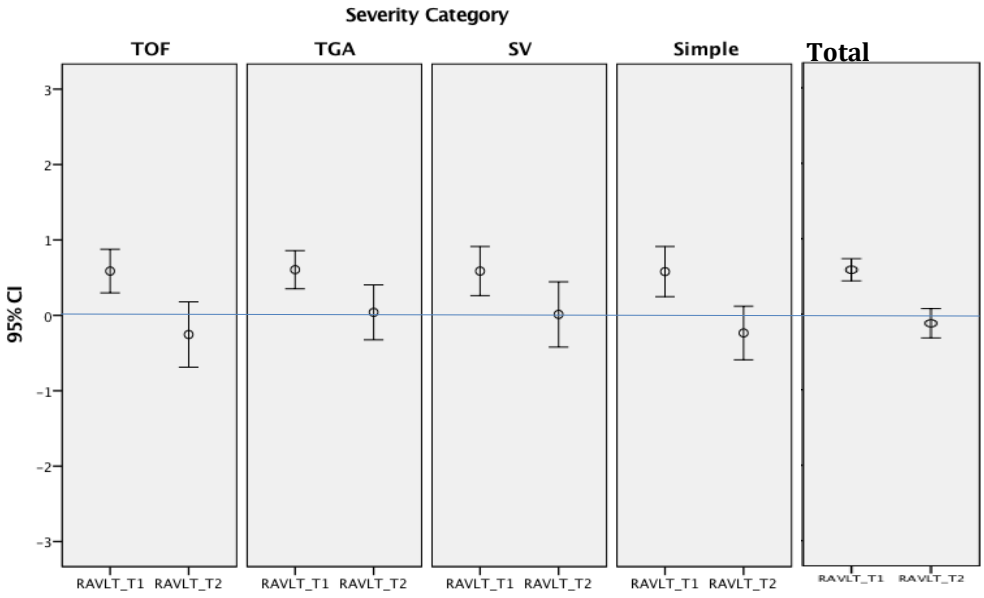


Figure 13.22 Error bar plot (Means and 95% CI) for RAVLT T1 and T2 scores

In Figure 13.22 the total sample showed RAVLT scores above the normative mean score at time1 but moved towards the normative mean at time 2, with 95% CI crossing the mean of the normative group. These results indicate that the sample performed better than the normative data at time 1 (more words correctly recited); however at time 2 the scores moved down and crossed the normative mean suggesting that the mean score of the sample was similar to the normative data at time 2.

With regards to the different complexity groups all groups followed a similar pattern to the overall sample i.e. time 1 mean scores were above the normative mean, and the 95% CI did not cross the normative mean. By time 2 the mean scores of all the groups shifted down showing a decline in scores over time, and crossed the normative mean. This pattern reflects the results of the MLM analysis (main effect of time), which reported a significant decrease in scores over time.

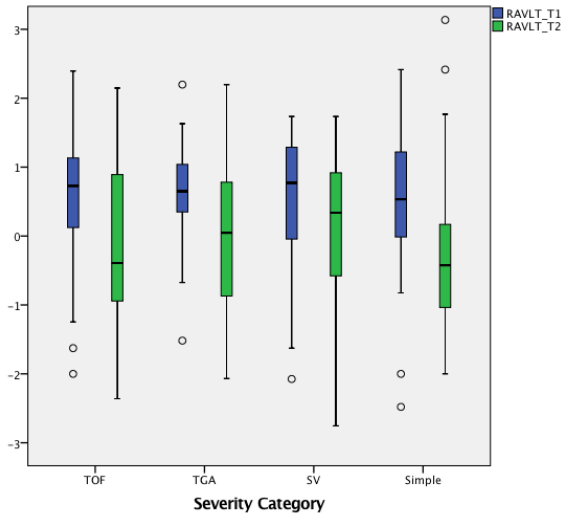


Figure 13.23: Variability of the RAVLT scores at both time points (Box plot)

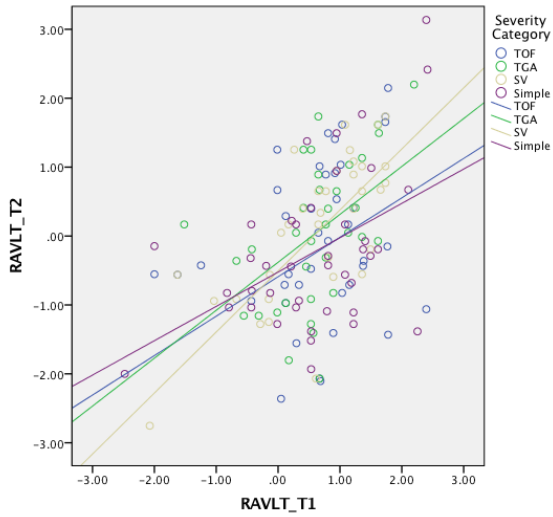


Figure 13.24 Correlation between T1 and T2 RAVLT scores (Scatter plot)

As seen in Figure 13.23 the median scores were lower at time 2 for all groups; with the IQR's overlapping between time points per group. A relative shift to lower scores and an overall higher spread in scores across all groups at time 2 was noted. The ToF, TGA and SV groups showed relatively greater spreads at time 2 in comparison to the Simple group, which showed a similar spread at time 2.

Figure 13.24 showed the lines of best fit for each group, which demonstrates that correlations between the time 1 and time 2 scores (i.e. the regression slopes for each group), which are in a similar direction for the ToF, TGA and simple group (ToF r=0.38, TGA r=0.48, Simple r=0.47). The SV group showed a larger correlation between time 1 and time 2 scores in comparison to the other groups (r=0.67) indicating that the scores for this group are more similar between time-points, thus indicating greater stability of scores over time.

When compared published test-retest reliability data in healthy adults (r=0.60, 12-month interval), the total sample showed a slightly smaller test re-test correlation in comparison to the normal population. With regards to the structural complexity groups the SV group showed comparable test-retest correlations indicating similar stability of scores over time when compared to a healthy normal population. On the contrary the ToF, TGA and Simple groups all showed a lower correlation demonstrating less stability of scores in comparison to the normal population (Carstairs, Shores and Myors, 2012) (See Table 13.3).

Summary of MLM and test retest analysis

Overall majority of test scores, across all assessed domains showed a significant difference in scores over time. It is of note that two tests RAVLT and SDMT-Oral subtest showed a statistically significant ($p<0.01$) decline in performance over time, with the change in memory showing a large effect size ($\eta_p^2= 0.23$). On the contrary, other tests (TMT-A, COWA) showed

an improvement in scores over time (with a large effect size -η_p^2 =0.15) thus demonstrating variability in the pattern of change across the different tests. The MLM results showed that the time x group interaction term consistently remained non-significant across all the domains assessed. These results suggest that there were no differences in the pattern of means between the four groups at each time-point and no differential change in the means of the groups was noted across the two time-points. A significant between group differences was only noted on the TMT-B test score (irrespective of time point).

With regards to the test-retest reliability the total sample showed some similarity in the test-retest correlations when compared to the normal data, with the exception of two scores (GP-ND and RAVLT) which showed smaller correlations. With regards to the different structural complexity groups; ToF, TGA and the Simple group showed lower test-retest reliabilities on tests of motor function, attention and memory, while the SV group had good test-retest reliability on all tests when compared to the normal population.

13.6 Which factors predict change in cognitive functioning over time in ACHD patients?

Multivariate hierarchical regression analysis was conducted to identify predictors of change in cognitive functioning. Residualised change scores were calculated for each variable that showed a significant difference in scores over time in the MLM analysis (e.g. COWA, RAVLT, TMT-A).

13.6.1 Univariate screening for potential predictors of change in cognitive functioning

Prior to conducting the multiple hierarchical regressions, a univariate screening of the potential predictor variables was undertaken, using simple linear regressions. Patients' demographic, clinical and mood residualized change scores were used as independent variables and each of

the NP residualized change scores were used as dependent variables in the simple linear regression analysis.

The data distribution of the NP change scores was assessed for normality using the Kolmogorov-Smirnov test, for which a statistical significance level of $p < 0.001$ was used to detect non-normality (The Kolmogorov-Smirnov statistic for each variable is provided in Appendix-X). Furthermore, a visual inspection of the distribution of the data points was also conducted using histograms. Regression analysis on the change scores was conducted despite any variables being non-normally distributed, as regression analysis does not assume a normal data distribution (Field, 2009).

Variables significant at $p<0.05$ in the univariate linear regressions were used in the hierarchical multiple regression models for the respective NP change scores. The order of the regression blocks was consistent with that utilized in the cross-section study analysis (See Figure 8.8). This decision was made for two reasons, firstly to maintain consistency in the approach taken to analyse the data, and secondly to enable drawing comparisons between the cross-sectional and follow-up study results.

Univariate predictors of change in cognitive functioning

Only demographic and clinical factors were significant univariate predictors of the NP Change scores (DV). None of the mood change scores were significant predictors of change in cognitive functioning over time, within this sample, thus demonstrating that a change in mood did not predict a change in cognitive functioning over time. The results of the univariate screening for each NP change score are presented in Appendix-Z.

13.6.2 Predictors of change in executive functioning over time in ACHD patients

With regards to the domain of executive functioning, only one test showed a significant difference in performance over time (COWA). The univariate predictors of the COWA change score were education and diuretic medication. Table 13.7 (below) presents the results of the hierarchical multiple regression analysis conducted to identify significant unique predictors of COWA change scores. The final model was not significant (F=5.609, p=0.019) and only explained a total of 4.1% variance in COWA change scores. None of the variables significantly explained any unique variance in change in executive functioning and verbal fluency as assessed by the COWA.

Table 13.7 Demographic and clinical predictors of change in executive functioning (COWA)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		0.036	0.029	0.036	5.609		0.019
	Education					0.189	0.019
2		0.054	0.041	0.018	2.892		0.091
	Education					0.160	0.05
	Diuretic medication					-0.138	0.091

13.6.3 Predictors of change in attention over time in ACHD patients

With regards to the domain of attention, two tests showed a significant difference in scores over time in the MLM analysis; the oral subtest of the SDMT test (SDMT-O), and the TMT test of divided attention (TMT-A).

13.6.3.1 Symbol digit modalities test (SDMT-O)

The univariate predictors of the SDMT-O change score included demographic (employment status) and clinical (total number of palliations, and anti-coagulant medication) variables. The results of the regression analysis identifying predictors of change in the SDMT-O scores are presented in Table 13.8. The results showed that neither the individual steps nor the final

regression model reached statistical significance ($p<0.01$). None of the demographic or clinical variables explained any significant unique variance in the change scores, at any step.

Table 13.8 Demographic and clinical predictors of change in attention (SDMT-Oral)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	B	*Sig.*
1		0.03	0.024	0.03	4.657		0.033
	Employment					0.174	0.033
2		0.053	0.04	0.023	3.565		0.061
	Employment					0.177	0.028
	Palliations total					-0.151	0.061
3		0.062	0.043	0.009	1.477		0.226
	Employment					0.162	0.046
	Palliations total					-0.113	0.189
	Anti-coagulant medication					-0.105	0.226

13.6.3.2 Trail Making Test - Part A (TMT-A)

The univariate predictors of change in TMT-A scores included education and a range of clinical variables including: NYHA classification, total numbers of intervention, years since the last intervention, number of days spent in hospital, age at repair, oxygen saturation levels, LVEF and the medication taken (beta-blocker medication, anti-arrhythmia medication and anti-coagulant medication).

The results of the multivariate regression model for the TMT-A change score are presented in Table 13.9**.** The first block showed education as a significant predictor of change in TMT-A. However, upon entering the complexity variables none of the variables remained significant. In the third block the age at repair variable emerged as a significant predictor ($p=0.009$) of TMT-A change scores. The following blocks (four - current saturation and, five- current health and medications) and the final model were not significant and none of the variables explained any significant unique variance in the outcome in the final model.

Table 13.9 Demographic and clinical predictors of change in attention (TMT-A)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		0.05	0.043	0.05	7.885		0.006**
	Education					-0.223	0.006**
2		0.094	0.076	0.044	3.632		0.029
	Education					-0.193	0.016
	NYHA					0.124	0.121
	HF clinic					0.152	0.057
3		0.215	0.153	0.121	2.711		0.008**
	Education					-0.19	0.017
	NYHA					0.062	0.442
	HF clinic					0.092	0.261
	Interventions total					0.174	0.073
	Yrs. Since last operation					-0.032	0.723
	Age at repair Q2					0.23	0.014
	Age at repair Q3					0.262	0.009**
	Age at repair Q4					0.136	0.186
	Hospital days Q2					0.045	0.631
	Hospital days Q3					-0.188	0.069
	Hospital days Q4					0.061	0.579
4		0.234	0.156	0.02	1.174		0.322
	Education					-0.205	0.010
	NYHA					0.042	0.601
	HF clinic					0.071	0.391
	Interventions total					0.15	0.129
	Yrs. Since last operation					-0.043	0.636
	Age at repair Q2					0.212	0.027
	Age at repair Q3					0.249	0.014
	Age at repair Q4					0.076	0.486
	Hospital days Q2					0.011	0.91
	Hospital days Q3					-0.216	0.042
	Hospital days Q4					0.024	0.832
	Current saturation Q1					0.156	0.113
	Current saturation Q1					-0.025	0.771
	Current saturation Q1					0.02	0.831
5		0.271	0.16	0.036	1.098		0.367
	Education					-0.209	0.011
	NYHA					0.004	0.961
	HF clinic					-0.029	0.761
	Interventions total					0.119	0.269
	Yrs. Since last operation					-0.034	0.718
	Age at repair Q2					0.208	0.031
	Age at repair Q3					0.221	0.031
	Age at repair Q4					0.04	0.725
	Hospital days Q2					-0.022	0.825
	Hospital days Q3					-0.225	0.037
	Hospital days Q4					-0.006	0.962
	Current saturation Q1					0.089	0.380
	Current saturation Q1					-0.046	0.602
	Current saturation Q1					0.015	0.874
	Pacemaker					0.042	0.663

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
	Beta-blocker medication					0.07	0.471
	Anti-arrhythmia medication					0.069	0.463
	Anti-coagulant medication					0.058	0.585
	LVEF					-0.156	0.073
	Medication total					0.038	0.723

**p<0.01, Q=Quartile, LVEF- Left Ventricular Ejection Fraction, HF-Heart Failure, NYHA= New York Health Assessment

13.6.4 Predictors of change in motor functioning over time in ACHD patients

The MLM analysis showed a significant change in motor functioning over time (on both the dominant & non-dominant hand scores). Results of the regression analysis to identify significant predictors of change in motor functioning are presented below in Table 13.10 (Dominant hand) and Table 13.11 (Non-dominant hand).

The univariate predictors of change in motor function as measured by the dominant hand included: NYHA classification, total number of interventions, ACE medication and the left and right ejection fraction. The first (p=.003) and second (p=.006) regression steps for the predictors of GP-Dominant hand score showed NYHA classification as a significant predictor of change in motor functioning over time. The final model explained 9.5% of the variance in the outcome; however, upon the addition of the current health status variables, the NYHA class was rendered non-significant. Thus no statistically significant predictors of change in motor functioning (GP-Dominant hand change scores) were identified.

The univariate regression analysis for the non-dominant hand score showed heart failure clinic attendance and years since last intervention as significant predictors. However, the final multivariate regression model for the non-dominant hand score did not show any significant unique predictors of change in motor functioning.

Table 13.10 Demographic and clinical predictors of change in motor functioning (GP-D)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		0.058	0.052	0.058	9.299		**0.003****
	NYHA					0.241	**0.003****
2		0.082	0.07	0.024	3.968		0.048
	NYHA					0.22	**0.006****
	Interventions total					0.157	0.048
3		0.125	0.095	0.043	2.395		0.071
	NYHA					0.17	0.036
	Interventions total					0.118	0.146
	ACE medication					0.147	0.069
	RVEF					-0.097	0.297
	LVEF					-0.071	0.434

**p<0.01, NYHA= New York Health Assessment, LVEF- Left Ventricular Ejection Fraction, RVEF- Right Ventricular Ejection Fraction, ACE- Angiotensin-Converting-Enzyme

Table 13.11 Demographic and clinical predictors of change in motor functioning (GP-ND)

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		0.038	0.032	0.038	6.025		0.015
	HF clinic					-0.196	0.015
2		0.07	0.058	0.032	5.138		0.025
	HF clinic					-2.337	0.021
	Yrs since last operation					2.267	0.025

HF clinic- Heart Failure clinic

13.6.5 Predictors of change in memory over time in ACHD patients

The results of the MLM analysis showed a significant change in memory over time (RAVLT score). The univariate predictors of change in memory included years of education achieved and the blood oxygen saturation levels. The results of the multivariate regression analysis to identify predictors of change in memory function are presented in Table 13.12. The first block was significant (p= 0.005), with education significantly predicting change in memory function over time, explaining 4.5% of the unique variance on the RAVLT change scores. The final block included current oxygen saturation variables, which explained additional unique variance. A total of 8% of the variance in memory change scores was explained by education and oxygen saturation. Both variables education and oxygen saturation were significant predictors of change in memory over time. The positive association of education (β = 0.227) and current saturation (β

= 0.249) with change in memory demonstrates that higher years of education and saturation levels were associated with higher scores suggesting improvement over time and vice versa, however the total variance explained by these variables was considerably small (8%), with the overall model not being significant.

Table 13.12 Demographic and clinical predictors of change in memory (RAVLT)

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		0.052	0.045	0.052	8.229		**0.005****
	Total years of education					0.227	**0.005****
2		0.104	0.08	0.052	2.874		0.038
	Total years of education					0.224	**0.005****
	Current saturation Q1					0.089	0.318
	Current saturation Q2					0.249	**0.004****
	Current saturation Q3					0.056	0.531

**p<0.01, Q= Quartile

13.7 Conclusions

The results of the MLM analysis conducted to identify changes in cognitive performance over time showed a significant difference in scores across all the domains assessed, but not across all test scores. There was variability in the directionality of change observed with some domains demonstrating an improvement over time while others a decline. However visual inspection of the data suggested that while there were changes across scores, they were not large enough to be of a clinically significant magnitude (i.e. the sample/group did not go from being impaired to non-impaired and vice versa). Hierarchical regression analysis conducted to identify predictors of change showed more years of education and higher oxygen saturation levels as significant predictors of change in memory function; however, the total proportion of the variance explained by these variables was small. No demographic, clinical or mood predictors were identified for the other domains of cognitive functioning that changed over time. The next chapter presents a discussion of the finding of the follow-up study in the context of the existing literature.

14 FOLLOW-UP STUDY DISCUSSION

14.1 Prologue

This chapter discusses the findings of the follow-up study in the context of the existing literature. The main findings from the follow up study are discussed under key themes, including i) stability of cognitive functioning in ACHD, and how this compares to the stability of cognitive functioning in the normal population; ii) differences in cognitive functioning across structural complexity groups; and iii) predictors of change in cognitive functioning. The limitations of the follow-up study and its implications will be discussed in the final discussion in Chapter 15.

14.2 Stability of cognitive functioning in ACHD

In order to investigate change and/or stability of cognitive functioning over time within and across the different structural complexity groups, MLM analyses were conducted. The results showed that the time x group interaction in each analysis was consistently non-significant indicating that the structural complexity groups did not change differentially over time across the domains assessed. The main effect of time was significant in some measures within the domains of attention, executive function and memory; indicating statistically significant changes over time within this ACHD sample. Further, the main effect of group on one test, (TMT-B) was significant, suggesting a difference in cognitive functioning between structural complexity groups.

The findings of the MLM analyses are discussed in depth below both for the main effect of time, followed by the main effect of group. First the stability and/or change of scores over time

is discussed (i.e. main effect of time). These results are discussed in conjunction with each measure's test-retest results and comparing the performance of the ACHD sample to that of the normal population (using visual representations) in order to evaluate if the mean performance of the group(s) differed over time relative to the normal population. It is of note that the test-rest comparisons were only done for those participants that had both time one and time two scores (due to the nature of the index calculation). However, given that no statistically significant differences were noted between the responders and non-responders at time two on any of the variables assessed, the performance of these could be considered comparable.

14.2.1 Changes in cognitive functioning over time

A considerable amount of variability was noted in changes across the different domains (tests); with five out of nine scores showing an improvement in performance over time while two scores showed a decline; and some showed no significant changes. However, no observable patterns were noted across the specific cognitive domains to indicate a significant, consistent trend in changes over time; these are explored in more detail below.

Measures within the domains of attention (TMT-A), executive functioning (COWA) and motor function (Grooved Pegboard) showed statistically significant improvement in scores over time, with the study sample showing better performance upon reassessment with medium to large effect sizes. In contrast, a statistically significant decline in performance over time was observed in measures within the domains of memory (RAVLT) and attention (SDMT-Oral subtest) with medium to large effect sizes. No other tests showed a statistically significant difference in scores over time. Each structural complexity group showed a consistent, similar pattern of change (improvement or decline); with no individual group changing in a different direction from the others (as evident from the regression slopes in scatterplots and mean scores).

14.2.1.1 Clinical significance of the observed change and stability of cognitive functioning when compared to the normal population

Having identified some *statistically* significant changes in cognitive functioning over time, it was important to ascertain whether the level of observed changes were also of clinically significant magnitudes, i.e. meaningful in practice. In order to do so a combination of factors was assessed.

First, the test-retest correlations of the study sample (total sample and each structural complexity groups) were compared to those of the normal healthy population to establish if the stability of cognitive functioning in ACHD was similar in comparison. Second, the change/stability of scores was assessed using visual representations of the data to evaluate how much the sample changed relative to the normative mean over the two time points; and to see if the magnitude of change was large enough for the sample (and each structural complexity group) mean scores to move from the impaired to non-impaired range over time or vice versa. The results for each of these evaluations are discussed below before providing potential explanations for the observed changes.

When assessing the test-retest reliability of scores, the determination of what constitutes good test–retest reliability largely depends on the time frame between two assessments, as with an increase in time between assessments the likelihood of the reliability coefficient being lower increases (Calamia, Markon and Tranel, 2012). These lower test-retest correlations are generally attributed to, i) the increased chances of change in the underlying function, ii) potential confounding factors that may emerge over a longer period of time (such as years) and iii) less influence of practice effects, as with a longer time between assessments individuals are more likely to have forgotten the way the test is performed. Conversely, when assessing test-retest reliabilities over a shorter period of time factors such as memory may facilitate performance, as

one is more likely to remember tests and its characteristics over a short period of time (such as a few weeks/months). Considering that the majority of the published test-retest data for the measures used, was based on a testing interval that ranged from a few months to a year; a less stringent reliability estimate (≥0.6) was considered acceptable within the present study to account for the time-frame between assessments, which was three times longer than the published data.

Nevertheless, within this study the *total sample* showed overall similar test-retest correlations when compared to the normative data ('healthy' reference groups) across most tests. Comparatively smaller test-retest correlations were only noted on two scores (GP-ND and RAVLT); however, these test-retest correlations were not very small (0.48 and 0.49) and could potentially be attributed to the differences in the test-retest interval of the present study and published data (i.e. 3.3 years vs. 1 year).

With regards to test-retest of the different *structural complexity groups*; i) the SV group had good test-retest correlations on all tests when compared to the normal population, this finding could be considered contrary to expectation given that the SV group had a considerable proportion of participants with cognitive impairment when compared to others groups such as the 'Simple group'; and ii) the ToF, TGA and the Simple group showed lower test-retest correlations on tests of motor function, attention and memory, suggesting poorer stability of scores on these domains of cognitive functioning within these structural complexity groups.

However, more than half of the test-retest values below the ≥0.6 cut off within these groups were nearing 0.5, thus not suggesting a very large drop in the reliability coefficients in comparison to the normal population. Therefore, it could be speculated that most of these differences may be indicative of a normal variation in scores (in either direction) that could also

be observed in a normal population if tested over such a long time interval. Also some level of changes or fluctuations in scores can be expected when using a repeated measures design in a healthy population (Calamia, Markol and Tranel, 2012; Drost, 2011).

With regards to the comparison of mean scores relative to the normative data, the visual representation of the results (e.g. box plots and error bar plots) indicated that despite the statistically significant changes observed within the MLM analyses, the level of change across the different domains was not large enough in the total study sample or within the different structural complexity groups to move the group mean from being impaired at time one to non-impaired at time two or vice versa. For instance, although some tests in the domains of memory and attention showed a decline in performance over time, the performances of the groups were still similar to that of the normative data; thus not suggesting a decline that may be of a clinically significant magnitude, or indicative of cognitive deterioration. Similarly, tests that showed an improvement in scores over time such as the COWA, were still performing below the mean of the normative data, not indicating improvement of a clinically significant magnitude. Therefore, the observed changes could be considered normal variations in scores that can be expected in repeated measures designs, when using the same or equivalent test on different occasions.

Collectively the findings showed relative stability of scores as the sample did not change level of impairment across the time points and overall had test retest correlations relatively comparable to those of the normal population on most tests of cognitive functioning. However, when drawing these conclusions, it must be considered that these are only speculative in nature, given the differences in the time frame between the assessments for the normal sample and the present study sample.

Future studies will benefit from including a comparator/control group which is followed up over the same time frame as the study sample, to be able to get more reliable and robust comparisons of the stability (and variability) of cognition in ACHD when compared to the normal population. Furthermore, such an analysis would also allow examining any differences in cognitive ageing i.e. age related changes in cognitive function in ACHD patients when compared to the normal healthy population. Assessing these changes could be considered important for the ACHD sample as patients with ACHD are cognitively impaired from childhood and continue to exhibit impairment into adulthood. Given that one would not expect any more developmental changes, any differences in scores could be indicative of a cognitive decline.

14.2.1.2 Potential explanations for the differential patterns of change in cognitive functioning

A wide range of NP tests were used to assess different aspects of the domains of cognitive functioning examined in this study. Interestingly despite the wide range of NP tests used to assess each domain, a significant improvement and/or decline in performance over time was only noted on one test in each of these domains. There could be a number of potential explanations for these differential changes observed across tests. These could include test related factors such as the nature of the test (i.e. testing modality), practice effects, the level of difficulty etc. Furthermore, these could also include other non-test related factors such as the testing environment and mood. Some of the potential factors that may explain the observed changes within this study are discussed below.

The results of this study showed a differential pattern of change both across and within the different domains assessed with some scores showing an improvement/decline while others remained unchanged. One potential explanation for only some tests demonstrating a significant

difference in scores over time within the different domains may be that the different tests assess different aspects of the cognitive domain being evaluated. For instance, the TMT-A test (which showed an improvement) assesses cognitive processing speed and visual numerical scanning, while the TMT-B test (showed no change) assesses divided attention, executive control and cognitive flexibility. Similarly, this explanation could also be applied to the SDMT test, whereby the oral subtest (which showed a decline) assesses verbal responses and complex visual scanning, while the written subtest (showed no change) assesses visuomotor responses and writing ability. Therefore, decline in performance on a specific subtest could be as a result of decline in that specific function or response modality (i.e. written versus verbal) *within* a domain. These results emphasize the importance of specificity when assessing change in cognitive function and suggest that different aspects of each domain need to be assessed independently as the change within domains can be variable, and using one test as a representative of a cognitive domain may not allow enough specificity to assess and detect subtle changes in cognitive domains.

Another potential explanation for some of the observed changes could be practice effects, which refers to an improvement in a subject's test scores as a result of prior exposure to the test. Studies have reported practice effects persisting for up to 3-5 years after initial assessment (Van Der Elst et al, 2008; Ronnlund et al, 2005). For instance, the Grooved Pegboard test of motor function used in this study, showed improvement on both components of the test (Grooved pegboard dominant and non-dominant hand score) with participants being faster and more efficient at completing the task at follow-up. However, there was no appropriate alternate form for the grooved pegboard test, therefore the improvement in motor function could be indicative of and interpreted as practice effects, as prior exposure to the test can enable participants to gain knowledge of the test structure and technique; thereby removing the element of novelty from the task and facilitating better performance.

Previous studies have reported that motor function tests which have a large speed component and/or an unfamiliar response such as inserting mental pegs into the pegboard in motor function tasks (e.g. grooved pegboard test), can easily be conceptualized once the correct response is attained, and therefore can be more susceptible to practice effects, which could also be interpreted as the ability of patients with ACHD to learn a strategy, suggestive of intellectual and cognitive abilities (Lezak et al, 2012; McCaffrey et al, 1992). Studies have reported practice effects on the Grooved Pegboard test over a period of 4-24 months (Dikmen et al, 1999; Strauss, Sherman and Spreen, 2006). A steady improvement in scores is reported when conducting repeated assessments using the Grooved Pegboard test to assess motor function (Strauss, Sherman and Spreen, 2006). The unusual nature of the task perhaps increases the likelihood of participants remembering the experience. This familiarity with the task could help explain the results of the present study, especially over the lengthened period between time points.

Along with practice effects some authors have also suggested the role of mood in the improvement of cognitive test performance over time, as test takers are likely to be less anxious during the second or third assessment given the familiarity with both the examiner and the test itself, potentially allowing them to perform better (Lezak et al, 2012). The potential association between change in mood state and change in cognition over time was examined in the present study. No significant association between a change in mood state and change in cognition were noted, within this sample (See Section 14.3 for predictors of change).

No particular patterns across test features were noted within these results for instance both tests with and without alternate forms showed improvement (e.g. TMT and GP), the type/difficulty of test i.e. more complex domains such as executive function and comparatively less complex domains such as motor function did not demonstrate a differential pattern of change

(interaction). Furthermore, both test with and without a speed component showed decline in performance (RAVLT and SDMT-O), and lastly tests with difference response modalities (tactile, verbal, and written) all showed improvement over time (GP, COWA). Lastly, mood did not seem to play a significant role in change in cognitive function over time within this study.

Overall the pattern of change in cognitive functioning over time was variable. This variability was noted within the same domains, across the different tests. Furthermore, it is of note that the variability in performance over time was not only observed between different domains and tests but also within tests. As discussed above one explanation for this could be that the different parts of the test assess different abilities, thereby leading to differential patterns of change over time (improvement and/or decline). These finding are not entirely unusual, as previous studies have established that the level of change in cognitive functioning is not uniform and can be variable across different domains of cognitive functioning (Glisky, 2007). These results emphasize the need to assess different domains of cognitive functioning independently, using a wide range of tests to be able to capture the variations in change across domains.

14.3 Differences between the structural complexity groups in cognitive function over time

The MLM analysis also assessed the overall difference in cognitive functioning between the four structural complexity groups (irrespective of time point). Across the battery of tests, only the TMT-B test of attention significantly differed between the four structural complexity groups (main effect of group – i.e. across the time-points as a whole). Pairwise comparisons showed that the Simple group performed significantly better than the SV group, suggesting that less structurally complex conditions (ASD, VSD) performed better than the more structurally complex conditions i.e. SV.

It is of note however that only the TMT-B test of attention demonstrated a significant difference between the different structural complexity groups both cross-sectionally and longitudinally, thus suggesting that divided attention was significantly different across different structural complexities. These findings are similar to those reported in the ACHD literature, which reports more structurally complex conditions performing worse on test of attention and executive function when compared to less structurally complex conditions (Franklin et al, 2014), a more detailed discussion on the subject is presented in Chapter 15.

As discussed in Chapter 9, a potential explanation for these differences between the groups on TMT-B could be the fact that the TMT-B is a cognitively challenging task, which assesses several domains including divided attention, executive functioning, and visual scanning, requiring the test taker to exercise multiple cognitive skills simultaneously. The complex nature of this task may increase the likelihood of identification of participants with subtle or specific cognitive impairments. Moreover, no differences between the groups were observed on Part A of the test, which is considered less complex and less cognitively demanding than part B.

14.4 Predictors of change in cognitive functioning over time in ACHD patients

A further objective of this study was to identify statistically significant predictors of change in cognitive functioning. Predictors were only identified for test scores that demonstrated a statistically significant change in scores over time in the MLM analysis (i.e. TMT-A, COWA, GP- dominant and non-dominant, RAVLT and SDMT-O). Furthermore, predictors of change were only identified for the total follow-up study sample, as sample size of the follow-up study did not allow sufficient statistical power to run sub-group analyses (i.e. assess each structural complexity group independently).

The results showed that overall while significant univariate associations of demographic, clinical and mood variables with cognitive functioning were noted, none of these factors explained any significant *unique* variance in changes in cognitive functioning over time within the multivariate analyses. The only exception to this was the domain of memory (RAVLT); where results demonstrated that a lower level of current oxygen saturation (at the time of first assessment) and fewer years of education were associated with a decline in memory function. Interestingly, the lower levels of oxygen saturation was not associated with memory scores in the cross-sectional study but was apparent when assessing predictors of change; perhaps suggesting the role that the level of oxygen saturation can play in predicting changes in cognitive performance (memory) over time.

A positive association between oxygen saturation levels and memory function in *healthy* adults has been reported. A statistically significant improvement in word recall rates with a 30% increase in oxygen saturation levels; suggestive of better memory function being associated with higher oxygen saturation levels was reported by Chung and Lim, (2008). Scholey and colleagues also reported that oxygen administration coinciding with word presentation resulted in enhanced word recall rates; thus suggesting that blood oxygen levels may be available to neural memory consolidation processes (Scholey, Moss and Wesnes, 1998). Although when drawing comparisons between the above mentioned studies and the present study it must be noted that the level of oxygen saturation within the present study sample was recorded at Time 1 (cross-sectional), whereas the studies discussed had a contemporaneous measure of oxygen saturation recorded at the time of assessment. Furthermore, these studies assessed the relationship between oxygen saturation levels and absolute NP scores, whereas the present study assessed NP change scores. Therefore, the association of oxygen saturation noted within the present study is specific to change in cognitive functioning (memory) over time and not performance on a memory test (at one time-point). One potential explanation for these findings

could be the role of other intervening or mediating factors that may not have been recorded or identified within the present study. Further work assessing the longitudinal relationship between these variables specifically in the ACHD patient population is warranted, to be able to draw more robust conclusions.

With regards to the association between years of education and memory, studies have reported that higher education is associated with less age related decline in memory function. An association between more years of education and a statistically significant improvement in memory performance in adulthood has been reported (Glymour et al, 2008). Furthermore, fewer years of education has been found to play a role in accelerating cognitive decline in memory and the onset of dementia (Schmand et al, 1997). A meta-analysis of the literature reported that fewer years of education might in fact be a risk factor for the onset of dementia (Caamaño-Isorna et al, 2006). One potential explanation for the findings of this study and the existing literature could be that more years or higher level of education could mean that the brain is more functionally active over the years, and the mental stimulation provided by educational process may play a potential role in maintaining cognitive functioning and preventing a decline in cognitive functioning (Bosma et al, 2003). Within the present study, years of education was associated with memory both cross-sectionally and longitudinally, demonstrating the stability of this association over time, and the potential role education may play in long-term memory function. However, this relationship was not noted within any other domains within the present study.

Furthermore, when interpreting the results of the regression analysis to identify predictors of change in memory function in the present study, it must be noted that the total amount of variance in memory explained by these variables (oxygen saturation and education) was considerably small (8%). These results showed that a large proportion of the variance in

changed memory scores was unaccounted for, and perhaps variables explaining this change were not measured or recorded within the present study. These could include a range of variables such as clinical factors including co-morbidities or other non-cardiac coexisting conditions, psychosocial factors such as social support and self-esteem (Daliento et al, 2005), and socio demographic factors such as socio-economic status (Wernovsky et al, 2000).

Another potential explanation for the lack of significant predictors of change identified in the present study could also be due to the approach undertaken to analyze the data, i.e. combining all complexity groups together. As seen in the results of the cross-sectional study (Chapter 8), doing so can lead to the dilution of specific effects which may explain significant variance in the outcomes for specific groups if assessed independently. However as discussed above the small sample size of the subgroups in the follow-up study did not allow enough statistical power to run sub-group analysis. Future studies may benefit from including a larger sample size and a longer follow up period to examine changes in cognition over time in this group. Furthermore, inclusion of a comparator group matched closely to the characteristics of the study sample will provide more robust and reliable comparisons to the normal population.

14.5 Summary

Overall the results of this study demonstrated considerable variability in the pattern of change across different domains of cognitive functioning. However, none of the changes observed were indicative of a clinically significant magnitude (over the given time period), and were mostly comparable to those of the normal population. But, given that some observable decline in cognitive function was noted over a period of three years, ongoing assessment of these domains is warranted. This ongoing assessment and more longitudinal research would help monitor the rate of decline within this patient group i.e. it would help assess if the impairment remained stable and/or increased with longer periods of time (relative to the normal population) and the

protective effects (in halting or reducing rates of decline) of clinical, demographic and psychological variables. Similar studies would help validate the results of the present study, and enable a better understanding of the stability of cognitive functioning in this patient population.

The current findings should be considered hypothesis generating, requiring future work to explore a wider range of variables (psychosocial, clinical, socio-demographic, and environmental) that may explain variation in cognitive outcomes over time. Furthermore, future studies may benefit from a larger sample size per condition that would allow investigating change in cognitive functioning independently in different structural complexity groups, to allow more specificity on the analysis, and a better understanding of the potentially different trajectories of change in cognition across different conditions. A fuller discussion on the strengths and limitations of this study and its implications will be addressed in more detail within the next chapter (Chapter 15).

15 OVERALL DISCUSSION

15.1 Prologue

This chapter presents the overall aims and objectives of this thesis, the findings and contributions of both the studies to the literature. It then discusses the overall strengths and limitations of this thesis, followed by the implications of the findings for clinical practice and future research.

15.2 Thesis aims and objectives

The overall aim of this thesis was to investigate the extent, impact and stability of cognitive functioning in ACHD patients with different levels of structural complexity. The cross-sectional study aimed to investigate the extent of cognitive impairment in ACHD patients with different levels of structural complexity. It also aimed to identify the different factors that may influence and or impact on cognitive functioning. It investigated the impact of impaired cognitive functioning on patient related outcomes including quality of life. The longitudinal study aimed to investigate the stability of cognitive functioning in ACHD patients, along with identifying predictors of change in cognitive functioning.

15.3 Novel contributions to the literature

This study addressed an area of research that has previously received little attention. It is one of the first and largest studies to assess and compare different structural complexity groups of ACHD on a comprehensive range of cognitive domains and investigate the stability of cognitive functioning over time. The contributions of this thesis to the literature are discussed below.

15.3.1 The extent and stability of cognitive functioning in the ACHD patient

An overview of the literature on cognitive functioning in CHD patients showed that the majority of the evidence in this area of research focused on children with CHD. However, given the fact that these studies did not follow up into adulthood no conclusions could be drawn about whether the findings in childhood persisted into adulthood. Investigation of cognitive function in adulthood enables an examination to be made, as to whether the same pattern of cognitive problems observed in childhood persists into adulthood.

A systematic review of the literature on cognitive functioning in ACHD was conducted. The results showed limited research conducted to investigate cognitive functioning in adult survivors of CHD. This paucity of evidence in ACHD is understandable given only the relatively recent increase in the survival rates of the CHD patient, due to improvements in treatment techniques and medical advances. Overall the presence of cognitive impairment in ACHD patients when compared to the normal healthy population was noted in the existing literature. With regards to the extent of cognitive impairment mixed findings in relation to IQ were observed (Wernovsky et al, 2000; Utens et al, 1998). Only two studies examined specific domains of cognitive functioning in ACHD, and reported impairments in the domains of executive functioning, attention and cognitive speed (Daliento et al, 2005; Idorn et al, 2013).

Along with the small number of studies, the existing literature on cognitive functioning in ACHD was marked by many methodological limitations including the small sample sizes, the overreliance on IQ as a composite measure of cognitive functioning, and the variability in the sampling procedures used across studies (i.e. heterogeneous versus homogeneous sampling of different structural complexities). These limitations made drawing generalizations across the studies difficult.

Extent of cognitive impairment in ACHD

In order to address these methodological limitations identified in the review and to bridge the gap in the literature with regards to the extent of cognitive impairment in ACHD, a cross-sectional study was undertaken to investigate a wide range of cognitive domains including attention executive function, memory and motor function in a large group of ACHD patients. Participants were recruited from across a range of common ACHD conditions in order to enable greater generalizability of the findings and also assess any differences in cognitive functioning across structural complexity groups.

The results of the cross-sectional study showed that a considerable proportion of patients with different forms of ACHD, higher than would be expected in the general population, exhibited impairment in a number of cognitive domains including executive functioning, attention and motor functioning and IQ. These results supported other studies that reported impairments in executive functioning and attention in ACHD patients (Daliento et al, 2005; Franklin et al, 2014).

The evidence with regards to IQ in the existing literature is inconclusive. Importantly the methodological limitations of the existing literature including large amounts of missing data, not using reliable normative data for the purposes of comparison, and variability in measures all make drawing conclusions challenging. In comparison the present study was the largest study conducted to date, that investigated the extent of cognitive impairment in a wide range of ACHD conditions by using reliable cognitive measures and a robust methodology, providing

more confidence in the finding that ACHD patients have impaired IQ when compared to the normal population.

The present study employed a four-group classification based on the level of structural complexity of ACHD to examine whether there were differences in cognitive performance between these groups. This is important as some of the previous literature used mixed groups and failed to examine for differences (Heinrichs et al, 2014) whilst others studied only one structural complexity group (Daliento et al, 2005). Between group test performance was compared to identify differences in cognitive functioning across different ACHD structural complexity levels. A significant group difference was noted in attention and the total mean composite NP score in the present study. In both instances the Simple group performed significantly better than the SV and TGA groups. These results are similar to those of Franklin et al, (2014) and Utens et al, (1998) who reported significant differences in complex attention, cognitive flexibility and overall executive functioning and IQ in ACHD patients; with patients with structurally complex conditions (SV, TGA) performing significantly worse when compared to less structurally complex conditions (ASD, VSD). The results of the present study added to this growing body of literature which suggests that more structurally complex conditions exhibit more cognitive impairment in comparison to less structurally complex conditions.

There are several factors that can contribute to these differences between complexity groups, for example patients with structurally complex forms of CHD are more likely to undergo surgical repairs and interventions, thus making them more vulnerable to brain injury and insults associated with cardiac surgery. Within the present study the more structurally complex condition underwent significantly more number of surgical procedures which may have made them more vulnerable to these impairments. Furthermore, more complex conditions such as SV

and TGA are cyanotic in nature, leading to a lack of blood oxygen supply to the body, including the brain. These differences were evident in the present study sample with more structurally complex conditions having a much longer duration of cyanosis and a lower level of blood oxygen saturation in comparison to the Simple group. Oxygen deprivation makes cyanotic patients more prone to cognitive impairment and brain injury, as the lack of oxygen supply to the brain can lead to death of brain tissue causing long term implications (Licht et al, 2004).

Factors associated with cognitive functioning in ACHD

Having established the extent of cognitive impairment in ACHD patients, it was considered important to understand the factors that have the potential to influence cognitive performance. The results of the systematic review discussed in Chapter 4 demonstrated some variables associated with cognitive functioning, including demographic (education and socio-economic status) (Eide et al 2006; Daliento et al, 2005), clinical (cyanosis, cardiac surgery) (Wernovsky et al, 2000) and psychosocial (self-esteem) factors (Daliento et al, 2005). The present study builds on these findings in the existing literature, with an extensive range of variables included to examine factors associated with cognitive functioning both in the total study sample and each of the structural complexity groups.

When considering the ACHD sample both as a whole and each of the structural complexity groups the factors most consistently associated with domains of cognitive functioning (attention, executive functioning and IQ) were post-operative CNS complications and years of education. Interestingly when the different structural complexity groups were assessed independently, greater variability was noted with a range of other variables found to be significantly associated with cognitive functioning within the specific structural complexity groups. For instance, factors such as age at surgical repair and oxygen saturation levels only

emerged significant when groups were assessed independently. Overall clinical factors (surgery related variables, medication) explained more unique variance in cognitive outcomes, when compared to demographic (employment, gender) or psychosocial (anxiety, depression) factors. These findings could be expected given the diverse nature of different forms of ACHD and their associated symptoms, treatments and prognosis, which vary greatly across conditions.

The findings with regards to the CNS complications could be considered particularly relevant to the current set of ACHD patients as this group of patients were born and treated approximately 30-40 years ago when the use of neuro-protective strategies to safeguard the CNS during a surgery were not well established and the primary focus of clinicians was to reduce mortality rates. With the advances in neuro-protective strategies it is hoped that the patients undergoing surgical correction in infancy in the current era will experience fewer of these long-term problems due to cardiac surgery and its associated post-surgical CNS complications (See Albers, Bichell and McLaughlin, (2010) for a review on the subject). The findings of the present study indicate the potential long-term role that surgical treatment and its associated complications can play in determining the level of cognitive functioning in ACHD.

Similarly, a better understanding of the association between CHD, education and cognition would be informative in enabling the provision of appropriate and timely support to these groups of patients earlier in life. This support could be offered to children in different forms targeting different areas of development. Firstly, support in the form of remedial or special education and additional one to one support may help children make up for lost time due to ill health and cope with any educational challenges that they may face in a supportive environment (Riehle-Colarusso et al, 2015). Secondly further support in the forms interventions or therapeutic techniques to improve cognitive functioning and strengthening cognitive skills could

help patients improve their levels of cognitive functioning, and perhaps reduce cognitive decline and the persistence of impairment in adulthood as noted within this study.

These results reflect the fact that different forms of ACHD are not only varied with regards to their structural complexity, treatments, morbidity and long-term disease trajectory but also with regards to the level of cognitive functioning and the factors that influence cognition. The results of this study highlight the fact that like the nature of the different ACHD conditions the long-term outcomes for each are also diverse, thus emphasizing the need to address the concerns of each condition independently. The clinical implications of these findings are discussed later in Section 15.5.

Lastly, the association between cognitive functioning and QoL was also assessed within the present study to get a better understanding of the potential impact cognitive functioning may have on patient related long term outcomes. The results of the present study indicated no significant association between cognition and QoL, suggesting that cognitive functioning and QoL in this patient group were not related.

Stability of cognitive functioning in ACHD

In order to assess whether the stability of cognitive functioning in ACHD patients differs from that of the normal population a longitudinal assessment of cognitive functioning was undertaken. This area of research has largely been overlooked, with no evidence on the stability of cognitive functioning in adult CHD patients. The present study was the first to assess cognitive stability in ACHD patients, compared to the normal population.

When the stability of the scores in this study sample was compared to the normal population data in the form of test retest correlations, the sample demonstrated relatively similar test-retest

correlations in comparison, particularly when taking into consideration the interval between the two assessments. Results of this follow-up study showed some variability in change across different domains of cognitive functioning, with some demonstrating an improvement and others a decline. The pattern of changes across the different cognitive domains in the present study demonstrated a large amount of intra-individual variability in cognitive functioning. It also emphasized the fact that different domains of cognition are subject to different degrees of change (improvement and/or decline), which can be expected as the rate of change is not uniform and can be variable across different domains of cognition (Glisky, 2007).

Overall however the observed changes within this study did not appear to be of a clinically significant magnitude, as the sample remained in the same relative category of impairment over time. No major shift in the pattern of cognitive impairment was noted across the total sample and the different complexity groups, suggesting that these may be normal variations in scores over time, associated with repeated measures designs.

Future research may benefit from conducting a comparative study of cognitive ageing in ACHD patients and healthy adults. This form of research could help inform important questions with regards to the rate of cognitive decline in ACHD and their susceptibility to age related cognitive impairments such as dementia, mild cognitive impairment and Alzheimer's disease in comparison to the normal population.

Cognitive impairment in ACHD –delay or deficit? A synthesis of the thesis findings

Overall the key findings of this thesis have implications for the delay versus deficit argument raised in Chapter three. The findings of the systematic review and the two present studies collectively showed the persistence of some cognitive impairments noted in childhood in the adult population. For instance, studies of ACHD patients continued to report the presence of

impairments in the domains of attention, executive function, and IQ (Daliento et al, 2005; Franklin et al, 2014). Similarly, both the child and the adult CHD literature report IQ as being lower in comparison to the normative data but within the 'normal range' as specified by the tests (Bellinger et al, 2003; Krueger et al, 2015; Wernovsky et al, 2000). These results offered some support to the deficit argument, suggesting that these impairments in childhood may actually be deficits in cognitive functioning as opposed to delays in development, which would have been resolved eventually and not still been evident in adulthood, as is the case in the present study.

This pattern of similarity was also evident across the different structural complexity groups with both the child and adult literature showing more cognitive impairments in the structurally complex conditions. Patients with ToF and TGA showed more impairment in attention and executive function when compared to the normal population and less structurally complex conditions including VSD and ASD across the two literatures (Cassidy et al, 2015; Hovels-Gurich et al, 2007).

The results of the follow-up study further support this argument, with these cognitive deficits still being apparent over time, suggesting that the cognitive impairments in children with CHD may in fact be deficits that last well into adulthood and continue to remain impaired.

The early onset and stability of these impairments in the ACHD population may also help explain the lack of association noted between cognition and QoL in the present study. Given that these patients have had impaired cognition since childhood, they are likely to have adjusted to this level of cognitive functioning and consider their level of cognitive ability as 'normal'. Therefore, they may not recognize and/or perceive it as a limitation on their QoL. Other evidence suggests that often patients diagnosed with chronic conditions adjust their aspirations

in the long term and may not view a limitation as one given that they have adjusted to the situation over time (Turner and Kelly, 2000).

A better understanding of the longevity of these impairments noted in children with CHD could have important implications for patient care, as this information could help inform future interventions designed to improve cognitive functioning and /or reduce the rate of cognitive impairment and potential decline at an early stage. This would not only help improve educational and academic achievement in these groups of patients when they are younger but also reduce the extent of cognitive impairment in adulthood, which could help patients lead more normal lives, and reduce the impact of impaired cognitive functioning on patient related long-term outcomes.

However, given that the findings of the child literature and the present study are from different samples, a more robust assessment of this theory is warranted in the ACHD population in the form of longitudinal research that follows up a group of patients from childhood into adulthood. Such a study would enable a more robust evaluation of the stability of the noted impairments along with assessing different developmental milestones in this patient population over time.

15.3.2 The use of structural complexity to categorize ACHD for the purpose of research

ACHD is a diverse group of conditions consisting of various diagnoses and, different levels of structural complexity, severity, prognosis and treatment courses etc. The majority of the existing literature on cognitive functioning in ACHD patients has included this heterogeneous collection of ACHD conditions as a single group, whereby conditions with levels of structural complexity and severity are assessed collectively. It is evident from the existing literature that the lack of a gold standard in classifying these conditions has led to mixed findings that limit the ability to draw clear inferences about the impact of different conditions that fall under the

umbrella term of ACHD.

Several governing bodies have attempted to impose a structure on the heterogeneous nature of CHD and ACHD. Guidelines from various organizations across the world have proposed various categorizations of ACHD, each suggesting that their categorization guide clinical practice and research within CHD.

Some of the most widely recognized categorizations include the Task force 1 classification of the American Heart Association, which uses the patient's diagnosis and the need for regular follow-up as a basis for their classification (Warnes et al, 2001). Another commonly used categorization is using functional status to classify patients by applying the New York Health Association (NYHA) classification. This is, however, not specific to ACHD.

These forms of categorizations have received criticism for their lack of specificity and inability to capture the true diverse nature of the condition and their impact on patient related outcomes and experiences. For instance, the Task force 1 categorization, groups a number of conditions under the label 'complex' and as a result this categorization classifies SV and TGA as complex conditions that are grouped together. However, what such a classification fails to take into account is the higher levels of long-term complications, morbidity and mortality that are associated with SV conditions, but may not be characteristic to the TGA patient (Jackson et al, 2015).

Most of the existing categorizations in the literature are broad and differ in the way they classify different conditions. However, they all usually include a varied range of conditions under broad labels such as severe, moderate, and simple/mild which are essentially categories based on a measure of severity, and do not capture and/or allow the assessment of the specific impact of

each of the conditions that make up CHD on patient related outcomes (Jackson et al, 2015). Consequently, the majority of the existing literature on cognitive functioning in ACHD patients includes heterogeneous samples with a range of conditions investigated collectively. It has become clear that for both research and clinical reasons there is a need to find some form of grouping or classification of patients with CHD.

Given the above-mentioned limitations of the existing classifications and the lack of specificity in the disease categorizations, these guidelines were not used to categorise CHD within this study. Instead a new classification was adopted based on the nature of the congenital heart problem and how it affected the anatomical structure of the heart.

The present study included four groups and distinguished between the four groups based on their level of structural complexity. This categorization was based on the anatomical description and complexity of the different forms of ACHD, and was also a general marker for the treatments required and the presence of cyanosis within these groups (See Chapter 1 for details). Unlike the other classifications in the literature the four group categorization adopted in the present study allowed each of the anatomically different conditions that make up CHD to be assessed independently, which enabled more specificity and a better understanding of the different long-term outcomes in these groups and factors that have the ability to influence them. Furthermore, such a categorization also enabled drawing comparisons across the different conditions included.

As discussed in Chapter 7, the classification adopted in this study was established using the clinical expertise of the consultant cardiologists at the Heart Hospital, London and follows the established subdivisions of CHD, as used widely in the literature, for instance by the American College of Cardiology and American Heart Association (Warnes et al, 2001; Warnes et al,

2008). The categorization was finalised after careful deliberation, evaluation and agreement of the cardiologists. The objective was to examine whether this categorization based on structural differences was useful both clinically and for research purposes.

The results of this study highlighted the advantage of using such a categorization as the findings not only showed differences in cognitive functioning across the different structural complexity groups, but also in factors associated with cognitive functioning in these different conditions. It is evident from the results that merging together these groups does not allow for a consideration of the specific factors that explain variability in cognitive functioning; as some of the clinical variables may not be applicable to all structural complexity groups included in the study. A good example of this is the variable 'cyanosis', which could be considered inapplicable to the Simple group, given that these conditions are acyanotic in nature. These differences emphasized the importance of assessing different conditions independently as examining a heterogeneous sample could lead to dilution of specific effects, which may be pertinent to some conditions.

Overall the use of structural complexity as a classification in the present study has provided some valuable insights and differentiation of the different forms of ACHD and cognitive outcomes. This form of categorization provides a working model for future studies to build upon. The merits of this form of categorization could be tested and used in future studies to evaluate other long-term outcomes specific to each complexity group.

15.4 Overall limitations and strengths of the studies in the thesis

15.4.1 Study limitations

15.4.1.1 Representativeness of study sample

With regards to the representativeness of the study sample, the exclusion criteria applied in this study may have limited the generalizability of the findings and potentially biased the results of

the study. For instance, this study excluded patients undergoing or about to undergo a surgical procedure, as with these cases it would be challenging to differentiate between the extent of cognitive impairment and change in cognitive functioning caused by CHD and that caused by the surgical procedures and anesthetics, as these factors are known to influence cognition functioning (Mason, Noel-Storr and Ritchie, 2011). The exclusion of these cases may have led to more seriously ill patients that require surgical treatment being excluded from the study, thereby resulting in the missed identification of the cognitive impairments and/or declines in the more seriously ill groups of patients in turn causing systematic bias. However the inclusion of these patients could have resulted in further challenges when assessing the stability of cognitive functioning over time, as any observed changes over time could have potentially been as a result of the recently conducted surgical procedures and/or anaesthetics.

Within the present study patients with chromosomal anomalies such as Downs (Trisomy21) and Di George (22q11 deletion) syndrome were excluded, as these conditions are known to have an impact on cognitive functioning, and would therefore make it difficult to identify the specific impact of ACHD on cognitive functioning, over and above chromosomal anomalies. However the exclusion of these patients restricts the generalization of the findings of this study to the CHD population as a whole. Furthermore this exclusion may also have led to the underestimation of the extent of cognitive impairment in CHD patients as a group.

Only patients fluent in English language were recruited in this study; this decision was made due to practical reasons, as there were limited resources to translate and interpret the cognitive tests and psychosocial questionnaires into different languages. Further changing the language of the NP tests could interfere with the psychometric properties of the instruments and also create additional challenges associated with identifying appropriate normative data for comparison in

different foreign languages. Therefore the findings of this study are limited to patients fluent in English language.

With regards to the ethnic representativeness of the sample, there was an overrepresentation of the White British population in this study, with other ethnic groups not being adequately represented, thus limiting the generalizability of the findings to all ethnic groups. As discussed in Chapter one there is evidence of ethnic susceptibility to different forms of CHD, and a largely White British population as in this study may not be representative of this (Nembhard et al, 2010). Lastly, the study eligibility criteria and the resulting sample limits the findings of this study to patients being treated within the UK. Furthermore, the data was gathered from a single specialist hospital site (although it has a wide catchment area), which may also reduce generalizability and variability in the data gathered.

Lastly, this study included a large heterogeneous group of patients with varying levels of structural complexity providing good differentiation in complexity levels while also including the most common form of ACHD. However, it must be stated that *not* all conditions encompassed in ACHD were included (e.g. less common conditions like Truncus arteriosus) thus limiting the findings of this study to the conditions involved. In a related matter, another limitation of the study relates to the 'Simple' category, which included a mixed diagnosis (ASD, VSD, and CoA), due to the small number of participants available for this study. This did not allow for specific 'Simple group' conditions to be examined independently. Further research is needed to be able to identify if conditions with a similar level of structural complexity (e.g. ASD, VSD) differ with regards to their cognitive outcomes.

15.4.1.2 Measures used for assessment and data collection

NP test battery

While a number of cognitive tests were employed, not all domains and sub-domains of cognitive functioning could be covered for instance not all types of memory could be assessed (e.g. long-term and episodic). Conducting a comprehensive NP assessment, is difficult and not always feasible in a research and/or clinical setting, as assessing a range of domains including its different aspects can be lengthy and time consuming and not feasible, given the burden this may place on the participants. As discussed earlier in Chapter two, it is difficult to assess a domain of cognition using a single test, and future studies may benefit from examining aspects of cognitive functioning that have not been investigated within this study.

It is also considered important to acknowledge that while the use of normative data to draw comparisons with the normal population is useful and informative, some caution must be exercised when using normative data particularly for tests of IQ. As most studies reporting normative data were conducted several years earlier; it may subject the results to the well-known "Flynn effect" (Flynn, 2007). The "Flynn effect" suggests a rise in the IQ curve i.e. an increase in the level of intelligence over generations. As a result using historically gathered normative data might not allow an accurate comparison, potentially leading to a false negative effect (Karsdorp et al, 2007). However, obtaining normative data that is a perfect match to a study sample may not always be possible or achievable. To limit potential biases of this type, existing normative datasets were evaluated and those that closely matched this study sample were chosen. All normative data was matched by age and method of test administration and the scoring procedures used within this study. Normative data was also matched by gender and education where available. Future studies may benefit from sampling a healthy comparator/control group matched on demographic factors such as age, gender and education, which may provide a better and more customized set of data, for the sample being assessed and allow for a more robust and reliable comparison. However, the sheer magnitude of the data

required could pose logistical challenges including the sample size required and the cost of running such a study, which would need to be considered.

Lastly, the short versions of some NP tests were used where appropriate and available, in order to reduce patient burden. However, this resulted in the omission of certain scales from some measures, for instance the measure used to assess IQ (WAIS-III), which may not be as sensitive as the full length measure. However as discussed in Chapter two using a shorter version of IQ tests to calculate an estimated IQ is common practice in a research setting.

Measures used to evaluate mood and QoL in ACHD

Given the wide range of variables assessed in this study the short versions of psychosocial questionnaires were used where appropriate and available, in order to reduce patient burden. However, this may have resulted in the measures not being sensitive enough to detect an association within this patient group. Further, a lack of disease specific QoL measure within this study may have reduced the sensitivity of the measure to detect group differences within the different forms of ACHD, given the generic nature of the questionnaire utilized.

Disease specific measures are often designed to measure aspects of ill health that are most salient to the condition in question, as opposed to the generic measures, making them a lot more sensitive. Furthermore with regards to the self-report measures used to assess QoL, depression and anxiety, the data was gathered in the presence of the researcher, which may have led to some bias as the responses could be subjected to experimental demand characteristics which refers to the artefact whereby participants subconsciously change their behaviour to fit their interpretation of the tasks purpose and/or social desirability bias; whereby the participant provides responses that they believe will be viewed favourably by the examiner (Stevenson et al, 2000).

Lastly, it is important to acknowledge that the CESD-10 questionnaire used to assess depressive symptomology in this study, includes somatic items that may inflate the rate of depression observed (e.g. my sleep was restless). However, given that mood was only included within the study as a control variable and not a key outcome variable, it allowed more stringent control of both depressive and physical symptomology that may impact cognitive functioning.

Clinical history data

A detailed clinical history was gathered for each participant, in order to be able to investigate the clinical factors that are most likely to affect cognitive functioning. However, it must be acknowledged that the presence of other co-morbidities or co-existing conditions may have obscured the effect of other variables on the outcomes being measured.

Further, it is acknowledged that one of the drawbacks of this study is the lack of data regarding the specific nature of the CNS complications experienced by the patients. Therefore, while the results of this study can be used to draw conclusions about the association of post-operative CNS complications and cognitive functioning; it cannot be specific regarding the precise nature of the CNS complications. Further work is required to identify and understand the specific mechanism underlying this association, and identification of the specific form of CNS complication associated with cognitive impairment in ACHD patients.

15.4.1.3 Follow-up data

The time constraints of the follow-up study did not allow the assessment of all participants at the same time-point; however, no statistically significant differences between the groups were noted on the time frame. Furthermore, given the time constraints the required sample size for

the follow-up study could not be achieved, leading to a difference in sample sizes across groups and the lack of sufficient power when conducting sub-group analysis.

Given that the test-retest data from a normal healthy control group was not available within the present study, the available published data was utilized to assess the stability of cognitive functioning over time. However, the considerable differences in the time interval between the assessments for the two groups posed some limitations and made drawing comparisons challenging.

15.4.1.4 Data analysis

Given that most studies conducted in the past utilised a heterogeneous sample with different forms of CHD assessed collectively, little was known about different conditions and what factors influenced cognitive functioning in these groups. The present study was exploratory in nature and aimed to assess each condition included independently, on each of the cognitive functions assessed. Consequently, this exploratory approach led to a large number of analyses being conducted. It is acknowledged that the large number of analysis as a result of conducting sub-group analysis and using each cognitive test score as a dependent variable could have resulted in some chance findings. However, where possible steps were undertaken to control for these limitations - for instance a more stringent p-value ($p<0.01$) was chosen. This method was preferred over the Bonferroni correction, which involves dividing the p-value by the number of tests used, as this approach was considered too conservative and may have obscured true effects that may exist.

15.4.2 Strengths of the study

This section addresses the strengths of the present study with regards to its design, measures utilized and sampling procedures.

15.4.2.1 Study design

One of the main strengths of the present study is the novelty of its design and research objectives; this study is one of the largest and first to assess and compare cognitive functioning in patients with ACHD, with varying levels of structural complexity both cross-sectionally and longitudinally. Thus providing specific insights into the long-term outcomes of the different structural complexity groups. Furthermore, this study includes a relatively large sample size in comparison to the existing literature, which provides more statistical power to detect significant effects and provides more confidence in the findings of the present study. Although the sample size for the sub-group analysis i.e. when the groups were assessed independently was considered small, statistically significant trends in the data were still evident with a range of small to large effect sizes. Future studies with larger sample sizes for each structural complexity group would aid conformation of the findings of this study.

15.4.2.2 Measurements of cognition

With regards to the assessment of cognitive functioning this study moved away from the trend in the literature to use a single composite measure of cognition (i.e. IQ), and assessed a wide range of cognitive domains. A comprehensive neuropsychological test battery was employed to assess the key domains of cognition including attention, executive functioning, memory and motor functioning. These tests enabled identification of specific areas of cognitive impairment within the different structural complexity groups. This was done to allow more specificity in measurement, as it could be that only some domains of cognition were impacted, and this could have been obscured if only a composite measure such as IQ was used. Nevertheless an IQ measure was included within this study to enable comparison with the existing literature, which primarily uses IQ as the only measure of cognitive functioning.

The advantage of conducting a comprehensive assessment was evident from the results of this study. For instance, the IQ within this study sample was in the normal range as classified by Wechsler, however there was a considerable proportion of participants with impairments in specific domains of cognitive functioning including executive functioning and motor function when compared to age matched normative data. Therefore, had only the measure of IQ been used one could conclude that the level of cognitive functioning in ACHD is largely comparable to the general population, while in fact these groups of patients experienced cognitive impairments in specific domains, that could have been overlooked in the absence of a comprehensive assessment.

Furthermore, when interpreting the magnitude of cognitive impairment, this study acknowledged the complexities associated with cognitive assessment and took into account the proportion of the normal healthy population that could be expected to exhibit the same level of impairment when drawing conclusions, to ensure that the estimated proportion of participants with impairments was not inflated (i.e. reduce false positives).

It has been established that the likelihood of the normal population scoring 1.5 SD below the normative mean score is 7% on any given test assuming a normal distribution. However, when using multiple tests of cognitive functioning as is the case in this study, this proportion is inflated dependent on the number of tests utilized. When comparing the performance of the study sample to the normative data, it is essential to take into account the number of tests utilized, in order to draw a more informed conclusion. Therefore, the mathematical formula provided by Ingraham and Aiken, (1996) was used in this study to establish the extent of cognitive impairment in comparison to the normal population (See Chapter 7 for a more detailed description).

In summary, this study addresses an important area of research that has previously been neglected. As evidenced from the systematic review very few studies have assessed cognitive functioning in the ACHD population. With the increase in the number of adult survivors of CHD, and the rapidly growing adult patient population this study provides valuable information regarding the long-term outcomes of this patient group. The results of the cross-sectional and follow-up study provides an insight into the long-term outcomes and repercussions of the treatments and the nature of the condition; allowing the identification of vulnerable patient groups that are more likely to experience cognitive impairment as a result of their condition and its treatments. Some of the potential contributions of this study to the clinical practice and care of these patients are discussed below.

15.5 Implications of the study findings

The findings of the present study have a number of implications for clinical practice. The results of the cross-sectional study demonstrated the potential impact of ACHD and its associated treatments on a patient's cognitive performance. A significant and consistent association between the treatment and surgery related factors (post-operative CNS complications, CPB and hypothermic arrest duration, age at repair etc.) and cognitive functioning was noted across different domains. Furthermore, the results of the follow-up study discussed in chapter 14 demonstrated that clinical factors such as oxygen saturation levels may play a role in predicting cognitive decline over time in patients with ACHD, however the mechanisms underlying these associations remains elusive and warrants further research.

These results could have implications for the surgeons and clinicians that are involved in the treatment and care of this patient population; as the results of this study highlight the factors that have the ability to cause impairment in cognitive functioning as this patient group ages into

adulthood. This information emphasises the importance of the treatments, in particular the surgical interventions on long term cognition. Whilst most of these are currently being taken into account it is worthwhile emphasizing that they are potentially modifiable factors that can be managed so as to reduce or mitigate the risk of cognitive impairments in ACHD. Some such potential factors could include minimizing the length of the surgery and a smaller duration of the use of CPB or HA. Furthermore, to reduce potential CNS complications, CNS protective strategies could be incorporated when conducting a surgical procedure.

The recognition of these cognitive impairments can have implications for patients and their families in the form of better management and increased support. The cognitive domains affected in ACHD appear important for an individual to function independently in day-to day activities such as self-care, adherence to medication and treatment, and social and work related demands. Identifying which ACHD patients have particular cognitive problems will help identify where health care resources should be directed. It is therefore useful to consider a routine screening cognitive assessment in ACHD clinics.

It is acknowledged that cognitive testing can be an expensive and time consuming exercise requiring expert psychologists, thus posing challenges in making this a part of routine care. However more advanced forms of cognitive testing such as computerized tests are now increasingly being used. These tests may help reduce the manpower and the potential costs needed to conduct such an assessment, making it more economically feasible in health care settings. It is hoped that this study and similar research along with routine assessment of patients would allow clinicians and researchers to identify vulnerable individuals/ groups and provide appropriate support and rehabilitation where necessary.

The evidence on the use of cognitive rehabilitative and remedial interventions within the ACHD population is limited, and could benefit from the application of techniques proven to be useful within the paediatric CHD literature; for instance, intensive computerised training to improve domains such as working memory (Calderon and Bellinger, 2015). Furthermore, there is some evidence of cognitive interventions including activities such as problem-solving, guided imagery and mnemonic training that have proven useful in improving cognitive outcomes in adults with mild cognitive impairment (Martin et al, 2011). Studies have also reported the usefulness of meditation and mindfulness training in the improvement of working memory, executive functioning and visuo-spatial processing (Zeidan et al, 2010). However, much work is needed to be able to assess the effectiveness and usefulness of these techniques in ACHD patients. Potentially such techniques may be useful for ACHD patients that have impairment in specific domains of cognitive functioning, that limit their ability to function in an optimal manner or interferes with their ability to function independently.

Lastly, the findings of this study could have implications for the education services that can be better informed and more mindful about the challenges faced by this group of patients. As seen from the results of the cross-sectional and longitudinal studies the impairments seen in childhood indicate the presence of cognitive deficits as opposed to delays, therefore suggesting the early onset of the impairments noted in the adult population. Acknowledging the problems faced by these groups of patients and providing the appropriate educational support in a timely manner could have long lasting implications for the patients, not just with regards to their academic performance but also their future employability and professional prospects.

15.6 Directions for future research

There are a number of avenues for research that have been generated from this study and the systematic review discussed in Chapter four. A general finding from the systematic review was

the overall lack of evidence on cognitive functioning in ACHD patients. More research is needed to strengthen and expand the findings of the present study, bearing in mind it's limitations. For example, the limitations associated with the use of normative data suggest that future studies may benefit from using a control or comparator group which is matched to the sample demographic characteristics such as age, gender and education.

The follow-up study conducted was one of the first to assess the stability of cognitive functions in ACHD patients along with identifying predictors of change in cognitive functioning. However, the results of this study could not identify significant predictors of change in cognition over time, with the exception of the domain of memory. Therefore, future research may benefit from looking at a longer time interval so as to examine the impact of ageing in the population.

In addition, exploring alternative variables that may not have been included within the present study may also illustrate the interaction of psychosocial factors and cognition. For example, one area of research could consider the impact of psychosocial factors such as social support and self-esteem on cognitive functioning; as there is some evidence to suggest an association between psychosocial functioning and cognitive outcomes in ACHD (Daliento et al, 2005).

Furthermore, the small sample size in this follow-up study did not allow enough statistical power to conduct a sub-group analysis, similar to that of the cross-sectional study. Future studies may benefit from a larger sample size that would enable examining change in independent complexity groups as this could allow more specificity in the identification of predictors of change pertinent to each complexity group.

Another area of research that has not received much attention is the patient's subjective perspective of their cognitive functioning and an account of how this impacts them on a day-to-day level. Qualitative investigation of the patient's subjective perception of their level of cognitive functioning was outside the scope of this thesis, but may provide a valuable contribution to the literature. A qualitative insight would provide information based on patients' first hand experiences, and would be useful for future research and practice to design interventions and support strategies specific to the patient group and their needs.

15.7 Overall conclusions

This study addressed a novel area of research and made several contributions to the existing literature. This thesis not only demonstrated the extent of cognitive impairments within domains such as executive functioning, attention and motor function in patients with ACHD, but also identified differences in cognitive outcomes among different levels of structural complexity. Furthermore, this study was the first to investigate the stability or change in cognitive functioning in ACHD patients, along with identifying factors associated with this change. The study addressed an important area of research with regards to the classification of ACHD, and demonstrated the benefits of using structural complexity as a way of grouping these heterogeneous conditions. Most importantly the findings of the present thesis highlight the potential early onset of cognitive impairment in ACHD patients, which could have major implications for this patient group if recognized and treated early. The findings from this thesis not only make contributions to the existing literature but can also be considered hypothesis generating offering several avenues for further research.

REFERENCES

Aboulhosen, J. & Child, J. 2006, "Congenital heart disease for the adult cardiologist. Left ventricular outflow obstruction. Subaortic stenosis, bicuspid aortic valve, supravalvar aortic stenosis, and coarctation of the aorta", *Circulation,* vol. 114, pp. 2412-2422.

Adólfsdóttir, S., Sorensen, L. & Lundervold, A.J. 2008, "The attention network test: a characteristic pattern of deficits in children with ADHD", *Behav Brain Funct,* vol. 4, no. 9.

Albers, E.L., Bichell, D.P. & McLaughlin, B. 2010, "New approaches to neuroprotection in infant heart surgery", *Pediatric research,* vol. 68, no. 1, pp. 1-9.

Aleem, I.S., Karamlou, T., Benson, L.N. & McCrindle, B.W. 2006, "Transcatheter device versus surgical closure of ventricular septal defects: a clinical decision analysis", *Catheterization and cardiovascular interventions,* vol. 67, no. 4, pp. 630-636.

Almeida, O.P. & Tamai, S. 2001, "Congestive heart failure and cognitive functioning amongst older adults", *Arquivos de Neuro-Psiquiatria,* vol. 59, no. 2B, pp. 324-329.

Andresen, E.M., Malmgren, J.A., Carter, W.B. & Patrick, D.L. 1994, "Screening for depression in well older adults: Evaluation of a short form of the CES-D", *American Journal of Preventive Medicine*, vol 10, no. 2 pp.77-84.

Andropoulos, D.B., Hunter, J.V., Nelson, D.P., Stayer, S.A., Stark, A.R., McKenzie, E.D., Heinle, J.S., Graves, D.E. & Fraser, C.D. 2010, "Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring", *The Journal of thoracic and cardiovascular surgery,* vol. 139, no. 3, pp. 543-556.

Arbuthnott, K. & Frank, J. 2000, "Trail making test, part B as a measure of executive control: validation using a set-switching paradigm", *Journal of clinical and experimental neuropsychology,* vol. 22, no. 4, pp. 518-528.

Arrowsmith, J.E., Grocott, H.P., Reves, J.G. & Newman, M.F. 2000, "Central nervous system complications of cardiac surgery", *British journal of anaesthesia,* vol. 84, no. 3, pp. 378-393.

Ashby, F.G. & Isen, A.M. 1999, "A neuropsychological theory of positive affect and its influence on cognition", *Psychological review,* vol. 106, no. 3, pp.529.

Attie, F., Rosas, M., Granados, N., Zabal, C., Buendía, A. & Calderón, J. 2001, "Surgical treatment for secundum atrial septal defects in patients> 40 years old: A randomized clinical trial", *Journal of the American College of Cardiology,* vol. 38, no. 7, pp. 2035-2042.

Austin, P.C. & Steyerberg, E.W. 2015, "The number of subjects per variable required in linear regression analyses", *Journal of clinical epidemiology,* vol. 68, no. 6, pp.627-636.

Ávila, P., Mercier, L., Dore, A., Marcotte, F., Mongeon, F., Ibrahim, R., Asgar, A., Miro, J., Andelfinger, G. & Mondésert, B. 2014, "Adult congenital heart disease: a growing epidemic", *Canadian Journal of Cardiology,* vol. 30, no. 12, pp. S410-S419.

Axelrod, B.N. 2001, "Administration duration for the Wechsler Adult Intelligence Scale-III and Wechsler Memory Scale-III", *Archives of Clinical Neuropsychology,* vol. 16, no. 3, pp. 293-301.

Baddeley, A.D., Kopelman, M. and Wilson, B.A. eds., 2004. "The psychology of memory", The essential handbook of memory disorders for clinicians. John Wiley & Sons, pp.1-13

Bailliard, F. 2009, "Tetralogy of Fallot", *Orphanet Journal of Rare Diseases,* vol. 4, no. 1, pp. 2.

Ballweg, J.A. 2007, "Neurodevelopmental Outcomes Following Congenital Heart Surgery", *Pediatric cardiology,* vol. 28, no. 2, pp. 126-133.

Barceló, F. & Knight, R.T. 2002, "Both random and perseverative errors underlie WCST deficits in prefrontal patients", *Neuropsychologia,* vol. 40, no. 3, pp. 349-356.

Barnett, A.G., van der Pols, J.C. & Dobson, A.J. 2005, "Regression to the mean: what it is and how to deal with it", *International journal of epidemiology,* vol. 34, no. 1, pp. 215-220.

Baron, I.S. 2004," *Neuropsychological evaluation of the child."* Oxford University Press.

Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V. & Ehrenreich, H. 2010, "Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing", *BMC neuroscience,* vol. 11, no. 1, pp. 118.

Bartolic, E., Basso, M., Schefft, B., Glauser, T. & Titanic-Schefft, M. 1999, "Effects of experimentally-induced emotional states on frontal lobe cognitive task performance", *Neuropsychologia,* vol. 37, no. 6, pp. 677-683.

Bass, J.L., Corwin, M., Gozal, D., Moore, C., Nishida, H., Parker, S., Schonwald, A., Wilker, R.E., Stehle, S. & Kinane, T.B. 2004, "The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence", *Pediatrics,* vol. 114, no. 3, pp. 805-816.

Basso, A. & Capitani, E. 1979, "Un test standardizzato per la diagnosi di acalculia. Descrizione e valori normativi", *Riv Appl psicol,* vol. 1, pp. 551-568.

Baumgartner, H., Bonhoeffer, P., De Groot, N.M., de Haan, F., Deanfield, J.E., Galie, N., Gatzoulis, M.A., Gohlke-Baerwolf, C., Kaemmerer, H., Kilner, P., Meijboom, F., Mulder, B.J., Oechslin, E., Oliver, J.M., Serraf, A., Szatmari, A., Thaulow, E., Vouhe, P.R., Walma, E., Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC), Association for European Paediatric Cardiology (AEPC) & ESC Committee for Practice Guidelines (CPG) 2010, "ESC Guidelines for the management of grown-up congenital heart disease (new version 2010)", *European heart journal,* vol. 31, no. 23, pp. 2915-2957.

Bayley, N. 1993," Bayley scales of infant development: Manual", Psychological Corporation.

Beca, J., Gunn, J., Coleman, L., Hope, A., Whelan, L., Gentles, T., Inder, T., Hunt, R. & Shekerdemian, L. 2009, "Pre-operative brain injury in newborn infants with transposition of the great arteries occurs at rates similar to other complex congenital heart disease and is not related to balloon atrial septostomy", *Journal of the American College of Cardiology,* vol. 53, no. 19, pp. 1807-1811.

Beca, J., Gunn, J.K., Coleman, L., Hope, A., Reed, P.W., Hunt, R.W., Finucane, K., Brizard, C., Dance, B. & Shekerdemian, L.S. 2013, "New white matter brain injury after infant heart surgery is associated with diagnostic group and the use of circulatory arrest", *Circulation,* vol. 127, no. 9, pp. 971-979.

Bellinger, D.C. 1995, "Developmental and Neurologic Status of Children after Heart Surgery with Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass", *New England Journal of Medicine,* vol. 332, no. 9, pp. 549-555.

Bellinger, D.C. 1999, "Developmental and Neurological Status of Children at 4 Years of Age after Heart Surgery With Hypothermic Circulatory Arrest or Low-Flow Cardiopulmonary Bypass", *Circulation,* vol. 100, no. 5, pp. 526-532.

Bellinger, D.C., Wypij, D., duPlessis, A.J., Rappaport, L.A., Jonas, R.A., Wernovsky, G. & Newburger, J.W. 2003, "Neurodevelopmental status at eight years in children with dextro-transposition of the great arteries: the Boston Circulatory Arrest Trial", *The Journal of thoracic and cardiovascular surgery,* vol. 126, no. 5, pp. 1385-1396.

Bellinger, D.C. & Newburger, J.W. 2010, "Neuropsychological, psychosocial, and quality-of-life outcomes in children and adolescents with congenital heart disease", *Progress in pediatric cardiology,* vol. 29, no. 2, pp. 87-92.

Bellinger, D.C., Wypij, D., Rivkin, M.J., DeMaso, D.R., Robertson, R.L.,Jr, Dunbar-Masterson, C., Rappaport, L.A., Wernovsky, G., Jonas, R.A. & Newburger, J.W. 2011, "Adolescents with d-transposition of the great arteries corrected with the arterial switch procedure: neuropsychological assessment and structural brain imaging", *Circulation,* vol. 124, no. 12, pp. 1361-1369.

Bellinger, D. & Newburger, J. 2016, "A Longitudinal Study From Infancy to Adolescence of the Neurodevelopmental Phenotype Associated With d-Transposition of the Great Arteries", *Congenital Heart Disease and Neurodevelopment: Understanding and Improving Outcomes,* pp. 27.

Benito-Leon, J., Morales, J. & Rivera-Navarro, J. 2002, "Health-related quality of life and its relationship to cognitive and emotional functioning in multiple sclerosis patients", *European journal of neurology,* vol. 9, no. 5, pp. 497-502.

Benton, A.L., Meyers, R. & Polder, G. 1962, "Some aspects of handedness", *European neurology,* vol. 144, no. 6, pp. 321-337.

Benton, A.L., Hamsher, K., Rey, G.L. & Sivan, A.B. 1994, "*Multilingual Aphasia Examination"* (3rd ed.). Iowa City, IA: AJA Associates.

Bernier, P., Stefanescu, A., Samoukovic, G. and Tchervenkov, C.I. 2010 "The Challenge of Congenital Heart Disease Worldwide: Epidemiologic and Demographic Facts", *Seminars in Thoracic and Cardiovascular Surgery: Pediatric Cardiac Surgery Annual,* vol. 13, no. 1, pp. 26-34.

Blalock, A. & Hanlon, C.R. 1950, "The surgical treatment of complete transposition of the aorta and the pulmonary artery", *Surgery, gynecology & obstetrics,* vol. 90, no. 1, pp. 1-15.

Block, A., McQuillen, P., Chau, V., Glass, H., Poskitt, K., Barkovich, A., Esch, M., Soulikias, W., Azakie, A. & Campbell, A. 2010, "Clinically silent preoperative brain injuries do not worsen with surgery in neonates with congenital heart disease", *The Journal of thoracic and cardiovascular surgery,* vol. 140, no. 3, pp. 550-557.

Boneva, R.S. 2001, "Mortality Associated With Congenital Heart Defects in the United States : Trends and Racial Disparities, 1979-1997", *Circulation,* vol. 103, no. 19, pp. 2376-2381.

Bosma, H., van Boxtel, M.P.J., Ponds, R.W.H.M., Houx, P.J.H. & Jolles, J. 2003, "Education and age-related cognitive decline: the contribution of mental workload", *Educational Gerontology,* vol. 29, no. 2, pp. 165-173.

Brandlistuen, R.E., Stene-Larsen, K., Holmstrom, H., Landolt, M.A., Eskedal, L.T. & Vollrath, M.E. 2011, "Occurrence and predictors of developmental impairments in 3-year-old children with congenital heart defects", *Journal of developmental and behavioral pediatrics : JDBP,* vol. 32, no. 7, pp. 526-532.

Breitbart, R. & Fyler, D., 2006, "*Tetralogy of Fallot. In Nadas' Pediatric Cardiology"*, 2ed, Ed. Keane, Locke, & Fyler, Philadelphia: Saunders-Elsevier".

Bremer, B.A., Wert, K.M., Durica, A.L. & Weaver, A. 1997, "Neuropsychological, physical, and psychosocial functioning of individuals with end-stage renal disease", *Annals of Behavioral Medicine,* vol. 19, no. 4, pp. 348-352.

Brickner, M.E., Hillis, L.D. & Lange, R.A. 2000, "Congenital heart disease in adults", *New England Journal of Medicine,* vol. 342, no. 4, pp. 256-263.

Brown, K.L. & Sullivan, I.D. 2014, "Prenatal detection for major congenital heart disease: a key process measure for congenital heart networks", *Heart (British Cardiac Society),* vol. 100, no. 5, pp. 359-360.

Bryk, A. & Raudenbush, S. 1992, "*Hierarchical linear models: Applications and data analysis methods.*", Newbury Park, CA: Sage.

Buskens, E., Grobbee, D.E., Frohn-Mulder, I.M., Wladimiroff, J.W. & Hess, J. 1995, "Aspects of the aetiology of congenital heart disease", *European heart journal,* vol. 16, no. 5, pp. 584-587.

Busl, K.M. & Greer, D.M. 2010, "Hypoxic-ischemic brain injury: pathophysiology, neuropathology and mechanisms", *NeuroRehabilitation,* vol. 26, no. 1, pp. 5-13.

Caamano-Isorna, F., Corral, M., Montes-Martinez, A. & Takkouche, B. 2006, "Education and dementia: a meta-analytic study", *Neuroepidemiology,* vol. 26, no. 4, pp. 226-232.

Cabell, C.H., Abrutyn, E. & Karchmer, A.W. 2003, "Bacterial Endocarditis: The Disease, Treatment, and Prevention", *Circulation,* vol. 107, no. 20, pp. e185-e187.

Calamia, M., Markon, K. & Tranel, D. 2012, "Scoring higher the second time around: Meta-analyses of practice effects in neuropsychological assessment", *The Clinical neuropsychologist,* vol. 26, no. 4, pp. 543-570.

Calderon, J. & Bellinger, D.C. 2015, "Executive function deficits in congenital heart disease: why is intervention important?", Cardiology in the young, vol. 25, no. 7, pp. 1238-1246.

Canivez, G.L. & Watkins, M.W. 2001, "Long-term stability of the Wechsler Intelligence Scale for Children-among students with disabilities", *School Psychology Review,* vol. 30, no. 3, pp. 438.

Carstairs, J.R., Shores, E.A. & Myors, B. 2012, "Australian norms and retest data for the Rey Auditory and Verbal Learning Test", *Australian Psychologist,* vol. 47, no. 4, pp. 191-197.

Car*twright, M., Traviss, G. & Blance, A. 2012, "*Murder, muddled thinking and multilevel modeling*" Psychologist vol. 25, no. 9, pp. 690-693.*

Cassidy, A.R., White, M.T., DeMaso, D.R., Newburger, J.W. & Bellinger, D.C. 2015, "Executive function in children and adolescents with critical cyanotic congenital heart disease", *Journal of the International Neuropsychological Society,* vol. 21, no. 01, pp. 34-49.

Chelune, G.J., Naugle, R.I., Lüders, H., Sedlak, J. & Awad, I.A. 1993, "Individual change after epilepsy surgery: Practice effects and base-rate information.", *Neuropsychology,* vol. 7, no. 1, pp. 41.

Chen, C.A., Liao, S.C., Wang, J.K., Chang, C.I., Chiu, I.S., Chen, Y.S., Lu, C.W., Lin, M.T., Chiu, H.H., Chiu, S.N., Hua, Y.C., Lue, H.C. & Wu, M.H. 2011, "Quality of life in adults with congenital heart disease: biopsychosocial determinants and sex-related differences", *Heart (British Cardiac Society),* vol. 97, no. 1, pp. 38-43.

Chira, M. & Ciotlaus, D. 2013, "Cognitive development after Tetralogy of Fallot repair", *Journal of Cardiothoracic Surgery,* vol. 8, no. Suppl 1, pp. O135.

Chung, S. & Lim, D. 2008, "Changes in memory performance, heart rate, and blood oxygen saturation due to 30% oxygen administration", *International Journal of Neuroscience,* vol. 118, no. 4, pp. 593-606.

Cohen, J. 1988, *Statistical power analysis for the behavioral sciences,* (2nd ed.), Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Cohen, R.A., Sparling-Cohen, Y.A. & O'Donnell, B.F. 1993, "*The neuropsychology of attention",* Springer.

Connelly, M.S., Webb, G.D., Somerville, J., WARNMES, C., Perloff, J.K., Liberthson, R.R., Puga, F.J., Collins-Nakai, R.L., Williams, W.G. & Mercier, L. 1998, "Canadian consensus conference on adult congenital heart disease 1996", *Canadian journal of cardiology,* vol. 14, no. 3, pp. 395-452.

Conolly, S., Arrowsmith, J.E. & Klein, A.A. 2010, "Deep hypothermic circulatory arrest", *Continuing Education in Anaesthesia, Critical Care & Pain,* vol. 10, no.5, pp. 138-142.

Crawford, J.R. & Henry, J.D. 2004, "The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample", *British Journal of Clinical Psychology,* vol. 43, no. 3, pp. 245-265.

Cuffaro, M.A. 2011, "Fine Motor Skills" in *Encyclopedia of Child Behavior and Development* Springer, pp. 657-657.

Dabrowski, W., Rzecki, Z., Pilat, J. & Czajkowski, M. 2012, "Brain damage in cardiac surgery patients", *Current opinion in pharmacology,* vol. 12, no. 2, pp. 189-194.

Dahan-Oliel, N., Majnemer, A. & Mazer, B. 2011, "Quality of life of adolescents and young adults born at high risk", *Physical & Occupational Therapy in Pediatrics,* vol. 31, no. 4, pp. 362-389.

Daliento, L., Mapelli, D., Russo, G., Scarso, P., Limongi, F., Iannizzi, P., Melendugno, A., Mazzotti, E. & Volpe, B. 2005, "Health related quality of life in adults with repaired tetralogy of Fallot: psychosocial and cognitive outcomes", *Heart (British Cardiac Society),* vol. 91, no. 2, pp. 213-218.

Deanfield, J., Thaulow, E., Warnes, C., Webb, G., Kolbel, F., Hoffman, A., Sorenson, K., Kaemmerer, H., Thilen, U., Bink-Boelkens, M. and Iserin, L. 2003, "Management of Grown Up Congenital Heart Disease", *European heart journal,* vol. 24, no. 11, pp. 1035-1084.

Deary, I.J., Corley, J., Gow, A.J., Harris, S.E., Houlihan, L.M., Marioni, R.E., Penke, L., Rafnsson, S.B. & Starr, J.M. 2009, "Age-associated cognitive decline", *British medical bulletin,* vol. 92, no.1, pp. 135-152.

Demakis, G.J. 2003, "A meta-analytic review of the sensitivity of the Wisconsin Card Sorting Test to frontal and lateralized frontal brain damage.", *Neuropsychology,* vol. 17, no. 2, pp. 255.

DeMaso, D.R., Beardslee, W.R., Silbert, A.R. & Fyler, D.C. 1990, "Psychological functioning in children with cyanotic heart defects", *Journal of Developmental & Behavioral Pediatrics,* vol. 11, no. 6, pp. 289-294.

DeMaso, D.R., Rao, S., Hirshberg, J. & Ibeziako, P. (eds) 2010, "*Heart Disease."*, Arlington, VA; American Psychiartic Publishing.

Dhinakaran, J., De Vos, M., Thorne, J.D., Braun, N., Janson, J. & Kranczioch, C. 2013, "Tough doughnuts: affect and the modulation of attention", *Frontiers in human neuroscience,* vol. 7.

Diamond, A. 2013, "Executive functions", *Annual Review of Psychology,* vol. 64, pp. 135-168.

Dikmen, S.S., Heaton, R.K., Grant, I. & Temkin, N.R. 1999, "Test–retest reliability and practice effects of expanded Halstead–Reitan Neuropsychological Test Battery", *Journal of the International Neuropsychological Society,* vol. 5, no. 04, pp. 346-356.

Donofrio, M., Bremer, Y., Schieken, R., Gennings, C., Morton, L., Eidem, B.W., Cetta, F., Falkensammer, C., Huhta, J. & Kleinman, C. 2003, "Autoregulation of cerebral blood flow in fetuses with congenital heart disease: the brain sparing effect", *Pediatric cardiology,* vol. 24, no. 5, pp. 436-443.

Donofrio, M.T. & Massaro, A.N. 2010, "Impact of congenital heart disease on brain development and neurodevelopmental outcome", *International journal of pediatrics,* vol. 2010.

Downs, S.H. & Black, N. 1998, "The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health

care interventions", *Journal of epidemiology and community health,* vol. 52, no. 6, pp. 377-384.

Dreisbach, G. & Goschke, T. 2004, "How positive affect modulates cognitive control: reduced perseveration at the cost of increased distractibility.", *Journal of Experimental Psychology: Learning, Memory, and Cognition,* vol. 30, no. 2, pp. 343.

Drost, E.A. 2011, "Validity and reliability in social science research", *Education Research and Perspectives,* vol. 38, no. 1, pp. 105.

Duff, K. 2012, "Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods", *Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists,* vol. 27, no. 3, pp. 248-261.

Dunbar-Masterson, C., Wypij, D., Bellinger, D.C., Rappaport, L.A., Baker, A.L., Jonas, R.A. & Newburger, J.W. 2001, "General health status of children with D-transposition of the great arteries after the arterial switch operation", *Circulation,* vol. 104, no. 12, Suppl. 1, pp. I138-42.

Eddy, C.M. & Rickards, H.E. 2013, "Impact of cognitive and behavioural changes on quality of life in Huntington's disease", *Basal Ganglia,* vol. 3, no. 2, pp. 123-126.

Eide, M.G., Skjærven, R., Irgens, L.M., Bjerkedal, T. & Øyen, N. 2006, "Associations of birth defects with adult intellectual performance, disability and mortality: population-based cohort study", *Pediatric research,* vol. 59, no. 6, pp. 848-853.

Erickson, M.E. 1972, "Test sophistication: An important consideration", *Journal of Reading, vol. 6, no.2,* pp. 140-144.

Eslami, B., Sundin, Ö., Macassa, G., Khankeh, H.R. & Soares, J.J. 2012, "Anxiety, depressive and somatic symptoms in adults with congenital heart disease", *Journal of psychosomatic research, vol.* 74, no. 1, pp 49-56 .

Fals-Stewart, W. 1992, "An interrater reliability study of the Trail Making Test (Parts A and B)", *Perceptual and motor skills,* vol. 74, no. 1, pp. 39-42.

Faul, F., Erdfelder, E., Lang, A. & Buchner, A. 2007, "G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences", *Behavior research methods,* vol. 39, no. 2, pp. 175-191.

Fekkes, M., Kamphuis, R.P., Ottenkamp, J., Verrips, E., Vogels, T., Kamphuis, M. & Verloove-vanhorick, S.P. 2001, "Health-related quality of life in young adults with minor congenital heart disease", *Psychology and Health,* vol. 16, no. 2, pp. 239-250.

Field, A. 2009, "*Discovering statistics using SPSS",* Sage Publications.

Field, A. 2013, "*Discovering statistics using IBM SPSS statistics",* Sage Publications.

Findlow, D. & Doyle, E. 1997, "Congenital heart disease in adults", *British journal of anaesthesia,* vol. 78, no. 4, pp. 416-430.

Fisher, J.D. 1972, "New York Heart Association Classification", *Archives of Internal Medicine,* vol. 129, no. 5, pp. 836-836.

Flaker, G.C., Pogue, J., Yusuf, S., Pfeffer, M.A., Goldhaber, S.Z., Granger, C.B., Anand, I.S., Hart, R., Connolly, S.J. & Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) Investigators 2010, "Cognitive function and anticoagulation control in patients with atrial fibrillation", *Circulation.Cardiovascular quality and outcomes,* vol. 3, no. 3, pp. 277-283.

Flynn, J.R. 2007, "*What is intelligence?: Beyond the Flynn effect",* Cambridge University Press.

Fontan, F. & Baudet, E. 1971, "Surgical repair of tricuspid atresia", *Thorax,* vol. 26, no. 3, pp. 240-248.

Forbess, J.M., Visconti, K.J., Hancock-Friesen, C., Howe, R.C., Bellinger, D.C. & Jonas, R.A. 2002, "Neurodevelopmental outcome after congenital heart surgery: results from an institutional registry", *Circulation,* vol. 106, no. 12 Suppl 1, pp. I95-102.

Franklin, R.C., Jacobs, J.P., Krogmann, O.N., Béland, M.J., Aiello, V.D., Colan, S.D., Elliott, M.J., William Gaynor, J., Kurosawa, H. & Maruszewski, B. 2008, "Nomenclature for congenital and paediatric cardiac disease: historical perspectives and The International Pediatric and Congenital Cardiac Code", *Cardiology in the young,* vol. 18, no. S2, pp. 70-80.

Franklin, W.J., Kloudas, L., Saraf, A., Karlsten, M., Parekh, D. & Schwartz, D.D. 2014, "Neurocognitive evaluation of adults with congenital heart disease: the niche study", *Journal of the American College of Cardiology,* vol. 63, no. 12, A489.

Franzen, M.D., Paul, D. & Iverson, G.L. 1996, "Reliability of alternate forms of the trail making test", *The Clinical Neuropsychologist,* vol. 10, no. 2, pp. 125-129.

Fteropoulli, T., Stygall, J., Cullen, S., Deanfield, J. & Newman, S.P. 2013, "Quality of life of adult congenital heart disease patients: a systematic review of the literature", *Cardiology in the young,* vol. 23, no. 04, pp. 473-485.

Garne, E. 2012, Olsen, M.S., Johnsen, S.P., Hjortdal, V., Andersen, H.Ø., Nissen, H., Søndergaard, L. and Videbæk, J., "How Do We Define Congenital Heart Defects for Scientific Studies?", *Congenital Heart Disease,* vol. 7, no. 1, pp. 46-49.

Gatzoulis, M.A., Swan, L., Therrien, J. & Pantely, G.A. 2008," *Adult congenital heart disease: a practical guide",* John Wiley & Sons.

Gatzoulis, M.A. & Swan, L. 2009, "Single ventricle physiology", *Adult Congenital Heart Disease,* pp. 157-173.

Gatzoulis, M.A., Webb, G.D. & Daubeney, P.E. 2010, *Diagnosis and Management of Adult Congenital Heart Disease: Expert Consult–Online and Print,* Elsevier Health Sciences.

Geva, T., Martins, J.D. & Wald, R.M. 2014, "Atrial septal defects", *The Lancet,* vol. 383, no. 9932, pp. 1921-1932.

Gilbert, S.J. & Burgess, P.W. 2008, "Executive function", *Current Biology,* vol. 18, no. 3, pp. R110-R114.

Glauser, T.A., Rorke, L.B., Weinberg, P.M. & Clancy, R.R. 1990, "Congenital brain anomalies associated with the hypoplastic left heart syndrome", *Pediatrics,* vol. 85, no. 6, pp. 984-990.

Glisky, E.L. 2007, "Changes in cognitive function in human aging", *Brain aging: Models, methods, and mechanisms,* pp. 3-20.

Glymour, M.M., Kawachi, I., Jencks, C.S. & Berkman, L.F. 2008, "Does childhood schooling affect old age memory or mental status? Using state schooling laws as natural experiments", *Journal of epidemiology and community health,* vol. 62, no. 6, pp. 532-537.

Goldberg, C.S., Schwartz, E.M., Brunberg, J.A., Mosca, R.S., Bove, E.L., Schork, M.A., Stetz, S.P., Cheatham, J.P. & Kulik, T.J. 2000, "Neurodevelopmental outcome of patients after the Fontan operation: a comparison between children with hypoplastic left heart syndrome and other functional single ventricle lesions", *The Journal of pediatrics,* vol. 137, no. 5, pp. 646-652.

Goldberg, T.E., Harvey, P.D., Wesnes, K.A., Snyder, P.J. & Schneider, L.S. 2015, "Practice effects due to serial cognitive assessment: Implications for preclinical Alzheimer's disease randomized controlled trials", *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring,* vol. 1, no. 1, pp. 103-111.

Gottesman, R.F., Grega, M.A., Bailey, M.M., Zeger, S.L., Baumgartner, W.A., McKhann, G.M. & Selnes, O.A. 2009, "Association between hypotension, low ejection fraction and cognitive performance in cardiac patients", *Behavioural neurology,* vol. 22, no. 1, pp. 63-71.

Griffin, K.J., Elkin, T.D. & Smith, C.J. 2003, "Academic outcomes in children with congenital heart disease", *Clinical pediatrics,* vol. 42, no. 5, pp. 401-409.

Griva, K., Thompson, D., Jayasena, D., Davenport, A., Harrison, M. & Newman, S.P. 2006, "Cognitive functioning pre- to post-kidney transplantation--a prospective study", *Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association,* vol. 21, no. 11, pp. 3275-3282.

Grooved Pegboard User's Manual, 2003, Lafayette Instrument Co., Lafayette IN 47903 USA.

Groth-Marnat, G. 2009, "*Handbook of psychological assessment",* John Wiley & Sons.

Gualtieri, C.T. & Johnson, L.G. 2006, "Reliability and validity of a computerized neurocognitive test battery, CNS Vital Signs", *Archives of Clinical Neuropsychology,* vol. 21, no. 7, pp. 623-643.

Hair, J.F., Anderson, R.E., Tatham, R.L. & Black, W. 1998, "*Multivariate data analysis*", Upper Saddle River.

Harrox, F. 2002, "*Manual of Neonatal and Paediatric Heart Disease"*. London; Philadelphia: Whurr.

Hawkins, D.M. 1980, "*Identification of outliers", (Vol. 11).* London: Chapman and Hall.

Hawkins, K.A. 2004, "Alternative forms of the Rey Auditory Verbal Learning Test: a review", *behavioural neurology,* vol. 15, no. 3-4, pp. 99.

Heaton, R., Chelune, G., Talley, J., Kay, G. & Curtiss, G. 1993, "*Wisconsin card sorting test manual revised and expanded*". Lutz, FL: Psychological Assessment Resources.

Heaton, R.K. 2004, *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults: Professional manual,* Psychological Assessment Resources.

Heck, R.H., Thomas, S.L., & Tabata, L.N. 2014, "*Multilevel modeling of categorical outcomes using IBM SPSS" ,* New York, Routledge.

Heinrichs, A.K.M., Holschen, A., Krings, T., Messmer, B.J., Schnitker, R., Minkenberg, R. & Hövels-Gürich, H.H. 2014, "Neurologic and psycho-intellectual outcome related to structural brain imaging in adolescents and young adults after neonatal arterial switch operation for transposition of the great arteries", *The Journal of thoracic and cardiovascular surgery,* vol. 148, no. 5, pp. 2190-2199.

Hignett, S., Otter, M.E. & Keen, C. 2016, "Safety risks associated with physical interactions between patients and caregivers during treatment and care delivery in Home Care settings: A systematic review", *International journal of nursing studies,* vol. 59, pp. 1-14.

Hill, A.C., Laird, A.R. & Robinson, J.L. 2014, "Gender differences in working memory networks: A BrainMap meta-analysis", *Biological psychology,* vol. 102, pp. 18-29.

Hinton-Bayre, A.D., Geffen, G.M., Geffen, L.B., McFarland, K.A. & Frijs, P. 1999, "Concussion in contact sports: reliable change indices of impairment and recovery", *Journal of Clinical and Experimental Neuropsychology,* vol. 21, no. 1, pp. 70-86.

Hinton-Bayre, A.D., Geffen G.M., 2005, "Comparibility, reliability and practice effects on alternate forms of the digit symbol substitution and symbol digit modalities test". *Psychological assessment*, vol.17, no. 2, pp. 237-241.

Hoffman, J.I. & Kaplan, S. 2002, "The incidence of congenital heart disease", *Journal of the American College of Cardiology,* vol. 39, no. 12, pp. 1890-1900.

Hoffman, J.I., Kaplan, S. & Liberthson, R.R. 2004, "Prevalence of congenital heart disease", *American Heart Journal,* vol. 147, no. 3, pp. 425-439.

Hövels-Gürich, H.H., Konrad, K., Skorzenski, D., Herpertz-Dahlmann, B., Messmer, B.J. & Seghaye, M. 2007, "Attentional dysfunction in children after corrective cardiac surgery in infancy", *The Annals of Thoracic Surgery,* vol. 83, no. 4, pp. 1425-1430.

Idorn, L., Jensen, A.S., Juul, K., Overgaard, D., Nielsen, N.P., Sørensen, K., Reimers, J.I. & Søndergaard, L. 2013, "Quality of life and cognitive function in Fontan patients, a

population-based study", *International journal of cardiology,* vol. 168, no. 4, pp. 3230-3235.

Ingraham, L.J. & Aiken, C.B. 1996, "An empirical approach to determining criteria for abnormality in test batteries with multiple measures.", *Neuropsychology,* vol. 10, no. 1, pp. 120.

Ivnik, R.J., Malec, J.F., Smith, G.E., Tangalos, E.G., Petersen, R.C., Kokmen, E. & Kurland, L.T. 1992, "Mayo's Older Americans Normative Studies: WAIS-R norms for ages 56 to 97", *The Clinical neuropsychologist,* vol. 6, S1, pp. 1-30.

Jackson, J.L., Misiti, B., Bridge, J.A., Daniels, C.J. & Vannatta, K. 2015, "Emotional Functioning of Adolescents and Adults with Congenital Heart Disease: A Meta-Analysis", *Congenital heart disease,* vol. 10, no. 1, pp. 2-12.

Jacobson, N.S. & Truax, P. 1991, "Clinical significance: a statistical approach to defining meaningful change in psychotherapy research.", *Journal of consulting and clinical psychology,* vol. 59, no. 1, pp. 12.

Jaquiss, R. & Imamura, M. 2009, "Single ventricle physiology: surgical options, indications and outcomes", *Current opinion in cardiology,* vol. 24, no. 2, pp. 113-118.

Jefferson, A.L., Himali, J.J., Au, R., Seshadri, S., DeCarli, C., O'Donnell, C.J., Wolf, P.A., Manning, W.J., Beiser, A.S. & Benjamin, E.J. 2011, "Relation of left ventricular ejection fraction to cognitive aging (from the Framingham Heart Study)", *The American Journal of Cardiology,* vol. 108, no. 9, pp. 1346-1351.

Jeyakumar, S.L., Warriner, E.M., Raval, V.V. & Ahmad, S.A. 2004, "Balancing the need for reliability and time efficiency: Short forms of the Wechsler Adult Intelligence Scale-III", *Educational and Psychological Measurement,* vol. 64, no. 1, pp. 71-87.

Kahr, P.C., Radke, R.M., Orwat, S., Baumgartner, H. & Diller, G. 2014, "Health Related Quality of Life in Patients with Congenital Heart Disease: a Meta-Analysis", *Circulation,* vol. 130, Suppl 2, pp. A17395-A17395.

Kamphuis, M., Ottenkamp, J., Vliegen, H.W., Vogels, T., Zwinderman, K.H., Kamphuis, R.P. & Verloove-Vanhorick, S.P. 2002, "Health related quality of life and health status in adult survivors with previously operated complex congenital heart disease", *Heart (British Cardiac Society),* vol. 87, no. 4, pp. 356-362.

Kaplan, M.F. & Eron, L.D. 1965, "Test sophistication and faking in the TAT situation", *Journal of Projective Techniques and Personality Assessment,* vol. 29, no. 4, pp. 498-503.

Karsdorp, P.A., Everaerd, W., Kindt, M. & Mulder, B.J. 2007, "Psychological and cognitive functioning in children and adolescents with congenital heart disease: a meta-analysis", *Journal of pediatric psychology,* vol. 32, no. 5, pp. 527-541.

Katz, A.M. 2010, "*Physiology of the Heart",* Lippincott Williams & Wilkins.

Khairy, P., Ionescu-Ittu, R., Mackie, A.S., Abrahamowicz, M., Pilote, L. & Marelli, A.J. 2010, "Changing mortality in congenital heart disease", *Journal of the American College of Cardiology,* vol. 56, no. 14, pp. 1149-1157.

Khalil, A., Suff, N., Thilaganathan, B., Hurrell, A., Cooper, D. & Carvalho, J. 2014, "Brain abnormalities and neurodevelopmental delay in congenital heart disease: systematic review and meta-analysis", *Ultrasound in Obstetrics & Gynecology,* vol. 43, no. 1, pp. 14-24.

King, M.E. & de Moor, M. 1999, "Ventricular septal defect", *Current treatment options in cardiovascular medicine,* vol. 1, no. 4, pp. 311-322.

Kinney, H.C., Panigrahy, A., Newburger, J.W., Jonas, R.A. & Sleeper, L.A. 2005, "Hypoxic-ischemic brain injury in infants with congenital heart disease dying after cardiac surgery", *Acta Neuropathologica,* vol. 110, no. 6, pp. 563-578.

Knox, R., Seth, R., Mcelveen, N., Bergstein, M. & Longo, J. 2007, "Short term memory based on gender", Pennsylvania: Penn State University.

Kongs, S.K., Thompson, L.L., Iverson, G.L. & Heaton, R.K. 2000, "*Wisconsin card sorting test-64 card version (WCST-64)*", *Odessa,* FL: Psychological Assessment Resources.

Kortte, K.B., Horner, M.D. & Windham, W.K. 2002, "The trail making test, part B: cognitive flexibility or ability to maintain set?", *Applied Neuropsychology,* vol. 9, no. 2, pp. 106-109.

Krueger, J.J., Brotschi, B., Balmer, C., Bernet, V. & Latal, B. 2015, "Postoperative hyperglycemia and 4-year neurodevelopmental outcome in children operated for congenital heart disease", *The Journal of pediatrics,* vol. 167, no. 6, pp. 1253-1258.

Lakens, D. 2013, "Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs", *Frontiers in psychology,* vol. 4, pp. 863.

Lane, D.A., Lip, G.Y. & Millane, T.A. 2002, "Quality of life in adults with congenital heart disease", *Heart (British Cardiac Society),* vol. 88, no. 1, pp. 71-75.

Latal, B. 2016, "Neurodevelopmental Outcomes of the Child with Congenital Heart Disease", *Clinics in perinatology,* vol. 43, no. 1, pp. 173-185.

Lee, C., Kwak, J.G. & Lee, C. 2014, "Primary repair of symptomatic neonates with tetralogy of Fallot with or without pulmonary atresia", *Korean journal of pediatrics,* vol. 57, no. 1, pp. 19-25.

Levine, A.J., Hinkin, C.H., Miller, E.N., Becker, J.T., Selnes, O.A. & Cohen, B.A. 2007, "The generalizability of neurocognitive test/retest data derived from a nonclinical sample for detecting change among two HIV cohorts", *Journal of clinical and experimental neuropsychology,* vol. 29, no. 6, pp. 669-678.

Lezak, M.D. 1983, "*Neuropsychological Assessment"*, 2nd edn. New York: Oxford University Press

Lezak, M.D. 1988, "Iq: Rip", *Journal of clinical and experimental neuropsychology,* vol. 10, no. 3, pp. 351-361.

Lezak, M.D. 1995, "*Neuropsychological Assessment"*, 3rd edn. New York: Oxford University Press

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D., 2012," Neuropsychological assessment" (5th ed.). New York: Oxford University Press

Licht, D.J., Wang, J., Silvestre, D.W., Nicolson, S.C., Montenegro, L.M., Wernovsky, G., Tabbutt, S., Durning, S.M., Shera, D.M. & Gaynor, J.W. 2004, "Preoperative cerebral blood flow is diminished in neonates with severe congenital heart defects", *The Journal of thoracic and cardiovascular surgery,* vol. 128, no. 6, pp. 841-849.

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rosenblatt, B., Rohlicek, C. & Tchervenkov, C. 1999, "Neurologic status of newborns with congenital heart defects before open heart surgery", *Pediatrics,* vol. 103, no. 2, pp. 402-408.

Limperopoulos, C., Majnemer, A., Shevell, M.I., Rohlicek, C., Rosenblatt, B., Tchervenkov, C. & Darwish, H. 2002, "Predictors of developmental disabilities after open heart surgery in young children with congenital heart defects", *The Journal of pediatrics,* vol. 141, no. 1, pp. 51-58.

Limperopoulos, C., Tworetzky, W., McElhinney, D.B., Newburger, J.W., Brown, D.W., Robertson, R.L.,Jr, Guizard, N., McGrath, E., Geva, J., Annese, D., Dunbar-Masterson, C., Trainor, B., Laussen, P.C. & du Plessis, A.J. 2010, "Brain volume and metabolism in fetuses with congenital heart disease: evaluation with quantitative

magnetic resonance imaging and spectroscopy", *Circulation,* vol. 121, no. 1, pp. 26-33.

Llabre, M.M., Spitzer, S.B., Saab, P.G., Ironson, G.H. & Schneiderman, N. 1991, "The reliability and specificity of delta versus residualized change as measures of cardiovascular reactivity to behavioral challenges", *Psychophysiology,* vol. 28, no. 6, pp. 701-711.

Losay, J., Touchot, A., Serraf, A., Litvinova, A., Lambert, V., Piot, J.D., Lacour-Gayet, F., Capderou, A. & Planche, C. 2001, "Late outcome after arterial switch operation for transposition of the great arteries", *Circulation,* vol. 104, no. 12, Suppl 1, pp. I121.

Lott, I.T. & Dierssen, M. 2010, "Cognitive deficits and associated neurological complications in individuals with Down's syndrome", *The Lancet Neurology,* vol. 9, no. 6, pp. 623-633.

Luria, A.R. 1976, "*The working brain: An introduction to neuropsychology",* Basic Books.

Luteijn, F. & Van der Ploeg, F. 1983, "*Groninger intelligentie test*", Handleiding (Groninger Intelligence Test.Manual).Lisse: Swets, Zeitlinger BV*,* .

Mahle, W.T. 2001, "Neurologic and cognitive outcomes in children with congenital heart disease", *Current opinion in pediatrics,* vol. 13, no. 5, pp. 482-486.

Mahle, W.T., Tavani, F., Zimmerman, R.A., Nicolson, S.C., Galli, K.K., Gaynor, J.W., Clancy, R.R., Montenegro, L.M., Spray, T.L., Chiavacci, R.M., Wernovsky, G. & Kurth, C.D. 2002, "An MRI study of neurological injury before and after congenital heart surgery", *Circulation,* vol. 106, no. 12, Suppl 1, pp. I109-14.

Marelli, A.J. 2006, "Congenital Heart Disease in the General Population: Changing Prevalence and Age Distribution", *Circulation,* vol. 115, no. 2, pp. 163-172.

Marelli, A.J., Ionescu-Ittu, R., Mackie, A.S., Guo, L., Dendukuri, N. & Kaouache, M. 2014, "Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010", *Circulation,* vol. 130, no. 9, pp. 749-756.

Marelli, A., Miller, S.P., Marino, B.S., Jefferson, A.L. & Newburger, J.W. 2016, "Brain in Congenital Heart Disease Across the Lifespan: The Cumulative Burden of Injury", *Circulation,* vol. 133, no. 20, pp. 1951-1962.

Marino, B.S., Beebe, D., Cassedy, A., Riedel, M., Burger, M., Medek, S., Finan, S., Andersen, C., Uzark, K. & Ross, J. 2011, "Executive functioning, gross motor ability and mood are key drivers of poorer quality of life in child and adolescent survivors with

complex congenital heart disease", *Journal of the American College of Cardiology,* vol. 57, no. 14s1, pp. E421-E421.

Marino, B., Lipkin, P., Newburger, J., Peacock, G., Gerdes, M., Gaynor, J., Mussatto, K., Uzark, K., Goldberg, C. & Johnson Jr, W. 2012, "on behalf of the American Heart Association Congenital Heart Defects Committee of the Council on Cardiovascular Disease in the Young, Council on Cardiovascular and Stroke Nursing, and Stroke Council. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association", *Circulation, vol. 126, no.9*, pp. 1143-1172.

Marques, M. & Hamilton, K. 2014, "Health Psychology and statistical methods: Out with the old and in with the new", *European Health Psychologist,* vol. 16, no. 2, pp. 36-40.

Marteau, T.M. & Bekker, H. 1992, "The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI)", *British Journal of Clinical Psychology,* vol. 31, no. 3, pp. 301-306.

Martin, M., Clare, L., Altgassen, A.M., Cameron, M.H. & Zehnder, F. 2011, "*Cognition-based interventions for healthy older people and people with mild cognitive impairment*", The Cochrane Library.

Martinez-Biarge, M., Jowett, V.C., Cowan, F.M. & Wusthoff, C.J. 2013, "Neurodevelopmental outcome in children with congenital heart disease", *Seminars in Fetal and Neonatal Medicine*Elsevier, vol. 18, no. 5, pp. 279-285.

Martins, P. & Castela, E. 2008, "Transposition of the great arteries", *Orphanet J Rare Dis,* vol. 3, no. 1, pp. 27.

Mason, S.E., Noel-Storr, A. & Ritchie, C.W. 2010, "The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis", *J Alzheimers Dis,* vol. 22, no. Suppl 3, pp. 67-79.

Matthews, C. & Klove, H. 1964*, "Instruction manual for the adult neuropsychology test battery"*, Madison, WI: University of Wisconsin Medical School.

McCaffrey, R.J., Ortega, A., Orsillo, S.M., Nelles, W.B. & Haase, R.F. 1992, "Practice effects in repeated neuropsychological assessments", *The Clinical neuropsychologist,* vol. 6, no. 1, pp. 32-42.

McMurray, J.J., Adamopoulos, S., Anker, S.D., Auricchio, A., Böhm, M., Dickstein, K., Falk, V., Filippatos, G., Fonseca, C. & Gomez-Sanchez, M.A. 2012, "ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012", *European journal of heart failure,* vol. 14, no. 8, pp. 803-869.

McQuillen, P.S. & Miller, S.P. 2010, "Congenital heart disease and brain development", *Annals of the New York Academy of Sciences,* vol. 1184, no. 1, pp. 68-86.

McRae, M.E. 2013, "Long-term issues after the Fontan procedure", *AACN advanced critical care,* vol. 24, no. 3, pp. 264-82.

Meijboom, F., Szatmari, A., Utens, E., Deckers, J.W., Roelandt, J.R., Bos, E. & Hess, J. 1994, "Long-term follow-up after surgical closure of ventricular septal defect in infancy and childhood", *Journal of the American College of Cardiology,* vol. 24, no. 5, pp. 1358-1364.

Miatton, M., De Wolf, D., François, K., Thiery, E. & Vingerhoets, G. 2006, "Neurocognitive consequences of surgically corrected congenital heart defects: a review", *Neuropsychology review,* vol. 16, no. 2, pp. 65-85.

Miatton, M., De Wolf, D., François, K., Thiery, E. & Vingerhoets, G. 2007a, "Neuropsychological performance in school-aged children with surgically corrected congenital heart disease", *The Journal of pediatrics,* vol. 151, no. 1, pp. 73-78.

Miatton, M., De Wolf, D., François, K., Thiery, E. & Vingerhoets, G. 2007b, "Intellectual, neuropsychological, and behavioral functioning in children with tetralogy of Fallot", *The Journal of thoracic and cardiovascular surgery,* vol. 133, no. 2, pp. 449-455.

Milner, B. 1971, "*Interhemispheric differences in the localization of psychological processes in man*.", British medical bulletin.

Ministeri, M., Alonso-Gonzalez, R., Swan, L. & Dimopoulos, K. 2016, "Common long-term complications of adult congenital heart disease: avoid falling in a HEAP", *Expert review of cardiovascular therapy,* vol. 14, no. 4, pp. 445-462.

Mitchell, R.L. & Phillips, L.H. 2007, "The psychological, neurochemical and functional neuroanatomical mediators of the effects of positive and negative mood on executive functions", *Neuropsychologia,* vol. 45, no. 4, pp. 617-629.

Mitrushina, M., Boone, K.B., Razani, J. & D'Elia, L.F. 2005, *Handbook of normative data for neuropsychological assessment (2nd ed.),* Oxford University Press, New York, NY US.

Moffitt, T.E., Caspi, A., Harkness, A.R. & Silva, P.A. 1993, "The Natural History of Change to Intellectual Performance: Who Changes? How Much? Is it Meaningful?", *Journal of Child Psychology and Psychiatry,* vol. 34, no. 4, pp. 455-506.

Moher, D., Liberati, A., Tetzlaff, J. & Altman, D.G. 2009, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement", *Annals of Internal Medicine,* vol. 151, no. 4, pp. 264-269.

Monaco, M. & Williams, I. 2012, "Tetralogy of Fallot: fetal diagnosis to surgical correction", *Minerva pediatrica,* vol. 64, no. 5, pp. 461-470.

Moons, P., Van Deyk, K., Marquet, K., De Bleser, L., Raes, E., Budts, W. & De Geest, S. 2006, "Quality of life in adults with congenital heart disease: Better than expected!", *GEDRAG EN GEZONDHEID,* vol. 34, no. 4, pp. 209.

Murphy, L.K., Compas, B.E., Reeslund, K.L., Gindville, M.C., Mah, M.L., Markham, L.W. & Jordan, L.C. 2015, "Cognitive and attentional functioning in adolescents and young adults with Tetralogy of Fallot and d-transposition of the great arteries", *Child Neuropsychology, vol.23, no.1*, pp. 1-12.

Nass, R.D. & Frank, Y. 2010, "*Cognitive and behavioral abnormalities of pediatric diseases",* Oxford University Press.

Neisser, U., Boodoo, G., Bouchard Jr, T.J., Boykin, A.W., Brody, N., Ceci, S.J., Halpern, D.F., Loehlin, J.C., Perloff, R. & Sternberg, R.J. 1996, "Intelligence: knowns and unknowns.", *American psychologist,* vol. 51, no. 2, pp. 77.

Nembhard, W.N., Wang, T., Loscalzo, M.L. & Salemi, J.L. 2010, "Variation in the prevalence of congenital heart defects by maternal race/ethnicity and infant sex", *The Journal of pediatrics,* vol. 156, no. 2, pp. 259-264.

Neumayer, U., Stone, S. & Somerville, J. 1998, "Small ventricular septal defects in adults", *European heart journal,* vol. 19, no. 10, pp. 1573-1582.

Newburger, J.W., Wypij, D., Bellinger, D.C., du Plessis, A.J., Kuban, K.C., Rappaport, L.A., Almirall, D., Wessel, D.L., Jonas, R.A. & Wernovsky, G. 2003, "Length of stay after infant heart surgery is related to cognitive outcome at age 8 years", *The Journal of Pediatrics,* vol. 143, no. 1, pp. 67-73.

Newburger, J.W. & Bellinger, D.C. 2006, "Brain injury in congenital heart disease", *Circulation,* vol. 113, no. 2, pp. 183-185.

Newman, M.F., Kirchner, J.L., Phillips-Bute, B., Gaver, V., Grocott, H., Jones, R.H., Mark, D.B., Reves, J.G. & Blumenthal, J.A. 2001, "Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery", *New England Journal of Medicine,* vol. 344, no. 6, pp. 395-402.

Newman, S.P. & Harrison, M.J. 2002, "Coronary-artery bypass surgery and the brain: persisting concerns", *The Lancet Neurology,* vol. 1, no. 2, pp. 119-125.

Newman, M.F., Mathew, J.P., Grocott, H.P., Mackensen, G.B., Monk, T., Welsh-Bohmer, K.A., Blumenthal, J.A., Laskowitz, D.T. and Mark, D.B. 2006 "Central nervous system injury associated with cardiac surgery", *Lancet,* vol. 368, no. 9536, pp. 694; 694-703; 703.

NEW-YORK HEART ASSOCIATION. The Critera Committee 1964, *Diseases of the Heart and Blood Vessels Nomenclature and Criteria for Diagnostic,* J. and A. Churchill.

Nussbaum, P.D., Allender, J. & Copeland, J. 1995, "Verbal learning in cardiac transplant candidates: a preliminary report", *International Journal of Rehabilitation and Health,* vol. 1, no. 1, pp. 5-12.

O'Donovan, C.E., Painter, L., Lowe, B., Robinson, H. & Broadbent, E. 2015, "The impact of illness perceptions and disease severity on quality of life in congenital heart disease", *Cardiology in the young,* vol 26, no. 1, pp. 100-109.

Oechslin, E.N., Harrison, D.A., Harris, L., Downar, E., Webb, G.D., Siu, S.S. & Williams, W.G. 1999, "Reoperation in adults with repair of tetralogy of Fallot: indications and outcomes", *The Journal of Thoracic and Cardiovascular Surgery,* vol. 118, no. 2, pp. 245-251.

Okano, H., Hirano, T. & Balaban, E. 2000, "Learning and memory", *Proceedings of the National Academy of Sciences of the United States of America,* vol. 97, no. 23, pp. 12403-12404.

Osborne, J. 2005, "Notes on the use of data transformations", *Practical Assessment, Research and Evaluation,* vol. 9, pp. 42-50.

Osterrieth, P.A. 1944, "*Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire*.", Archives de Psychologie.

Owen, M., Shevell, M., Majnemer, A. & Limperopoulos, C. 2011, "Abnormal brain structure and function in newborns with complex congenital heart defects before open heart

surgery: a review of the evidence", *Journal of Child Neurology,* vol. 26, no. 6, pp. 743-755.

Owen, M., Shevell, M., Donofrio, M., Majnemer, A., McCarter, R., Vezina, G., Bouyssi-Kobar, M., Evangelou, I., Freeman, D. & Weisenfeld, N. 2014, "Brain Volume and Neurobehavior in Newborns with Complex Congenital Heart Defects", *The Journal of pediatrics,* vol. 164, no. 5, pp. 1121-1127.

Pallant, J. 2007, "*SPSS Survival manual: A step by step guide to data analysis using SPSS for Windows Version 15*", Open University Press, UK.

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

Park, M. 1997, "Routine cardiac evaluation in children", *The pediatric cardiology handbook,* vol. 2, pp. 1-65.

Park, J. & Banaji, M.R. 2000, "Mood and heuristics: the influence of happy and sad states on sensitivity and bias in stereotyping.", *Journal of Personality and Social Psychology,* vol. 78, no. 6, pp. 1005.

Park, D.C. & Reuter-Lorenz, P. 2009, "The adaptive brain: aging and neurocognitive scaffolding", *Annual Review of Psychology,* vol. 60, pp. 173-196.

Payne, T.W. & Schnapp, M.A. 2014, "The Relationship between Negative Affect and Reported Cognitive Failures", *Depression Research and Treatment,* vol. 2014, pp. 396195.

Perloff, J.K. & Warnes, C.A. 2001, "Challenges posed by adults with repaired congenital heart disease", *Circulation,* vol. 103, no. 21, pp. 2637-2643.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G. & Kokmen, E. 1999, "Mild cognitive impairment: clinical characterization and outcome", *Archives of Neurology,* vol. 56, no. 3, pp. 303-308.

Petersen, R.C. 2004, "Mild cognitive impairment as a diagnostic entity", *Journal of Internal Medicine,* vol. 256, no. 3, pp. 183-194.

Phillips-Bute, B., Mathew, J.P., Blumenthal, J.A., Grocott, H.P., Laskowitz, D.T., Jones, R.H., Mark, D.B. & Newman, M.F. 2006, "Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery", *Psychosomatic Medicine,* vol. 68, no. 3, pp. 369-375.

Pillutla, P. 2009, Shetty KD, Foster E."Mortality associated with adult congenital heart disease: Trends in the US population from 1979 to 2005", *American Heart Journal,* vol. 158, no. 5, pp. 874-879.

Popelova, J., Oechslin, E., Kaemmerer, H. & Sutton, Martin G St John 2008, "*Congenital Heart Disease in Adults",* Informa Health Care.

Prochaska, J.J., Velicer, W.F., Nigg, C.R. & Prochaska, J.O. 2008, "Methods of quantifying change in multiple risk factor interventions", *Preventive Medicine,* vol. 46, no. 3, pp. 260-265.

Quené, H. & Van den Bergh, H. 2004, "On multi-level modeling of data from repeated measures designs: A tutorial", *Speech Communication,* vol. 43, no. 1, pp. 103-121.

Rabin, L.A., Barr, W.B. & Burton, L.A. 2005, "Assessment practices of clinical neuropsychologists in the United States and Canada: A survey of INS, NAN, and APA Division 40 members", *Archives of Clinical Neuropsychology,* vol. 20, no. 1, pp. 33-65.

Ragland, J.D., Coleman, A.R., Gur, R.C., Glahn, D.C. & Gur, R.E. 2000, "Sex differences in brain-behavior relationships between verbal episodic memory and resting regional cerebral blood flow", *Neuropsychologia,* vol. 38, no. 4, pp. 451-461.

Rastelli, G.C. 1969, "Anatomic correction of transposition of the great arteries with ventricular septal defect and subpulmonary stenosis.", J*ournal of Thoracic and Cardiovascular Surgery,* vol. 58, no. 4, pp. 545.

Raven, J.C. 1978, "*Standard progressive matrices: sets A, B, C, D and E".* London: HK Lewis.

Raven, J.C., Raven, J.C. & De Lemos, M.M. 1990, "*Standard progressive matrices",* Oxford Psychologists Press Oxford, United Kingdom.

Raven, J.C. & John Hugh Court 1998, "*Raven's progressive matrices and vocabulary scales",* Oxford Psychologists Press Oxford, UK.

Razzaghi, H., Oster, M. & Reefhuis, J. 2015, "Long-term outcomes in children with congenital heart disease: national health interview survey", *The Journal of pediatrics,* vol. 166, no. 1, pp. 119-124.

Reisman, M. & Fuller, C.J. 2009, "Is patent foramen ovale closure indicated for migraine?: patent foramen ovale closure for migraine", *Circulation. Cardiovascular interventions,* vol. 2, no. 5, pp. 468-474.

Reitan, R.M. 1958, "Validity of the Trail Making Test as an indicator of organic brain damage", *Perceptual and motor skills,* vol. 8, no. 3, pp. 271-276.

Reitan, R.M. & Wolfson, D. 1985, "*The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation",* Reitan Neuropsychology.

Reitan, R.M. & Wolfson, D. 1995, "Category Test and Trail Making Test as measures of frontal lobe functions", *The Clinical Neuropsychologist,* vol. 9, no. 1, pp. 50-56.

Report of the British Cardiac Society Working Party 2002, "Grown-up congenital heart (GUCH) disease: current needs and provision of service for adolescents and adults with congenital heart disease in the UK", *Heart (British Cardiac Society),* vol. 88 Suppl 1, pp. i1-14.

Rey, A. 1941, "L'examen psychologique dans les cas d'encéphalopathie traumatique.(Les problems.).", *Archives de psychologie,* .

Riddle, D.R. & Glisky, E.L. 2007, "Changes in Cognitive Function in Human Aging", Brain Aging: Models, methods and mechanisms, pp.3-20

Riehle-Colarusso, T., Autry, A., Razzaghi, H., Boyle, C.A., Mahle, W.T., Van Naarden Braun, K. & Correa, A. 2015, "Congenital Heart Defects and Receipt of Special Education Services", *Pediatrics,* vol. 136, no. 3, pp. 496-504.

Rodriguez-Lopez, J. 2014, "Pulmonary hypertension in adult congenital heart disease", *Current treatment options in cardiovascular medicine,* vol. 16, no. 8, pp. 1-12.

Rollins, C.K., Watson, C.G., Asaro, L.A., Wypij, D., Vajapeyam, S., Bellinger, D.C., DeMaso, D.R., Robertson, R.L., Newburger, J.W. & Rivkin, M.J. 2014, "White matter microstructure and cognition in adolescents with congenital heart disease", *The Journal of pediatrics,* vol. 165, no. 5, pp. 936-944.

Rönnlund, M., Nyberg, L., Bäckman, L. and Nilsson, L.G., 2005. "Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study.", *Psychology and aging*, vol. 20, no. 1, pp.3.

Roos-Hesselink, J.W., Meijboom, F.J., Spitaels, S.E., Van Domburg, R., Van Rijen, E.H., Utens, E.M., Bogers, A.J. & Simoons, M.L. 2004, "Outcome of patients after surgical closure of ventricular septal defect at young age: longitudinal follow-up of 22-34 years", *European heart journal,* vol. 25, no. 12, pp. 1057-1062.

Rose, D. & Pevalin, D. 2010, "Volume 3 the national statistics socio-economic classification: (rebased on the SOC2010) user manual", Basingstoke, England: Palgrave Macmillan.

Rose, M., Köhler, K., Köhler, F., Sawitzky, B., Fliege, H. & Klapp, B.F. 2005, "Determinants of the quality of life of patients with congenital heart disease", *Quality of life research,* vol. 14, no. 1, pp. 35-43.

Russell, M. 2000, "*Summarizing change in test scores: shortcomings of three common methods",* ERIC Clearinghouse on Assessment and Evaluation, University of Maryland.

Ryan, J.J., Sattler, J.M. & Lopez, S.J. 2000, "Age effects on Wechsler adult intelligence scale-III subtests", *Archives of Clinical Neuropsychology,* vol. 15, no. 4, pp. 311-317.

Saliba, Z., Butera, G., Bonnet, D., Bonhoeffer, P., Villain, E., Kachaner, J., Sidi, D. & Iserin, L. 2001, "Quality of life and perceived health status in surviving adults with univentricular heart", *Heart (British Cardiac Society),* vol. 86, no. 1, pp. 69-73.

Samartzis, L., Gavala, E., Zoukos, Y., Aspiotis, A. & Thomaides, T. 2014, "Perceived cognitive decline in multiple sclerosis impacts quality of life independently of depression", *Rehabilitation research and practice,* vol. 2014, pp. 128751.

Samuels, M.A. 2007, "The brain-heart connection", *Circulation,* vol. 116, no. 1, pp. 77-84.

Sarajuuri, A., Jokinen, E., Mildh, L., Tujulin, A.M., Mattila, I., Valanne, L. & Lonnqvist, T. 2012, "Neurodevelopmental burden at age 5 years in patients with univentricular heart", *Pediatrics,* vol. 130, no. 6, pp. e1636-46.

Saris-Baglama, R., Dewey, C., Chisholm, G., Plumb, E., Kosinski, M., Bjorner, J. & Ware, J. 2010, "*QualityMetric Health Outcomes™ scoring software 4.0 user's guide*", Lincoln, RI: QualityMetric Incorporated.

Sarris, G.E., Chatzis, A.C., Giannopoulos, N.M., Kirvassilis, G., Berggren, H., Hazekamp, M., Carrel, T., Comas, J.V., Di Carlo, D. & Daenen, W. 2006, "The arterial switch operation in Europe for transposition of the great arteries: a multi-institutional study from the European Congenital Heart Surgeons Association", *The Journal of thoracic and cardiovascular surgery,* vol. 132, no. 3, pp. 633-639.

Schinka, J.A., Loewenstein, D.A., Raj, A., Schoenberg, M.R., Banko, J.L., Potter, H. & Duara, R. 2010, "Defining mild cognitive impairment: impact of varying decision criteria on

neuropsychological diagnostic frequencies and correlates", *The American Journal of Geriatric Psychiatry,* vol. 18, no. 8, pp. 684-691.

Schmand, B., Smit, J., Lindeboom, J., Smits, C., Hooijer, C., Jonker, C. & Deelman, B. 1997, "Low education is a genuine risk factor for accelerated memory decline and dementia", *Journal of clinical epidemiology,* vol. 50, no. 9, pp. 1025-1033.

Schmidt, M. 1996, "*Rey auditory verbal learning test: A handbook",* Western Psychological Services Los Angeles.

Schoenberg, M.R., Duff, K., Scott, J.G. & Adams, R.L. 2003, "An evaluation of the clinical utility of the OPIE-3 as an estimate of premorbid WAIS-III FSIQ", *The Clinical neuropsychologist,* vol. 17, no. 3, pp. 308-321.

Scholey, A.B., Moss, M.C. & Wesnes, K. 1998, "Oxygen and cognitive performance: the temporal relationship between hyperoxia and enhanced memory", *Psychopharmacology,* vol. 140, no. 1, pp. 123-126.

Shallice, T. 1982, "Specific impairments of planning", *Philosophical transactions of the Royal Society of London.Series B, Biological sciences,* vol. 298, no. 1089, pp. 199-209.

Shen, X.Q., Zhou, S.H. & Gao, M. 2003, "Percutaneous transcatheter closure for secundum atrial septal defect", *Hunan yi ke da xue xue bao = Hunan yike daxue xuebao = Bulletin of Hunan Medical University,* vol. 28, no. 6, pp. 635-637.

Silva, A.M., Vaz, C., Areias, M.E., Vieira, D., Proença, C., Viana, V., Moura, C. & Areias, J.C. 2011, "Quality of life of patients with congenital heart diseases", *Cardiology in the young,* vol. 21, no. 06, pp. 670-676.

Silversides, C.K., Granton, J.T., Konen, E., Hart, M.A., Webb, G.D. & Therrien, J. 2003, "Pulmonary thrombosis in adults with Eisenmenger syndrome", *Journal of the American College of Cardiology,* vol. 42, no. 11, pp. 1982-1987.

Silversides, C.K., Kiess, M., Beauchesne, L., Bradley, T., Connelly, M., Niwa, K., Mulder, B., Webb, G., Colman, J. & Therrien, J. 2010, "Canadian Cardiovascular Society 2009 Consensus Conference on the management of adults with congenital heart disease: outflow tract obstruction, coarctation of the aorta, tetralogy of Fallot, Ebstein anomaly and Marfan's syndrome", *Canadian Journal of Cardiology,* vol. 26, no. 3, pp. e80-e97.

Smith, A. 1978, "*Symbol Digit Modalities Test*", Western Psychological Services.

Smith, A. 1982, "*Symbol digit modalities test (SDMT) manual" (revised)* Western Psychological Services, Los Angeles.

Smith, A. 2002, "*Symbol digit modalities test: Manual",* Western Psychological Corporation.

Snookes, S.H., Gunn, J.K., Eldridge, B.J., Donath, S.M., Hunt, R.W., Galea, M.P. & Shekerdemian, L. 2010, "A systematic review of motor and cognitive outcomes after early surgery for congenital heart disease", *Pediatrics,* vol. 125, no. 4, pp. e818-27.

Somerville, MD, FRCP, FACC, FESC, Jane 1997, "Management of adults with congenital heart disease: an increasing problem", *Annual Review of Medicine,* vol. 48, no. 1, pp. 283-293.

Spielberger, C.D. 1983, "Manual for the State-Trait Anxiety Inventory STAI" (Form Y)(" Self-Evaluation Questionnaire")".

Spinnler, H. & Tognoni, G. 1987, "Italian Group on the Neuropsychological Study of Ageing: Italian standardization and classification of neuropsychological tests", *Ital J Neurol Sci,* vol. 6, suppl 8, pp. 1-120.

Starkstein, S.E., Mayberg, H.S., Leiguarda, R., Preziosi, T.J. & Robinson, R.G. 1992, "A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease", *Journal of neurology, neurosurgery, and psychiatry,* vol. 55, no. 5, pp. 377-382.

Sterken, C., Lemiere, J., Vanhorebeek, I., Van den Berghe, G. & Mesotten, D. 2015, "Neurocognition after paediatric heart surgery: a systematic review and meta-analysis", *Open heart,* vol. 2, no. 1, pp. 1-10.

Stevens, J.P. 1984, "Outliers and influential data points in regression analysis.", *Psychological bulletin,* vol. 95, no. 2, pp. 334.

Stevenson, F., Britten, N., Barry, C., Barber, N. & Bradley, C. 2000, "Qualitative methods and prescribing research", *Journal of clinical pharmacy and therapeutics,* vol. 25, no. 5, pp. 317-324.

Strauss, E., Sherman, E.M. & Spreen, O. 2006, "*A compendium of neuropsychological tests: Administration, norms, and commentary",* American Chemical Society.

Stygall, J., Newman, S.P., Fitzgerald, G., Steed, L., Mulligan, K., Arrowsmith, J.E., Pugsley, W., Humphries, S. & Harrison, M.J. 2003, "Cognitive change 5 years after coronary artery bypass surgery.", *Health Psychology,* vol. 22, no. 6, pp. 579.

Sundet, J.M., Tambs, K., Magnus, P. & Berg, K. 1988, "On the question of secular trends in the heritability of intelligence test scores: A study of Norwegian twins", *Intelligence,* vol. 12, no. 1, pp. 47-59.

Swenson, S.L., Rose, M., Vittinghoff, E., Stewart, A. & Schillinger, D. 2008, "The influence of depressive symptoms on clinician-patient communication among patients with type 2 diabetes", *Medical care,* vol. 46, no. 3, pp. 257-265.

Tabachnick, B.G. & Fidell, L.S. 2013, *"Using multivariate statistics"*, Allyn and Bacon Boston.

Tabbutt, S., Gaynor, J.W. and Newburger, J.W., 2012, "Neurodevelopmental outcomes after congenital heart surgery and strategies for improvement", *Current opinion in cardiology,* vol. 27, no. 2, pp. 82-91.

Talwar, S., Nair, V.V., Choudhary, S.K. & Airan, B. 2014, "The Hemi-Fontan operation: A critical overview", *Annals of pediatric cardiology,* vol. 7, no. 2, pp. 120-125.

Tan, A.M.Y. & Amoako, D. 2013, "Postoperative cognitive dysfunction after cardiac surgery", *Continuing Education in Anaesthesia, Critical Care & Pain,* vol. 13, no. 6, pp. 218-223.

Tavani, F., Zimmerman, R., Clancy, R., Licht, D. & Mahle, W. 2003, "Incidental intracranial hemorrhage after uncomplicated birth: MRI before and after neonatal heart surgery", *Neuroradiology,* vol. 45, no. 4, pp. 253-258.

Taylor, M.J. & Heaton, R.K. 2001, "Sensitivity and specificity of WAIS–III/WMS–III demographically corrected factor scores in neuropsychological assessment", *Journal of the International Neuropsychological Society,* vol. 7, no. 07, pp. 867-874.

Teng, E., Tassniyom, K. & Lu, P.H. 2012, "Reduced quality-of-life ratings in mild cognitive impairment: analyses of subject and informant responses", *The American Journal of Geriatric Psychiatry,* vol. 20, no. 12, pp. 1016-1025.

Terman, L.M. & Merrill, M.A. 1960, *"Stanford-Binet Intelligence Scale: Manual for the third revision, Form LM"*, Houghton Mifflin.

Ternestedt, B., Wall, K., Oddsson, H., Riesenfeld, T., Groth, I. & Schollin, J. 2001, "Quality of life 20 and 30 years after surgery in patients operated on for tetralogy of Fallot and for atrial septal defect", *Pediatric cardiology,* vol. 22, no. 2, pp. 128-132.

Tewes, U. 1994, "*Hamburg-Wechsler-Intelligenztest für Erwachsene*" (Revision 1991), Bern: Verlag Hans Huber.

Thacker, E.L., McKnight, B., Psaty, B.M., Longstreth, W.T.,Jr, Sitlani, C.M., Dublin, S., Arnold, A.M., Fitzpatrick, A.L., Gottesman, R.F. & Heckbert, S.R. 2013, "Atrial fibrillation and cognitive decline: a longitudinal cohort study", *Neurology,* vol. 81, no. 2, pp. 119-125.

Thompson, E.R. 2007, "Development and validation of an internationally reliable short-form of the positive and negative affect schedule (PANAS)", *Journal of cross-cultural psychology,* vol. 38, no. 2, pp. 227-242.

Thuny, F., Di Salvo, G., Belliard, O., Avierinos, J.F., Pergola, V., Rosenberg, V., Casalta, J.P., Gouvernet, J., Derumeaux, G., Iarussi, D., Ambrosi, P., Calabro, R., Riberi, A., Collart, F., Metras, D., Lepidi, H., Raoult, D., Harle, J.R., Weiller, P.J., Cohen, A. & Habib, G. 2005, "Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective multicenter study", *Circulation,* vol. 112, no. 1, pp. 69-75.

Tluczek, A., Henriques, J.B. & Brown, R.L. 2009, "Support for the reliability and validity of a six-item state anxiety scale derived from the State-Trait Anxiety Inventory", *Journal of nursing measurement,* vol. 17, no. 1, pp. 19-28.

Tombaugh, T.N., Kozak, J. and Rees, L., 1999, "Normative Data Stratified by Age and Education for Two Measures of Verbal Fluency:: FAS and Animal Naming", *archives of clinical neuropsychology,* vol. 14, no. 2, pp. 167.

Tombaugh, T. 2004, "Trail Making Test A and B: Normative data stratified by age and education", *Archives of Clinical Neuropsychology,* vol. 19, no. 2, pp. 203-214.

Trennery, M.R., Crosson, B., DeBoe, J. & Leber, W.R. 1988, "*Stroop Neuropsychological Screening Test Manual",* Odessa, FL: Psychological Assesment Resources.

Trenerry, M.R., Crosson, B., DeBoe, J. & Leber, W. 1989, "*Stroop neuropsychological screening test manual",* Odessa, FL: Psychological Assesment Resources.

Trittenwein, G., Nardi, A., Pansi, H., Golej, J., Burda, G., Hermon, M., Boigner, H. & Wollenek, G. 2003, "Early postoperative prediction of cerebral damage after pediatric cardiac surgery", *The Annals of Thoracic Surgery,* vol. 76, no. 2, pp. 576-580.

Turner, J. & Kelly, B. 2000, "Emotional dimensions of chronic disease", *Western Journal of Medicine,* vol. 172, no. 2, pp. 124.

Tyagi, M., Austin, K., Stygall, J., Deanfield, J., Cullen, S. & Newman, S.P. 2013, "What do we know about cognitive functioning in adult congenital heart disease?", *Cardiology in the young, vol. 24, no.1*, pp. 13-19.

Utens, E.M., Verhulst, F.C., Erdman, R.A., Meijboom, F.J., Duivenvoorden, H.J., Bos, E., Roelandt, J.R. & Hess, J. 1994, "Psychosocial functioning of young adults after surgical correction for congenital heart disease in childhood: a follow-up study", *Journal of psychosomatic research,* vol. 38, no. 7, pp. 745-758.

Utens, E.M., Bieman, H.J., Verhulst, F.C., Meijboom, F.J., Erdman, R.A. & Hess, J. 1998, "Psychopathology in young adults with congenital heart disease. Follow-up results", *European heart journal,* vol. 19, no. 4, pp. 647-651.

Uysal, S., Lin, H., Fischer, G.W., Di Luozzo, G. & Reich, D.L. 2012, "Selective cerebral perfusion for thoracic aortic surgery: association with neurocognitive outcome", *The Journal of thoracic and cardiovascular surgery,* vol. 143, no. 5, pp. 1205-1212.

Uzark, K., Lincoln, A., Lamberti, J.J., Mainwaring, R.D., Spicer, R.L. & Moore, J.W. 1998, "Neurodevelopmental outcomes in children with Fontan repair of functional single ventricle", *Pediatrics,* vol. 101, no. 4, pp. 630-633.

Uzark, K. 2016, "Challenges of Assessing Quality of Life in Congenital Heart Disease Globally", *Journal of the American College of Cardiology,* vol. 67, no. 19, pp. 2246-2248.

Van Deelen, B.A., van den Bemt, Patricia MLA, Egberts, T.C., van't Hoff, A. & Maas, H.A. 2005, "Cognitive impairment as determinant for sub-optimal control of oral anticoagulation treatment in elderly patients with atrial fibrillation", *Drugs & aging,* vol. 22, no. 4, pp. 353-360.

Van den Burg, W. & Kingma, A. 1999, "Performance of 225 Dutch school children on Rey's Auditory Verbal Learning Test (AVLT): parallel test-retest reliabilities with an interval of 3 months and normative data", *Archives of Clinical Neuropsychology,* vol. 14, no. 6, pp. 545-559.

Van der Bom, T., Zomer, A.C., Zwinderman, A.H., Meijboom, F.J., Bouma, B.J. and Mulder, B.J.2011, "The changing epidemiology of congenital heart disease", *Nature Reviews Cardiology,* vol. 8, no. 1, pp. 50-60.

Van Der Elst, W., Van Boxtel, M.P., Van Breukelen, G.J. & Jolles, J. 2008, "Detecting the significance of changes in performance on the Stroop Color-Word Test, Rey's

Verbal Learning Test, and the Letter Digit Substitution Test: the regression-based change approach", *Journal of the International Neuropsychological Society,* vol. 14, no. 01, pp. 71-80.

Van der Linde, D., Konings, E.E., Slager, M.A., Witsenburg, M., Helbing, W.A., Takkenberg, J.J. & Roos-Hesselink, J.W. 2011, "Birth Prevalence of Congenital Heart Disease WorldwideA Systematic Review and Meta-Analysis", *Journal of the American College of Cardiology,* vol. 58, no. 21, pp. 2241-2247.

Vis, J., Duffels, M., Winter, M., Weijerman, M., Cobben, J., Huisman, S. & Mulder, B. 2009, "Down syndrome: a cardiovascular perspective", *Journal of intellectual disability research,* vol. 53, no. 5, pp. 419-425.

Vogels, R.L., Scheltens, P., Schroeder-Tanka, J.M. & Weinstein, H.C. 2007, "Cognitive impairment in heart failure: a systematic review of the literature", *European Journal of Heart Failure,* vol. 9, no. 5, pp. 440-449.

Walsh, E.P. & Cecchin, F. 2007, "Arrhythmias in adult patients with congenital heart disease", *Circulation,* vol. 115, no. 4, pp. 534-545.

Ware, J.E., Kosinski, M., Dewey, J.E. & Gandek, B. 2000, "*SF-36 health survey: manual and interpretation guide",* Quality Metric Inc.

Warnes, C.A., Liberthson, R., Danielson, G.K., Dore, A., Harris, L., Hoffman, J.I., Somerville, J., Williams, R.G. and Webb, G.D., 2001, "Task force 1: the changing profile of congenital heart disease in adult life", *Journal of the American College of Cardiology,* vol. 37, no. 5, pp. 1170.

Warnes, C.A., Williams, R.G., Bashore, T.M., Child, J.S., Connolly, H.M., Dearani, J.A., del Nido, P., Fasules, J.W., Graham, T.P. & Hijazi, Z.M. 2008, "ACC/AHA 2008 Guidelines for the Management of Adults With Congenital Heart DiseaseA Report of the American College of Cardiology/American Heart Associ", *Journal of the American College of Cardiology,* vol. 52, no. 23, pp. e143-e263.

Watson, D., Clark, L.A. & Tellegen, A. 1988, "Development and validation of brief measures of positive and negative affect: the PANAS scales.", *Journal of personality and social psychology,* vol. 54, no. 6, pp. 1063.

Webb, G.D. & Williams, R.G. 2001, "32nd Bethesda Conference: "care of the adult with congenital heart disease" 1", *Journal of the American College of Cardiology,* vol. 37, no. 5, pp. 1162-1165.

Webb, G. 2005, "Improving the care of Canadian adults with congenital heart disease", *The Canadian journal of cardiology,* vol. 21, no. 10, pp. 833-838.

Wechsler D, S.C. 1974, *"Wechsler memory scale II manual".* New York: The Psychological Corporation.

Wechsler, D. 1981, "*WAIS-R manual: Wechsler adult intelligence scale-revised",* New York: Psychological Corporation.

Wechsler D., 1987, "*Wechsler memory scale: revised manual". San Antonio: The Psychological Corporation*.

Wechsler, D. 1997, "*WAIS-III Administration and Scoring manual".* Harcourt Brace & Co., San Antonio.

Wechsler, D. 2008, "*Wechsler adult intelligence scale–Fourth Edition (WAIS–IV)*", San Antonio, TX: NCS Pearson.

Wechsler, D. 2014, "*Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV)*, San Antonio, TX: NCS Pearson.

Welsh, M., Groisser, D. & Pennington, B. 1988, "A normative-developmental study of performance on measures hypothesized to tap prefrontal functions", *Neuropsychology,* vol. 9, pp. 28.

Wernovsky, G., Stiles, K.M., Gauvreau, K., Gentles, T.L., duPlessis, A.J., Bellinger, D.C., Walsh, A.Z., Burnett, J., Jonas, R.A., Mayer, J.E.,Jr & Newburger, J.W. 2000, "Cognitive development after the Fontan operation", *Circulation,* vol. 102, no. 8, pp. 883-889.

Wernovsky, G., Shillingford, A.J. & Gaynor, J.W. 2005, "Central nervous system outcomes in children with complex congenital heart disease", *Current opinion in cardiology,* vol. 20, no. 2, pp. 94-99.

Wiig, E.H., Nielsen, N.P., Minthon, L. & Warkentin, S. 2002, *"A quick test of cognitive speed (AQT)"*, San Antonio, TX.PsychCorp.

Wilson, N.J., Clarkson, P.M., Barratt-Boyes, B.G., Calder, A.L., Whitlock, R.M., Easthope, R.N. and Neutze, J.M., 1998, *Journal of the American College of Cardiology,* vol. 32, no. 3, pp. 758-765.

Wozakowska-Kaplon, B., Opolski, G., Kosior, D., Jaskulska-Niedziela, E., Maroszynska-Dmoch, E. & Wlosowicz, M. 2009, "Cognitive disorders in elderly patients with permanent atrial fibrillation", *Kardiologia polska,* vol. 67, no. 5, pp. 487-493.

Wray, J. & Sensky, T. 2001, "Congenital heart disease and cardiac surgery in childhood: effects on cognitive function and academic ability", *Heart (British Cardiac Society),* vol. 85, no. 6, pp. 687-691.

Wray, J. 2006, "Intellectual development of infants, children and adolescents with congenital heart disease", *Developmental science,* vol. 9, no. 4, pp. 368-378.

Wren, C.*, Reinhardt, Z. and Khawaja, K.,* 2008, "Twenty-year trends in diagnosis of life-threatening neonatal cardiovascular malformations", *Archives of Disease in Childhood - Fetal and Neonatal Edition,* vol. 93, no. 1, pp. F33-F35.

Wypij, D., Newburger, J.W., Rappaport, L.A., duPlessis, A.J., Jonas, R.A., Wernovsky, G., Lin, M. & Bellinger, D.C. 2003, "The effect of duration of deep hypothermic circulatory arrest in infant heart surgery on late neurodevelopment: the Boston Circulatory Arrest Trial", *The Journal of thoracic and cardiovascular surgery,* vol. 126, no. 5, pp. 1397-1403.

Yuan, S. & Jing, H. 2009, "Palliative procedures for congenital heart defects", *Archives of cardiovascular diseases,* vol. 102, no. 6, pp. 549-557.

Zeidan, F., Johnson, S.K., Diamond, B.J., David, Z. & Goolkasian, P. 2010, "Mindfulness meditation improves cognition: evidence of brief mental training", *Consciousness and cognition,* vol. 19, no. 2, pp. 597-605.

Zhang, W., O'Brien, N., Forrest, J.I., Salters, K.A., Patterson, T.L., Montaner, J.S., Hogg, R.S. & Lima, V.D. 2012, "Validating a shortened depression scale (10 item CES-D) among HIV-positive people in British Columbia, Canada", *PLoS One,* vol. 7, no. 7, pp. e40793.

Ziganshin, B.A. & Elefteriades, J.A. 2013, "Deep hypothermic circulatory arrest", *Annals of Cardiothoracic Surgery,* vol. 2, no. 3, pp. 303-315.

APPENDICES

Appendix A: Prisma (2009) Checklist Used In Systematic Review

Section/topic	#	Checklist item	Reported on page #	Notes
TITLE				
Title	1	Identify the report as a systematic review, meta-analysis, or both.	73	-
ABSTRACT				
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	No	Not a published review (but undertaken for publication)
INTRODUCTION				
Rationale	3	Describe the rationale for the review in the context of what is already known.	73	-
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	74	-
METHODS				
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No	No review protocol
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	76-77	-
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	75	-
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix C and D	-

Section/topic	#	Checklist item	Reported on page #	Notes
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	77-79	-
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	78	-
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	77-79	-
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	No	Study quality was assessed not risk of bias
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	No	Data was not meta-analysed
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	80-99	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	No	Study quality was assessed not risk of bias
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	No	No additional analysis conducted
RESULTS				
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	81	-
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	81-86	-

Section/topic	#	Checklist item	Reported on page #	Notes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	No	Study quality was assessed not risk of bias
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	80-99	-
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	No	Data was not meta-analysed
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	No	Study quality was assessed not risk of bias
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a	-
DISCUSSION				
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	95-99	-
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	99-100	-
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	100	-
FUNDING				
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No	Will be provided for publication

Appendix B: Published Literature Review

Appendix C: Systematic Review Literature Search Strataegy

Database	Key word search (same for all databases and consistent with paper)	Subject heading search (selected from those provided by the database)	Total hits
Allied and complementary Medicine Database (AMED)	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) Cognition disorders/ or Cognition/ or cognitive functioning.mp ii) Adult/ or adult.mp. iii) Heart defects congenital/	0
Excerpta Medica dataBASE (EMBASE)	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) neuropsychological test/ or cognitive defect/ or memory/ or cognition/ or cognitive functioning.mp. or executive function/ ii) adult iii) congenital heart malformation/ or congenital heart disease/ or congenital heart block/ or congenital heart.mp. or heart ventricle septum defect/	177
CHOCORANE REVIEWS	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) cognitive functioning.mp ii) adult iii) congenital heart malformation/ or congenital heart disease/ or congenital heart block/ or congenital heart.mp. or heart ventricle septum defect/	2
GOOGLE SCHOLAR	(cognitive* and neurocognitive* or neuropsychology* or intelligence or IQ) and (adults or "grown up") and ("congenital heart")		25
MEDLINE	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) (MH "Cognition") OR (MH "Executive Function") OR "cognitive functioning" OR (MH "Mild Cognitive Impairment") OR (MH "Intellectual Disability") ii) (MH "Adult") OR "adult" OR (MH "Young Adult") iii)(MH "Heart Defects, Congenital") OR (MH "Hypoplastic Left Heart Syndrome") OR "congenital heart"	278
Cumulative Index to Nursing and Allied Health Literature (CINHAL)	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) cognitive functioning ii) (MH "Adult") OR "adult" OR (MH "Young Adult") OR (MH "Wechsler Adult Intelligence Scale-Revised") iii) MH "Hypoplastic Left Heart Syndrome") OR (MH "Heart Septal Defects, Ventricular") OR (MH "Heart Septal Defects, Atrial") OR (MH "Tetralogy of Fallot") OR (MH "Transposition of Great Arteries") OR (MH "Tricuspid Atresia") OR (MH "Heart Defects, Congenital") OR (MH	24

Database	Key word search (same for all databases and consistent with paper)	Subject heading search (selected from those provided by the database)	Total hits
		"Aortic Coarctation") OR (MH "Ventricular Outflow Obstruction")	
PSYCHINFO	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) "Executive Function" OR DE "Neuropsychology" OR DE "Problem Solving" OR DE "Memory" OR DE "Cognitive Impairment" OR DE "Cognitive Ability" OR DE "Cognitive Assessment" ii) (DE "Wechsler Adult Intelligence Scale") OR (DE "Adult") iii) congenital heart	15
WEB OF SCIENCE	i) cognition terms: cogniti* OR neuropsycholog* OR neurocogniti* OR intelligence OR IQ ii) adult terms: adult OR "grown up" iii) CHD terms: congenital heart disease OR congenital heart defect	i) (MH "Cognition") OR (MH "Executive Function") OR "cognitive functioning" OR (MH "Mild Cognitive Impairment") OR (MH "Intellectual Disability") ii) (MH "Adult") OR "adult" OR (MH "Young Adult") iii) (MH "Heart Defects, Congenital") OR (MH "Hypoplastic Left Heart Syndrome") OR "congenital heart"	31
TOTAL			**552**

Note- all terms searched only in abstract and abstract and title where the option of only abstract was not available in the database

Appendix D: Example of One Electronic Database Search Strategy

Database searched = Psychinfo

Interface used = Ebscohost

Search string including key words and subject headings=

“cogniti*” OR “neuropsycholog*” OR “neurocogniti*” OR “intelligence” OR “IQ” AND "Executive Function" OR DE "Neuropsychology" OR DE "Problem Solving" OR DE "Memory" OR DE "Cognitive Impairment" OR DE "Cognitive Ability" OR DE "Cognitive Assessment"

AND

“adult” OR "grown up" AND (DE "Wechsler Adult Intelligence Scale") OR (DE "Adult")

AND

“congenital heart disease” OR “congenital heart defect” AND “congenital heart*”

Limits **instated**= none

Total hits= 15

Appendix E: Data Extraction Form used for the Systematic Review

General Information
Article Title: Author(s): Source:
Sample Characteristics
Study sample size: Inclusion Criteria: Exclusion Criteria: Sample Characteristics/ structural complexity groups: Normative/Control group:
Study Characteristics
Aim(s): Design: Cognitive impairment criteria: Neuropsychological assessment measures: Other Measures: Statistical Analysis:
Main Findings:

Appendix F: Quality Index used for Systematic Review

Quality index items	Yes (Score=2)	Partially (Score=1)	No (Score=0)	Unable to determine (Score=0)
REPORTING				
The hypothesis/ aim/ objective(s) of the study were clearly described				
The main outcomes to be measured were clearly described in the Introduction or Methods section				
The characteristics of the patients included in the study were clearly described				
Is the definition of cognitive impairment clearly defined in the study				
The principal confounders in the sample were clearly described				
The main findings of the study were clearly described				
Does the study provide estimates of the random variability in the data for the main outcomes?				
Actual probability values have been reported (e.g. .035 rather than <.05) for the main outcomes except where the probability value was less than .001				
EXTERNAL VALIDITY				
The persons asked to participate in the study were representative of the entire population from which they were recruited				
The persons who were prepared to participate were representative of the entire population from which they recruited				
Is the context/ location of the study clearly described?				
INTERNAL VALIDITY (Bias)				
Were the statistical tests used to assess the main outcomes were appropriate				
Did the study include a normative/control group for comparison on the NP tests?				
Were the main outcome measures used accurate? (valid and reliable)				
INTERNAL VALIDITY (Selection bias)				
Where there any participants excluded from the study that may result in a bias? (for e.g syndrome patients)[a]				
Were all patients recruited over the same period of time?				
There were adequate adjustment for confounding in the analyses from which the main findings were drawn				
Was a power calculation reported?				
Did the study meet sample size requirement?				

Note: Maximum possible score = 38, with higher scores representing better study quality; [a]Item reverse scored

Appendix G: Cross-Sectional Study Patient Information Sheet

University College London Hospitals NHS
NHS Foundation Trust

Consultants:
Dr Shay Cullen
Dr Fiona Walker
Prof Philipp Bonhoeffer
Prof John Deanfield

Surgeons:
Mr Victor Tsang
Ms Carin van Doorn
Mr Martin Kostolny

Clinical Nurse Specialists:
Ruth Brooks
Marie Francis
Fiona Kennedy
Kerry Romer

GUCH Office
The Heart Hospital
16-18 Westmoreland Street
London W1G 8PH
Tel: [redacted]
Nurses: [redacted]
Fax: [redacted]
Email: [redacted]
Website: [redacted]

UCLH Project ID number : 08/0326

CONFIDENTIAL
INFORMATION SHEET (Version 2-12/08)

Quality of life in GUCH patients.

Investigators:	Professor Stanton Newman, Professor John Deanfield, Dr Shay Cullen, Jan Stygall, Fiona Kennedy, Marie Francis, Nathalie Picaut, Katie Austin, Theodora Fteropoulli, Manavi Tyagi, Anna Davies.
Contact details:	[redacted] Tel: [redacted]

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Although various studies have been conducted into the quality of life of children with congenital heart disease very little has been carried out with adults with congenital heart disease. In order to better plan our services to support long term care we would find it extremely valuable to have an understanding of how congenital heart disease affects quality of life. Therefore, we in the GUCH Unit at the Heart Hospital, UCLH, and the Unit of Behavioural Medicine at UCL would like to find out how your heart condition affects your life and your functioning. The information you give us will then be used to improve the long-term care of adults with congenital heart disease.

Why have I been chosen?

You are being asked to take part in this study because you have a diagnosis of congenital heart disease. Approximately, 360 patients will take part in this study over the next 3 years.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What is involved in the study?

If you agree to take part in this study you will be asked to attend the Heart Hospital on the same day of your next outpatient appointment. During the research appointment a researcher will take you through some questionnaires aimed to find out how your heart condition has impacted upon your life. The appointment will take approximately 45 mins.

What are the possible benefits of taking part?

Whilst there are no immediate benefits for people participating in this study, it is hoped that this work will contribute to improving the long-term care of adults with congenital heart disease.

Confidentiality of records

We also need permission to access your medical records, which relate directly to this study. All the information we obtain will be strictly confidential. UCL will overview the collection, storage and handling of the data and Professor Newman, in his capacity of chief investigator, will be responsible for security and access to the data. Only study investigators (named above) will have access to the data. The information collected during the study, with exception of your name, will be stored and analysed confidentially in a computer. No identifiers on the data held by computer will enable a third party to link the data to you. A study ID number will be assigned to you and this will appear on all data including medical information and questionnaires. All data will be kept strictly confidential and secured under lock and key in UCL. The data will be stored for 5 years after the study has been completed. The results of this study may be published within the medical literature, however, no personal details will be revealed. Copies of the publications will be available to you from the researchers. A report of the findings of the research will be sent to all interested participants in approximately 3½ years from the start of the study.

Comments or concerns during the study

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions either at your appointment or on [redacted]. If you remain unhappy and wish to complain formally you can do this through the Complaints Manager, [redacted]. Please quote the UCLH project number at the top of this information sheet.

Ethics Committee Review

All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Ethics Committee in Ethics of Human Research.

Thank you for taking the time to read this. If you decide to take part you will be given a copy of this information sheet and a signed consent form to keep.

Appendix H: NP Test Battery Cross-Sectional Study

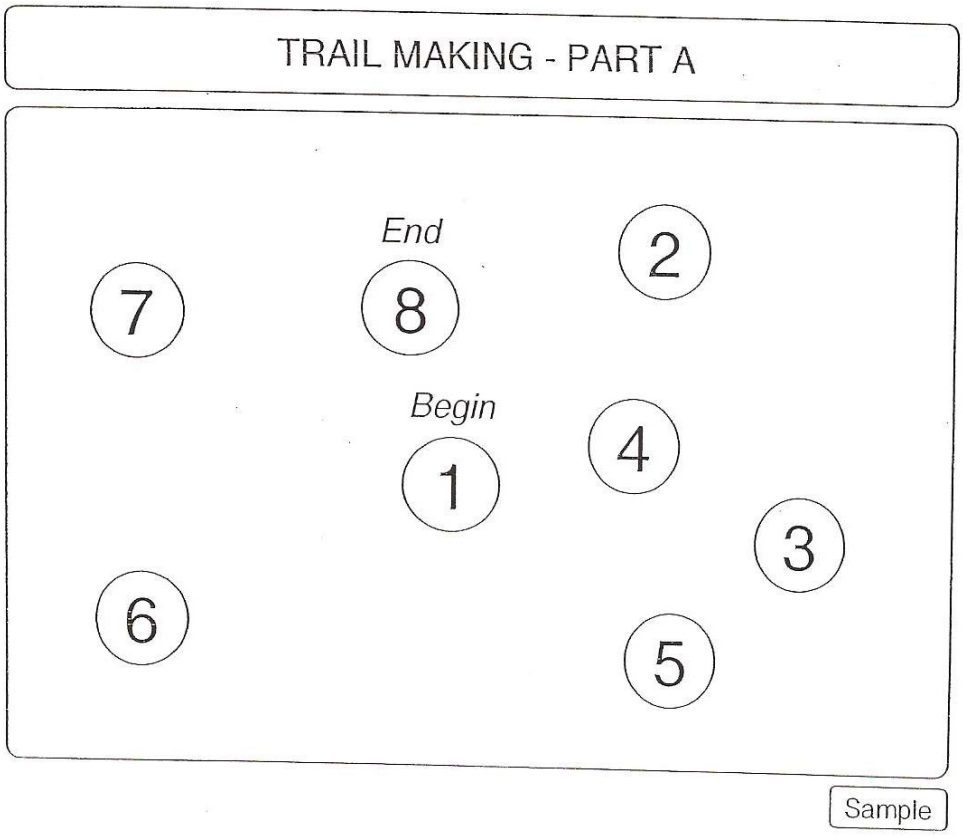
Neuropsych Checklist:

Patient ID:
Date:

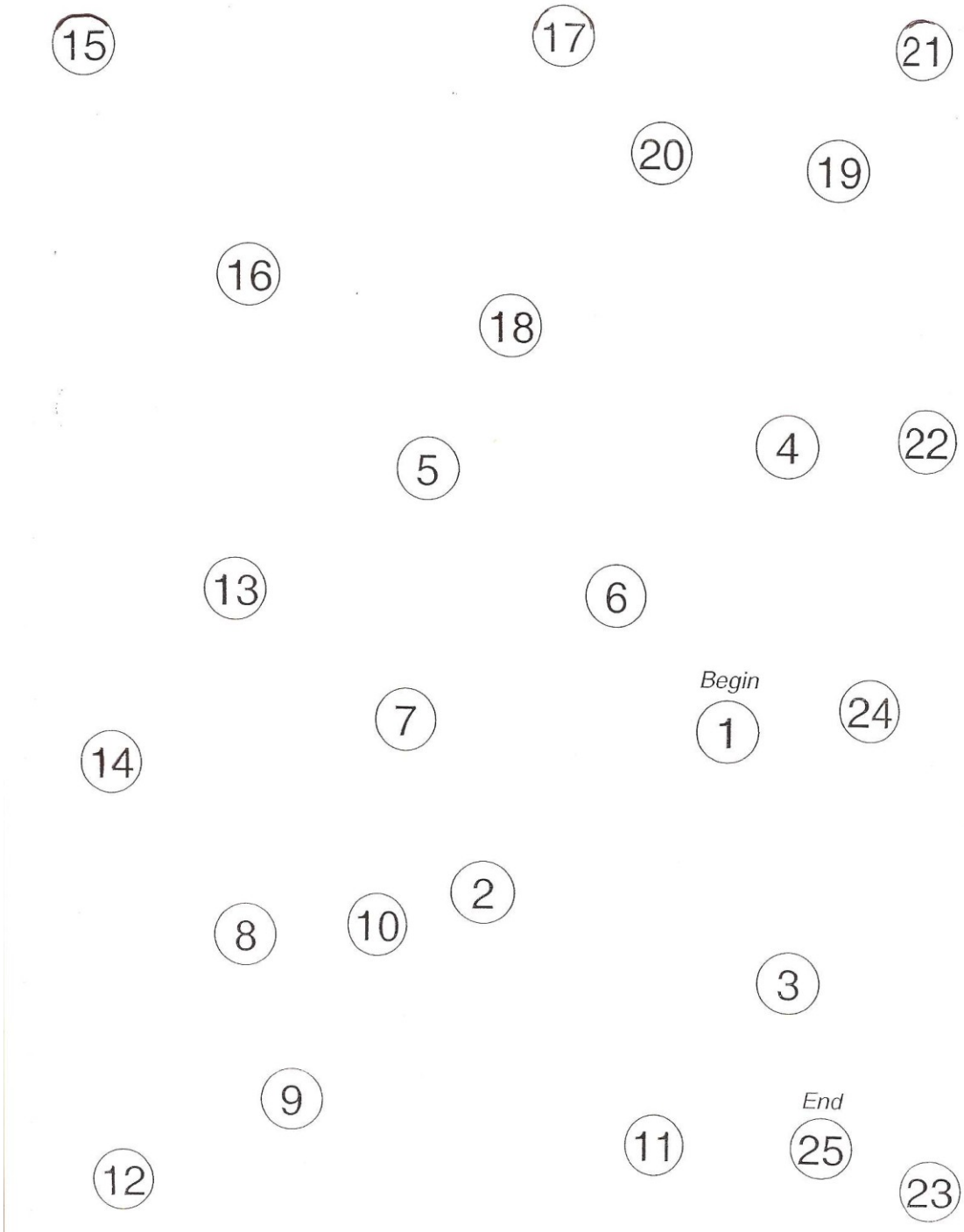
Task	Tick/Cross	Comments
Trail Making A		
Trail Making B		
Digit Symbol Coding		
Cowa		
Stroop: C		
Stroop: C-W		
Arithmetic		
Grooved Pegboard		
Knowledge		
WCST		
Rey		
Symbol Written		
Symbol Oral		

Any additional comments

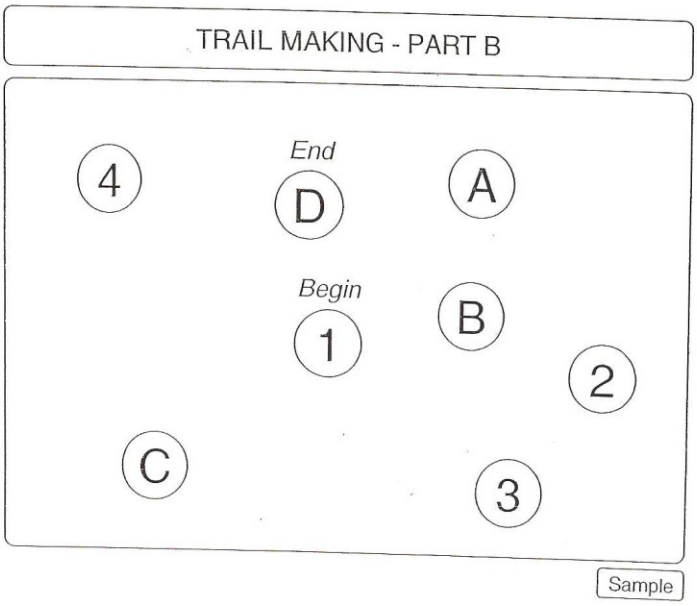
Researcher's Signature.....


TRAIL MAKING - PART A
End
2
7
8
Begin
4
1
3
6
5
Sample

TRAIL MAKING - PART A PATIENT ID _____ TIME:



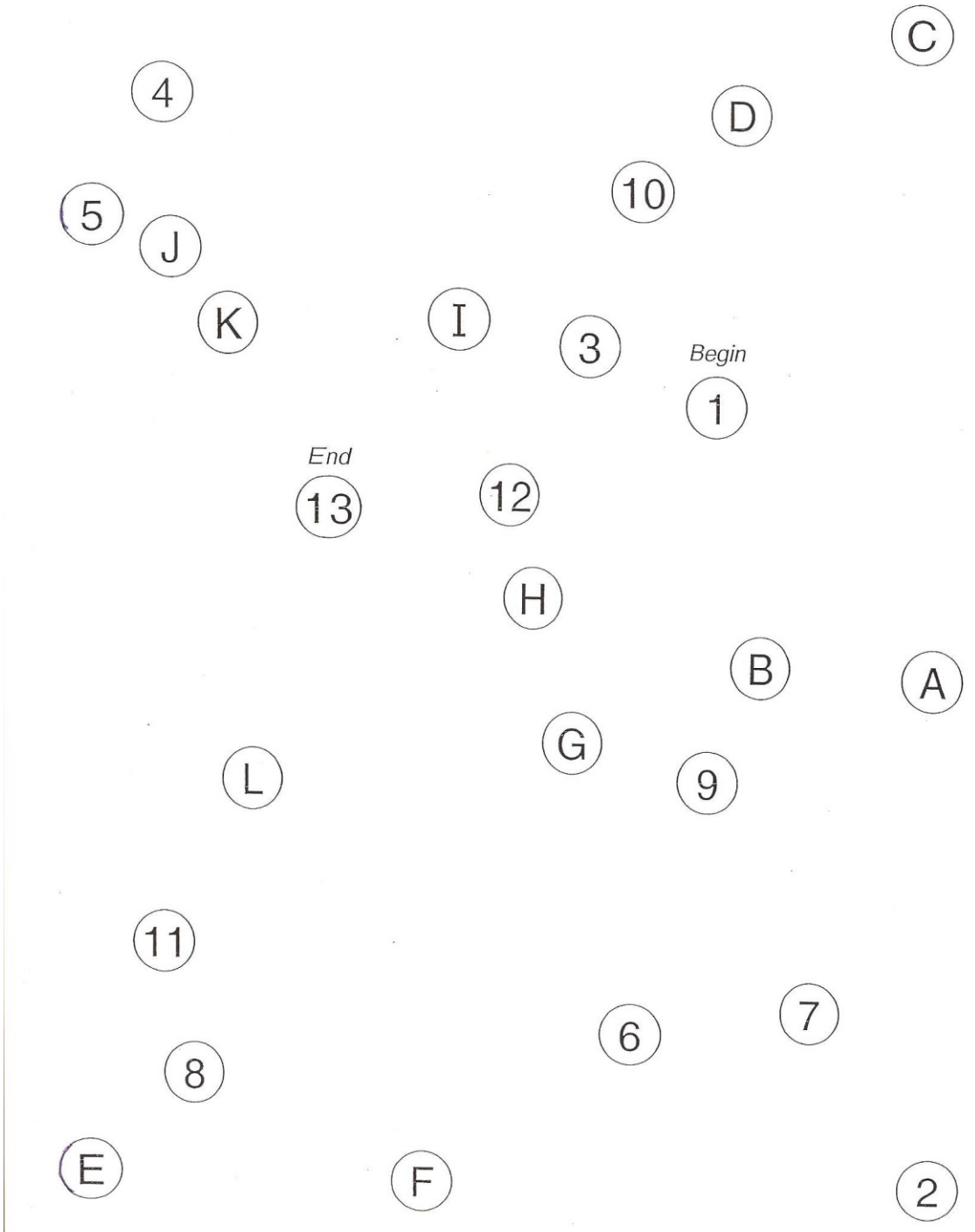
PATIENT ID ____



TRAIL MAKING - PART B

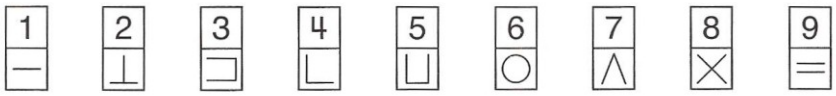
PATIENT ID____

TIME:



PATIENT ID_____

Digit Symbol—Coding



Sample Items

2	1	3	7	2	4	8	2	1	3	2	1	4	2	3	5	2	3	1	4

5	6	3	1	4	1	5	4	2	7	6	3	5	7	2	8	5	4	6	3

7	2	8	1	9	5	8	4	7	3	6	2	5	1	9	2	8	3	7	4

6	5	9	4	8	3	7	2	6	1	5	4	6	3	7	9	2	8	1	7

9	4	6	8	5	9	7	1	8	5	2	9	4	8	6	3	7	9	8	6

2	7	3	6	5	1	9	8	4	5	7	3	1	4	8	7	9	1	4	5

7	1	8	2	9	3	6	7	2	8	5	2	3	1	4	8	4	2	7	6

PATIENT ID_____

COWA

Practice. Give me some words you can think of that begin with the letter **C** excluding proper nouns, numbers and the same word with different suffix.

Now I will be timing you.

Give as **many** words as you can think of that begin with the letter:- (**Time for 1 minute each letter).**

F **A** **S**

1E _____

Form C Responses – Color Task

1 BLUE_____	29 RED_____	57 TAN_____	85 RED_____
2 GREEN_____	30 GREEN_____	58 RED_____	86 TAN_____
3 TAN_____	31 TAN_____	59 TAN_____	87 RED_____
4 RED_____	32 BLUE_____	60 BLUE_____	88 TAN_____
5 GREEN_____	33 GREEN_____	61 TAN_____	89 BLUE_____
6 BLUE_____	34 BLUE_____	62 RED_____	90 GREEN_____
7 GREEN_____	35 TAN_____	63 GREEN_____	91 RED_____
8 BLUE_____	36 GREEN_____	64 RED_____	92 BLUE_____
9 RED_____	37 TAN_____	65 BLUE_____	93 RED_____
10 BLUE_____	38 BLUE_____	66 TAN_____	94 TAN_____
11 TAN_____	39 GREEN_____	67 RED_____	95 GREEN_____
12 RED_____	40 BLUE_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 GREEN_____	69 RED_____	97 BLUE_____
14 GREEN_____	42 RED_____	70 TAN_____	98 RED_____
15 BLUE_____	43 BLUE_____	71 BLUE_____	99 BLUE_____
16 TAN_____	44 GREEN_____	72 TAN_____	100 RED_____
17 GREEN_____	45 TAN_____	73 GREEN_____	101 GREEN_____
18 RED_____	46 RED_____	74 TAN_____	102 RED_____
19 TAN_____	47 TAN_____	75 BLUE_____	103 BLUE_____
20 RED_____	48 GREEN_____	76 TAN_____	104 TAN_____
21 TAN_____	49 TAN_____	77 BLUE_____	105 BLUE_____
22 RED_____	50 RED_____	78 GREEN_____	106 GREEN_____
23 GREEN_____	51 BLUE_____	79 RED_____	107 BLUE_____
24 RED_____	52 RED_____	80 GREEN_____	108 RED_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 BLUE_____
26 BLUE_____	54 RED_____	82 RED_____	110 TAN_____
27 GREEN_____	55 TAN_____	83 GREEN_____	111 BLUE_____
28 TAN_____	56 BLUE_____	84 BLUE_____	112 GREEN_____

TIME _____ Form C-W Responses—Color-Word Task PATIENT ID: _____

1 RED_____	29 BLUE_____	57 BLUE_____	85 TAN_____
2 BLUE_____	30 TAN_____	58 TAN_____	86 RED_____
3 GREEN_____	31 GREEN_____	59 RED_____	87 GREEN_____
4 BLUE_____	32 RED_____	60 GREEN_____	88 BLUE_____
5 RED_____	33 BLUE_____	61 TAN_____	89 TAN_____
6 TAN_____	34 GREEN_____	62 RED_____	90 GREEN_____
7 BLUE_____	35 BLUE_____	63 GREEN_____	91 RED_____
8 RED_____	36 GREEN_____	64 BLUE_____	92 TAN_____
9 TAN_____	37 RED_____	65 GREEN_____	93 BLUE_____
10 GREEN_____	38 TAN_____	66 TAN_____	94 GREEN_____
11 BLUE_____	39 BLUE_____	67 BLUE_____	95 RED_____
12 RED_____	40 RED_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 BLUE_____	69 RED_____	97 RED_____
14 BLUE_____	42 TAN_____	70 BLUE_____	98 GREEN_____
15 GREEN_____	43 RED_____	71 RED_____	99 RED_____
16 RED_____	44 TAN_____	72 GREEN_____	100 BLUE_____
17 TAN_____	45 BLUE_____	73 BLUE_____	101 RED_____
18 GREEN_____	46 RED_____	74 TAN_____	102 BLUE_____
19 BLUE_____	47 GREEN_____	75 GREEN_____	103 TAN_____
20 RED_____	48 BLUE_____	76 BLUE_____	104 GREEN_____
21 TAN_____	49 TAN_____	77 RED_____	105 RED_____
22 GREEN_____	50 GREEN_____	78 TAN_____	106 TAN_____
23 BLUE_____	51 RED_____	79 GREEN_____	107 BLUE_____
24 GREEN_____	52 TAN_____	80 RED_____	108 TAN_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 RED_____
26 BLUE_____	54 TAN_____	82 BLUE_____	110 BLUE_____
27 TAN_____	55 BLUE_____	83 GREEN_____	111 GREEN_____
28 RED_____	56 RED_____	84 BLUE_____	112 TAN_____

6. Arithmetic

PATIENT ID: _____

REVERSE RULE
Score of 0 on Item 5 or 6, administer Items 4–4 in reverse sequence until two consecutive perfect scores are obtained.

DISCONTINUE RULE
4 consecutive scores of 0

SCORING RULE
Items 1–18: 0 or 1 pt. for each response
Items 19–20: 0, 1, or 2 pts.

START

Problem	Time Limit	Completion Time in Seconds	Correct Response	Response	Score (0 or 1)	Problem	Time Limit	Completion Time in Seconds	Correct Response	Response	Score (0 or 1)
1.	15"		3			11.	30"		£10.50		
2.	15"		7			12.	60"		30p		
3.	15"		5			13.	60"		£186.00		
4.	15"		2			14.	60"		10		
5.	15"		£9.00			15.	60"		£600.00		
6.	15"		£4.00			16.	60"		43		
7.	30"		5			17.	60"		£51.00		
8.	30"		£1.50			18.	60"		£49.50		
9.	30"		8			19.	60"		1 of 4 or 5 of 20		(0, 1, or 2) 0 / 11"–60" 1 / 1"–10" 2
10.	30"		£3.60			20.	120"		96		0 / 11"–120" 1 / 1"–10" 2

Total Raw Score (Maximum = 22)

TIME_____ PATIENT ID _____

Grooved Pegboard

Dominant Hand

Number of drops _____ Total ___

Time _____

Non-Dominant Hand

Number of drops _____ Total ___

Time _____

9. Information

PATIENT ID_____

REVERSE RULE
Score of 0 on Item 5 or 6, administer Items 1-4 in reverse sequence until two consecutive perfect scores are obtained.

DISCONTINUE RULE
6 consecutive scores of 0

SCORING RULE
All Items: 0 or 1 pt. for each response

Item	Response	Score (0 or 1)	Item	Response	Score (0 or 1)
1.	Saturday		8.	Hamlet	
2.	Age		9.	Brazil	
3.	Ball		10.	MLK	
4.	Months		11.	British Prime Minister	
START 5.	Thermometer		12.	Cleopatra	
6.	Sunrise		13.	Italy	
7.	Weeks		14.	Relativity	

9. Information *(continued)*

Item	Response	Score (0 or 1)	Item	Response	Score (0 or 1)
15.	Olympics		22.	Vessels	
16.	Sahara Desert		23.	Catherine	
17.	Genesis		24.	Continents	
18.	Sistine Chapel		25.	Curie	
19.	Gandhi		26.	World Population	
20.	Koran		27.	Speed of Light	
21.	Water		28.	Faust	

Total Raw Score (Maximum = 28)

PATIENT ID _____

CATEGORY SEQUENCE: C F N C F N

___ 1. C F N O	___ 17. C F N O	___ 33. C F N O	___ 49. C F N O
___ 2. C F N O	___ 18. C F N O	___ 34. C F N O	___ 50. C F N O
___ 3. C F N O	___ 19. C F N O	___ 35. C F N O	___ 51. C F N O
___ 4. C F N O	___ 20. C F N O	___ 36. C F N O	___ 52. C F N O
___ 5. C F N O	___ 21. C F N O	___ 37. C F N O	___ 53. C F N O
___ 6. C F N O	___ 22. C F N O	___ 38. C F N O	___ 54. C F N O
___ 7. C F N O	___ 23. C F N O	___ 39. C F N O	___ 55. C F N O
___ 8. C F N O	___ 24. C F N O	___ 40. C F N O	___ 56. C F N O
___ 9. C F N O	___ 25. C F N O	___ 41. C F N O	___ 57. C F N O
___ 10. C F N O	___ 26. C F N O	___ 42. C F N O	___ 58. C F N O
___ 11. C F N O	___ 27. C F N O	___ 43. C F N O	___ 59. C F N O
___ 12. C F N O	___ 28. C F N O	___ 44. C F N O	___ 60. C F N O
___ 13. C F N O	___ 29. C F N O	___ 45. C F N O	___ 61. C F N O
___ 14. C F N O	___ 30. C F N O	___ 46. C F N O	___ 62. C F N O
___ 15. C F N O	___ 31. C F N O	___ 47. C F N O	___ 63. C F N O
___ 16. C F N O	___ 32. C F N O	___ 48. C F N O	___ 64. C F N O

PATIENT ID _____

A

DRUM	DRUM	DRUM	DRUM	DRUM	DESK	DRUM
CURTAIN	CURTAIN	CURTAIN	CURTAIN	CURTAIN	RANGER	CURTAIN
BELL	BELL	BELL	BELL	BELL	BIRD	BELL
COFFEE	COFFEE	COFFEE	COFFEE	COFFEE	SHOVEL	COFFEE
SCHOOL	SCHOOL	SCHOOL	SCHOOL	SCHOOL	STOVE	SCHOOL
PARENT	PARENT	PARENT	PARENT	PARENT	MOUNTAIN	PARENT
MOON	MOON	MOON	MOON	MOON	GLASSES	MOON
GARDEN	GARDEN	GARDEN	GARDEN	GARDEN	TOWEL	GARDEN
HAT	HAT	HAT	HAT	HAT	CLOUD	HAT
FARMER	FARMER	FARMER	FARMER	FARMER	BOAT	FARMER
NOSE	NOSE	NOSE	NOSE	NOSE	LAMB	NOSE
TURKEY	TURKEY	TURKEY	TURKEY	TURKEY	GUN	TURKEY
COLOUR	COLOUR	COLOUR	COLOUR	COLOUR	PENCIL	COLOUR
HOUSE	HOUSE	HOUSE	HOUSE	HOUSE	CHURCH	HOUSE
RIVER	RIVER	RIVER	RIVER	RIVER	FISH	RIVER

TIME _____ KEY PATIENT ID _____

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1	2	3	4	5	6	7	8	9

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⌐	⊣	+	)	(	⊢	+	⌐	)	⊣	÷	÷	⊢	⌐	+

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⊣	÷	(	>	⌐	÷	(	>	÷	+	⊢	⊣	⌐	)	÷

TOTAL SCORE = ☐

Appendix I: Cross-Sectional Study Questionnaires

CITY UNIVERSITY LONDON

EST 1894

THE HEART HOSPITAL

Quality of Life in GUCH patients

Participant Questionnaire Booklet

Researcher Notes

Participant ID

Questionnaire - SF-36 (v1)

This questionnaire asks about **your personal views** about your health. The information will keep track of how you feel and how well you are able to do your usual activities.

Please answer every question by putting a cross in the box number that best corresponds to **you**. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2. Compared to one year ago, how would you rate your health **now** in general?

Much better than 1 year ago	Somewhat better than 1 year ago	About the same as 1 year ago	Somewhat worse now than 1 year ago	Much worse now than 1 year ago
☐	☐	☐	☐	☐

3. The following questions are about activities you might do during a typical day. Does **your health now** limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports.	☐	☐	☐
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.	☐	☐	☐
c. Lifting or carrying groceries.	☐	☐	☐
d. Climbing **several** flights of stairs.	☐	☐	☐
e. Climbing **one** flight of stairs.	☐	☐	☐

	Yes, limited a lot	Yes, limited a little	No, not limited at all
f. Bending , kneeling or stooping.	☐	☐	☐
g. Walking **more than a mile**.	☐	☐	☐
h. Walking **half a mile**.	☐	☐	☐
i. Walking **one hundred yards**.	☐	☐	☐
j. Bathing or dressing yourself.	☐	☐	☐

4. During the **past four weeks**, have you had any of the following problems in your work or other regular daily activities as a result of your **physical health** (tick one box on each line)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities.	☐	☐
b. Accomplished less than you would like.	☐	☐
c. Were limited in the kind of work and other activities.	☐	☐
d. Had difficulty performing the work and other activities (for example it took extra effort).	☐	☐

5. During the **past four weeks**, have you had any of the following problems in your work or other regular daily activities as a result of any **emotional problems** (such as feeling depressed or anxious)?

	Yes	No
a. Cut down on the amount of time you spent on work or other activities.	☐	☐
b. Accomplished less than you would like.	☐	☐
c. Didn't do work or other activities as carefully as usual.	☐	☐

6. During the **past four weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7. How much bodily pain have you had during the **past four weeks**?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8. During the **past four weeks**, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9. These questions are about how you feel and how things have been with you during the **past four weeks**. How much of the time during the **past four weeks:**

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐	☐	☐	☐	☐	☐
b. Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c. Have you felt so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d. Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e. Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f. Have you felt downhearted and low?	☐	☐	☐	☐	☐	☐
g. Did you feel worn out?	☐	☐	☐	☐	☐	☐
h. Have you been a happy person?	☐	☐	☐	☐	☐	☐
i. Did you feel tired?	☐	☐	☐	☐	☐	☐
j. Has your health limited your social activities?	☐	☐	☐	☐	☐	☐

10. How **true or false** each of the following statements is for **you**?

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a. I seem to get ill more easily than other people.	☐	☐	☐	☐	☐
b. I am as healthy as anybody I know.	☐	☐	☐	☐	☐
c. I expect my health to get worse.	☐	☐	☐	☐	☐
d. My health is excellent.	☐	☐	☐	☐	☐

Thank you for your responses to this questionnaire, please check that you have answered all the items.

Your responses will be kept confidential.

Questionnaire - PANAS

This scale consists of a number of words that describe different feelings and emotions. Read each item and put a cross in the box to the right of that word which indicates to what extent you ***generally*** feel...

I generally feel	Very slightly or not at all	A little	Moderately	Quite a bit	Extremely
1. Interested	☐	☐	☐	☐	☐
2. Distressed	☐	☐	☐	☐	☐
3. Excited	☐	☐	☐	☐	☐
4. Upset	☐	☐	☐	☐	☐
5. Strong	☐	☐	☐	☐	☐
6.Guilty	☐	☐	☐	☐	☐
7. Scared	☐	☐	☐	☐	☐
8. Hostile	☐	☐	☐	☐	☐
9. Enthusiastic	☐	☐	☐	☐	☐
10. Proud	☐	☐	☐	☐	☐
11. Irritable	☐	☐	☐	☐	☐
12. Alert	☐	☐	☐	☐	☐
13. Ashamed	☐	☐	☐	☐	☐
14. Inspired	☐	☐	☐	☐	☐
15. Nervous	☐	☐	☐	☐	☐
16. Determined	☐	☐	☐	☐	☐
17. Attentive	☐	☐	☐	☐	☐
18. Jittery	☐	☐	☐	☐	☐
19. Active	☐	☐	☐	☐	☐
20. Afraid	☐	☐	☐	☐	☐

Thank you for your responses to this questionnaire, please check that you have answered all the items.

Your responses will be kept confidential.

Questionnaire – STAI-6

A number of statements which people have used to describe themselves are given below. Read each statement and then put a **cross** in the appropriate box to indicate how you feel ***right now, at this moment***. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer that seems to describe your **present feelings** best.

Right now, at this moment

	Not at all	Somewhat	Moderately	Very Much
1. I feel calm.	☐	☐	☐	☐
2. I am tense.	☐	☐	☐	☐
3. I feel upset.	☐	☐	☐	☐
4. I am relaxed.	☐	☐	☐	☐
5. I feel content.	☐	☐	☐	☐
6. I am worried.	☐	☐	☐	☐

Thank you for your responses to this questionnaire, please check that you have answered all the items.

Your responses will be kept confidential.

Questionnaire- CESD-10

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the **past week** (please put a cross in one box on each row).

During the Past Week	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	All of the time (5-7 days)
1. I was bothered by things that don't usually bother me.	☐	☐	☐	☐
2. I had trouble keeping my mind on what I was doing.	☐	☐	☐	☐
3. I felt depressed.	☐	☐	☐	☐
4. I felt that everything I did was an effort.	☐	☐	☐	☐
5. I felt hopeful about the future.	☐	☐	☐	☐
6. I felt tearful.	☐	☐	☐	☐
7. My sleep was restless.	☐	☐	☐	☐
8. I was happy.	☐	☐	☐	☐
9. I felt lonely.	☐	☐	☐	☐
10. I could not "get going".	☐	☐	☐	☐

Thank you for your responses to this questionnaire, please check that you have answered all the items.

Your responses will be kept confidential.

Appendix J: Cross-Sectional Study Consent Form

University College London Hospitals NHS
NHS Foundation Trust

GUCH Office
The Heart Hospital
[redacted]
Tel: [redacted]
Nurses: [redacted]
Fax: [redacted]
Email: [redacted]
Website: www.uclh.org

UCLH Project ID number: 08/0326

CONFIDENTIAL
CONSENT FORM (Version 2-12/08)

Quality of life in GUCH patients.

Investigators:	Professor Stanton Newman, Professor John Deanfield, Dr Shay Cullen, Jan Stygall, Fiona Kennedy, Marie Francis, Nathalie Picaut, Katie Austin, Theodora Fteropoulli, Manavi Tyagi.
Contact details:	[redacted] Tel: [redacted]

Please read the following statements and initial box

1. I confirm that I have read and understand the information sheet (version2-12/08) for the above study and have had the opportunity to ask questions. ☐

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I understand that all data will be kept strictly confidential to this research and give permission for the above investigators to have access to my medical records. ☐

5. I agree to take part in the above study. ☐

Continued on next page/

UCLH Project ID number: 08/0326

CONFIDENTIAL
CONSENT FORM (Version 2-12/08)

Signed: _____ Date: _____

Full name in block letters: _____

Signed (investigator): _____ Date: _____

Full name in block letters: _____

Comments or concerns during the study.

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions either at your appointment or on (telephone number yet to be provided). If you remain unhappy and wish to complain formally you can do this through the Complaints Manager, UCLH, 2nd Floor West, 250, Euston Road, London NW1 2PQ. Please quote the UCLH project number at the top of this consent form.

1 form for patient
1 to be kept as part of the study documentation
1 to be kept with hospital notes

Appendix K: Cross-Sectional Study Missing Data

Variable	Missing data (%)
Clinical variables	
Age At Repair	11.8
Interventions Total	1.0
Repair total	1.6
Palliation total	1.6
Catheter lab total	1.6
Palliation before repair	1.6
RVEF	.0
LVEF	.0
Cyanosis Total	1.0
Current Saturation	1.3
ICU Total days	7.0
CPB Total minutes	11.1
HA Total minutes	13.4
In Hospital Days	2.5
Co-Morbidities Total	1.0
Arrhythmias	1.0
Hypertension	1.0
Medication Total	1.0
Yrs Since Last Intervention	2.9
Post-op CNS Complications	12.4
Post-op Infections	11.8
HF Clinic	1.0
NYHA classification	1.0
Pacemaker	1.0
ACE medication	1.0
Diuretic medication	1.0
BBlocker medication	1.0
Anti Arrythmia medication	1.0
Anticoagulant medication	1.0
Category	.0
RepairsTotal	2.5
PalliationsTotal	2.5
Cath LabsTotal	2.5
Palliation before repair	2.5
NP measures	
PegDom Tim	1.3
PegNonDoTime	2.5
WCST Errors	2.5
WCS Conceptual Level	2.5
WCT No Categories	2.5
WST Trials1stCategory	2.5
CST Failure To Maintain Set	2.5
RAVLT TRIAL 1	1.6
RAVLT TRIAL 2	2.9
RAVLT TRIAL 3	14.0

Variable	Missing data (%)
RAVLT TRIAL 4	28.3
RAVLT TRIAL 5	48.1
RAVLT TRIAL 6	1.9
RAVLT TRIAL 7	1.6
Psychosocial measures	
SF36_PhysicalFunctioning_2	3.5
SF36_PhysicalFunctioning_3	3.5
SF36_PhysicalFunctioning_4	3.5
SF36_PhysicalFunctioning_5	3.5
SF36_PhysicalFunctioning_6	3.5
SF36_PhysicalFunctioning_7	3.8
SF36_PhysicalFunctioning_8	4.1
SF36_PhysicalFunctioning_9	4.1
SF36_PhysicalFunctioning_10	3.5
SF36_RolePhysical_1	3.8
SF36_RolePhysical_2	3.8
SF36_RolePhysical_3	4.1
SF36_RolePhysical_4	3.8
SF36_RoleEmotional_1	4.1
SF36_RoleEmotional_2	3.8
SF36_RoleEmotional_3	3.8
SF36_SocialFunctioning_1	3.8
SF36_Pain_1	3.5
SF36_Pain_2	3.5
SF36_Vitality_1	3.8
SF36_MentalHealth_1	3.8
SF36_MentalHealth_2	3.5
SF36_MentalHealth_3	3.8
SF36_Vitality_2	3.5
SF36_MentalHealth_4	3.8
SF36_Vitality_3	3.5
SF36_MentalHealth_5	3.8
SF36_Vitality_4	3.5
SF36_SocialFunctioning_2	3.5
SF36_GeneralHealthPerception_2	3.8
SF36_GeneralHealthPerception_3	4.1
SF36_GeneralHealthPerception_4	3.8
SF36_GeneralHealthPerception_5	3.8
PANAS_PA_1	3.8
PANAS_NA_1	4.1
PANAS_NA_2	3.8
PANAS_PA_3	4.5
PANAS_NA_3	4.1
PANAS_NA_4	3.8
PANAS_NA_5	4.1
PANAS_PA_4	3.8
PANAS_PA_5	3.8

Variable	Missing data (%)
PANAS_NA_6	4.5
PANAS_PA_6	4.8
PANAS_NA_7	4.1
PANAS_PA_7	3.8
PANAS_NA_8	3.8
PANAS_PA_8	4.1
PANAS_PA_9	4.1
PANAS_NA_9	4.1
PANAS_PA_10	3.8
PANAS_NA_10	3.8
STAI_1	3.5
STAI_2	3.5
STAI_3	3.5
STAI_4	3.5
STAI_5	3.5
STAI_6	3.5
CESD10_1	4.5
CESD10_2	3.8
CESD10_3	4.1
CESD10_4	4.1
CESD10_5	4.1
CESD10_6	4.1
CESD10_7	4.5
CESD10_8	4.1
CESD10_9	4.1
CESD10_10	4.5
Demographic variables	
Years of Education	3.5
Gender	.0
Ethnicity	.0
Marital Status	.0
Living Status	.0
Employment Status	3.5
Occupation Category	3.5

NYHA= New York Health Assessment, CNS= Central Nervous System, Q=Quartile, CPB= Cardio Pulmonary Bypass, ACE= Angiotensin-Converting-Enzyme Inhibitor, RVEF= Right Ventricular Ejection Fraction LVEF= Left Ventricular Ejection Fraction.

Appendix L: Cross-Sectional Study Kolmogorov-Smirnov Test Results

Kolmogorov-Smirnov test results for the clinical variables

Variables	Kolmogorov-Smirnov	
	Statistic	p value
Age at repair	0.263	<0.001
Interventions total	0.259	<0.001
Repair Surgeries total	0.373	<0.001
Palliation Interventions total	0.398	<0.001
Catheter lab interventions total	0.309	<0.001
Palliation Before Repair	0.344	<0.001
Years Since Last Operation	0.135	<0.001
Cyanotic Days Total	0.316	<0.001
Current Saturation	0.266	<0.001
Intensive Care Unit Days	0.188	<0.001
Peri-Op Cardiopulmonary Bypass Minutes	0.102	<0.001
Peri-Op Hypothermic Arrest Minutes	0.138	<0.001
Post-Op CNS Complications	0.539	<0.001
Post-Op Infection	0.469	<0.001
Post-Op Ventricular Dysfunction	0.533	<0.001
Hospitalisation Days	0.231	<0.001
Heart Failure Clinic	0.501	<0.001
Co-Morbidities Total	0.244	<0.001
Arrhythmias	0.461	<0.001
Hypertension	0.529	<0.001
Medication Total	0.356	<0.001
Pacemaker	0.548	<0.001
ACE inhibitor Medication	0.485	<0.001
Diuretic Medication	0.526	<0.001
B-Blocker Medication	0.505	<0.001
Anti-Arrhythmic Medication	0.525	<0.001
Anti-Coagulant Medication	0.469	<0.001
NYHA classification	0.509	<0.001
LVEF	0.153	<0.001
RVEF	0.132	<0.001

Note- CNS- Central Nervous System, ACE-angiotensin converting enzyme, NYHA- New York Health Association, LVEF- Left Ventricular Ejection Fraction, RVEF- Right Ventricular Ejection Fraction
Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov test results for the psychosocial variables (Scaled scores)

Variables	Kolmogorov-Smirnov	
	Statistic	p value
SF-36 Physical Functioning	0.219	<0.001
SF-36 Role Physical	0.403	<0.001
SF-36 Bodily Pain	0.279	<0.001
SF-36 General Health	0.107	<0.001
SF-36 Vitality	0.112	<0.001
SF-36 Social Functioning	0.263	<0.001
SF-36 Role Emotional	0.432	<0.001
SF-36 Mental Health	0.126	<0.001
Physical component summary	0.132	<0.001
Mental component summary	0.151	<0.001
PANAS- Positive affect	0.093	<0.001
PANAS- Negative affect	0.143	<0.001
Sum STAI	0.125	<0.001
Sum CESD-10	0.156	<0.001

Note- SF= Short Form, PANAS= Positive and Negative Scale, STAI= State and Trait Anxiety Inventory, CESD= Centre for Epidemiology Short Depression Scale,
Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov test results for the demographic variables

Variables	Kolmogorov-Smirnov	
	Statistic	p value
Employment status	0.435	<0.001
Occupation Category	0.473	<0.001
Gender	0.373	<0.001
Ethnicity	0.511	<0.001
Marital Status	0.346	<0.001
Living Status	0.509	<0.001
Total Years in Education	0.224	<0.001
Age	0.122	<0.001

Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov test results for the Neuropsychological test scores (raw scores)

Variables	Kolmogorov-Smirnov	
	Statistic	p value
Trail Making Test A	0.132	<0.001
Trail Making Test B	0.118	<0.001
Controlled Oral Word Association Test - F	0.091	<0.001
Controlled Oral Word Association Test – A	0.075	<0.001
Controlled Oral Word Association Test – S	0.094	<0.001
Stroop colour correct	0.489	<0.001
Stroop word correct	0.233	<0.001
WAIS-III – Arithmetic	0.086	<0.001
WAIS-III – Information	0.088	<0.001
WAIS-III – Digit symbol	0.052	0.039
Grooved pegboard time – Dominant hand	0.118	<0.001
Grooved pegboard time – Non-Dominant hand	0.143	<0.001
WCST- Error	0.129	<0.001
WCST-Conceptual level	0.134	<0.001
WCST-No. categories	0.184	<0.001
WCST-trials to complete first category	0.395	<0.001
WCST-failure to maintain set	0.419	<0.001
Rey Auditory Verbal Learning Test – Trial 1	0.133	<0.001
Rey Auditory Verbal Learning Test – Trial 2	0.115	<0.001
Rey Auditory Verbal Learning Test – Trial 3	0.156	<0.001
Rey Auditory Verbal Learning Test – Trial 4	0.164	<0.001
Rey Auditory Verbal Learning Test – Trial 5	0.152	<0.001
Rey Auditory Verbal Learning Test – Trial 6	0.125	<0.001
Rey Auditory Verbal Learning Test – Trial 7	0.141	<0.001
Symbol Digit Modalities Test – written	0.048	0.076
Symbol Digit Modalities Test – oral	0.038	0.200

Note- WCST- Wisconsin Card Sorting Test, WAIS- Wechsler Adult Intelligence Scale
Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution

Appendix M: Normative Data Mean Scores for the Neuropsychological Test Battey used

Normative data scores for the Trail making test A and B

TMT age groups		Trail making A		Trail making B	
		Normative data	Study sample score	Normative data	Study sample score
18-24 years	Mean	22.93	29.46	48.97	64.51
	Std. Deviation	6.87	10.293	12.69	23.977
	N	155	65	155	65
	Education	12.92 (1.01)	14.28(2.72)	12.92 (1.01)	14.28(2.72)
25-34 years	Mean	24.40	31.51	50.68	61.16
	Std. Deviation	8.71	11.891	12.36	19.370
	N	33	135	33	128
	Education	14.18 (1.61)	14.61(2.86)	14.18 (1.61)	14.61(2.86)
35-44 years	Mean	28.54	31.97	58.46	63.83
	Std. Deviation	10.09	9.706	16.41	21.127
	N	39	67	39	65
	Education	13.59 (2.06)	13.23(3.11)	13.59 (2.06)	13.23(3.11)
45-54 years	Mean	31.78	33.68	63.76	58.74
	Std. Deviation	9.93	15.283	14.42	16.802
	N	41	25	41	23
	Education	13.68 (2.80)	13.88(3.44)	13.68 (2.80)	13.88(3.44)
55-59 years	Mean	31.72	38.29	68.74	72.14
	Std. Deviation	10.14	9.742	21.02	27.619
	N	37	7	37	7
	Education (12+ years)	15.32 (1.93)	12.43(1.81)	15.32 (1.93)	12.43(1.81)
60-64 years	Mean	33.22	41.00	74.55	82.00
	Std. Deviation	9.10	9.648	19.55	36.241
	N	86	11	86	11
	Education (0-12 years)	10.84 (1.27)	10.33(0.81)	10.84 (1.27)	10.33(0.81)
65-69 years	Mean	39.14	42.6	91.32	118.67
	Std.Deviation	11.84	7.09	28.89	53.17
	N	65	3	65	3
	Education (0-12 years)	10.87 (1.71)	6.50	10.87 (1.71)	6.50
75-79 years	Mean	41.74	33.50	100.68	65.5
	Std.Deviation	15.32	23.33	44.16	44.54
	N	34	2	34	2
	Education (12+ years)	15.29 (1.80)	14.50	15.29 (1.80)	14.50

*No participants in age group 70-74 in study sample therefore not included in table

Normative data for the Stroop Neuropsychological Screening Test

Age groups		Stroop colour no correct		Stroop word no correct	
		Normative data	Study sample	Normative data	Study sample
15-49 years	Mean	111.94	111.81	104.90	101.55
	Std. Deviation	0.23	.840	10.22	15.634
	N	106	278	106	275
50+ years	Mean	111.92	111.79	93.98	95.28
	Std. Deviation	0.27	.774	18.41	16.699
	N	50	29	50	29

Normative data scores for the symbol digit modalities test

Age groups		Symbol digit copy		Symbol digit Oral	
		Normative data	Study sample	Normative data	Study sample
18-24 years	Mean	55.2	54.20	62.7	66.09
	Std. Deviation	7.5	10.393	9.1	14.675
	N	69	65	69	65
25-34 years	Mean	53.6	54.10	61.2	64.90
	Std. Deviation	6.6	11.985	7.8	12.821
	N	72	135	72	135
35-44 years	Mean	51.1	52.52	59.7	61.39
	Std. Deviation	8.1	9.963	9.7	10.982
	N	76	67	76	67
45-54 years	Mean	46.8	50.68	54.5	60.36
	Std. Deviation	8.4	8.577	9.1	12.741
	N	75	25	75	25
55-64 years	Mean	41.5	46.77	48.4	55.54
	Std. Deviation	8.6	12.995	9.1	16.384
	N	67	13	67	13
65-75 years	Mean	37.4	44.80	46.2	53.60
	Std. Deviation	11.4	22.231	12.8	31.667
	N	61	5	61	5

Normative data scores for the grooved pegboard test

Age Groups		Peg dominant hand time		Peg Non-dominant hand time	
		Normative data	Study sample	Normative data	Study sample
15-19 years	Mean	66.05	72.45	70.50	78.18
	Std. Deviation	10.40	16.597	11.10	18.600
	N	172	11	172	11
20-29 years	Mean	63.40	71.11	69.10	79.36
	Std. Deviation	7.90	12.700	18.70	18.971
	N	*	122	*	121
30-39 years	Mean	62.95	71.38	67.15	76.96
	Std. Deviation	8.40	14.562	12.20	16.008
	N	319	109	319	106
40-49 years	Mean	63.50	75.23	69.05	80.21
	Std. Deviation	7.20	17.600	9.80	15.215
	N	319	39	319	39
50-59 years	Mean	68.10	70.33	74.70	77.44
	Std. Deviation	9.42	9.456	10.51	12.430
	N	134	18	134	18
60+ years	Mean	82.70	81.09	87.95	105.00
	Std. Deviation	18.70	14.003	26.20	27.796
	N	100	11	100	11

*Data not available

Normative data scores for the WCST-64 test

WCST age groups		WCST Errors		WCST Conceptual Level		WCST No. Categories		WCST Trials1st Category		WCST Failure to Maintain set	
		Norms	Study sample	Norms	Study sample	Norms	Study sample	Norms	Study sample	Norms	Study sample
18-19 years	Mean	16.24	14.82	42.94	45.09	3.39	3.82	14.53	11.18	0.42	0.18
	SD	8.78	5.896	13.75	7.930	1.38	.982	9.57	1.328	0.78	.405
	N	62	11	62	11	62	11	62	11	62	11
20-29 years	Mean	13.10	16.75	48.07	43.01	3.90	3.42	11.67	12.84	0.39	0.34
	SD	6.69	8.527	9.19	11.624	1.16	1.347	2.44	7.611	0.76	.625
	N	67	122	67	122	67	122	67	122	67	122
30-39 years	Mean	12.16	16.74	48.89	43.28	4.10	3.38	13.05	11.88	0.30	0.49
	SD	7.90	7.966	10.92	11.312	1.25	1.380	8.17	3.426	0.80	.823
	N	63	109	63	109	63	109	63	109	63	109
40-49 years	Mean	12.02	19.95	49.30	38.95	4.21	3.11	12.95	15.89	0.27	0.30
	SD	7.82	9.866	11.18	13.317	1.26	1.410	7.92	14.375	0.60	.520
	N	63	37	63	37	63	37	63	37	63	37
50-59 years	Mean	13.69	19.35	47.37	39.65	3.91	3.06	13.58	12.82	0.30	0.41
	SD	7.70	6.264	10.77	10.295	1.29	1.144	9.37	6.277	0.58	.712
	N	67	17	67	17	67	17	67	17	67	17
60-64 years	Mean	17.64	17.00	41.92	41.00	3.20	3.40	13.00	11.20	0.56	0.00
	SD	9.03	7.810	12.34	11.247	1.47	1.517	5.64	.837	0.92	.000
	N	25	5	25	5	25	5	25	5	25	5
65-69 years	Mean	20.53	31.33	37.84	22.33	2.75	1.67	20.06	18.33	0.50	0.33
	SD	10.96	9.292	15.61	8.083	1.52	.577	16.73	3.055	0.72	.577
	N	32	3	32	3	32	3	32	3	32	3
75-79 years	Mean	26.56	10.00	28.88	51.50	1.81	4.50	18.81	10.00	0.63	0.00
	SD	8.76	4.243	11.37	3.536	0.91	.707	15.14	.000	0.81	.000
	N	16	2	16	2	16	2	16	2	16	2

*No participants in age group 70-74 in study sample therefore not included in table

Normative data scores for the WAIS –III (Scaled Scores equivalents for the mean raw score of study sample)

WAISIII Age group categories		Mental Arithmetic		Information		Digit Symbol	
		Scaled Score comparison	Study sample score	Scaled Score comparison	Study sample score	Scaled Score comparison	Study sample score
18-19 years	Mean	11	14.27	10	14.45	9	74.55
	Std. Deviation		3.771		7.353		23.114
	N		11		11		11
20-24 years	Mean	10	12.69	11	15.89	9	75.33
	Std. Deviation		3.705		5.712		12.921
	N		54		54		54
25-29 years	Mean	10	11.78	11	16.22	9	74.37
	Std. Deviation		4.288		5.843		15.708
	N		68		67		68
30-34 years	Mean	10	12.61	11	17.15	10	75.88
	Std. Deviation		4.034		5.249		16.922
	N		67		67		67
35-44 years	Mean	9	12.34	10	16.57	9	70.28
	Std. Deviation		4.198		4.890		15.081
	N		67		67		67
45-54 years	Mean	9	13.32	10	18.16	10	68.80
	Std. Deviation		4.432		4.810		13.748
	N		25		25		25
55-64 years	Mean	9	12.46	11	17.69	11	68.46
	Std. Deviation		4.719		4.768		17.343
	N		13		13		13
65-69 years	Mean	6	7.67	9	14.67	9	50.67
	Std. Deviation		1.528		4.041		20.648
	N		3		3		3
70-74 years	Mean	12	14.50	13	22.00	18	86.00
	Std. Deviation		3.536		1.414		46.669
	N		2		2		2

Normative data for the Controlled Oral Word Association Test

Age groups		Controlled Oral Word Association test	
		Normative data	Study sample
16-59 years	Mean	111.94	111.81
	Std. Deviation	0.23	.840
	Education [range/mean (SD)]	16-59	13.52 (2.79)
	N	242	278
60-79 years	Mean	111.92	111.79
	Std. Deviation	0.27	.774
	Education [range/mean (SD)]	9-12	9.90 (2.13)
	N	292	29

Normative data for the Rey Auditory Verbal Learning Test

Age groups		Rey auditory verbal learning test	
		Normative data	Study sample
16-19 years	Mean	53.90	56.81
	Std. Deviation	6.70	11.11
	N	78	11
20-29 years	Mean	56.10	58.96
	Std. Deviation	7.30	6.75
	N	498	123
30-39 years	Mean	53.60	58.81
	Std. Deviation	8.30	6.75
	N	1,081	109
40-49 years	Mean	51.10	55.20
	Std. Deviation	8.60	9.48
	N	522	39
50-59 years	Mean	47.60	54.11
	Std. Deviation	8.10	10.20
	N	161	18
60-69 years	Mean	43.40	50.55
	Std. Deviation	7.70	10.33
	N	166	9
70-79 years	Mean	37.10	46.00
	Std. Deviation	7.50	9.73
	N	143	1

Appendix N: Univariate Screening for Factors Associated with Cognitive Outcomes for the Total Study Sample and the Four Structural Complexity Groups

Univariate regression (screening) for factors associated with cognitive functioning in the total study sample (all groups combined)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP-W (β)	WAIS-III (β)	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NO CAT (β)	FTM (β)	TTC (β)	SDMTW (β)	SDMT-O (β)	RAVLT (β)
Age	-.157**	-.194**	.169**	-.022	-.018	-.041	.045	.092	-.086	-.113*	.022	-.019	.075	-.025	.104
Education (yrs)	-.065	-.175**	.286***	.238***	.531***	-.181**	-.155**	-.311***	.294***	.288***	-.071	-.126*	.303***	.257***	.258***
Gender (Males)	-.011	-.032	.038	.035	.068	.173**	.114*	.023	-.050	-.094	.074	-.064	-.081	-.076	-.232***
Employment	-.062	-.200***	.090	.160**	.142*	-.017	-.015	-.045	.070	.025	-.012	-.069	.215***	.103	-.001
ToF vs. Simple	.071	.210**	-.108	-.117*	-.154	.151*	.094	.147	-.147	-.212**	.136	.027	-.150	-.096	.013
TGA vs. Simple	.138	.161*	-.122	-.162*	-.147	.158*	.141	.119	-.130	-.181**	.086	.050	-.125	-.078	-.079
SV vs. Simple	.124	.206**	.028	-.196**	-.101	.172*	.116	.075	-.083	-.120*	.080	.107	-.103	-.030	-.007
Arrhythmia	.023	.055	.059	-.119*	-.081	.001	.045	.072	-.095	-.122*	.044	.030	-.021	-.066	-.001
Hypertension	-.107	-.078	.007	-.012	-.015	-.070	-.071	.096	-.103	-.065	-.046	.015	.061	.017	-.155**
NYHA	.032	.112*	-.058	-.120*	-.136*	.033	.097	.087	-.086	-.120*	.132*	.106	-.090	-.093	-.032
Interventions total	.061	.159**	.007	-.042	-.171**	.031	.012	.071	-.080	-.106	.072	.038	-.116*	-.084	.083
Repair total	-.009	.024	.016	.002	-.044	-.012	-.045	.102	-.102	-.107	.155**	-.019	-.030	-.020	-.008
Palliation before repair	.094	.119*	-.065	-.144*	-.162**	.111	.107	.144*	-.146*	-.203	.099	.101	-.144*	-.067	-.024
Years since last operation	-.043	-.116*	.010	.012	.055	.022	.053	-.015	.011	-.023	.098	-.019	.069	.044	.027

Univariate regression (screening) for factors associated with cognitive functioning in the total study sample (all groups combined)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP-W (β)	WAIS-III (β)	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NO CAT (β)	FTM (β)	TTC (β)	SDMTW (β)	SDMT-O (β)	RAVLT
Post-op CNS	.096	.188**	-.135*	-.244**	-.284***	.096	.127*	.245***	-.273***	-.238***	-.057	.293**	-.224***	-.171**	-.103
Post-op infection	.088	.157**	-.091	-.184**	-.188**	.088	.153**	.156**	-.187	-.204***	.086	.105	-.202***	-.115*	-.099
Post-op VD	.022	.087	.049	-.121*	-.047	.022	-.044	.028	-.040	-.082	.055	-.027	-.052	-.069	-.043
HF clinic	.076	.098	-.046	-.159**	-.148**	.087	.119*	.093	-.099	-.125*	.071	.031	-.073	-.100	-.096
Pacemaker	.138*	.084	.067	-.056	-.097	-.014	.013	.044	-.033	-.027	.031	-.003	-.072	-.067	-.048
ACE medication	.024	.035	-.067	-.109	-.140*	.123*	.186**	.097	-.109	-.127*	.034	.007	.000	-.100	-.186**
Diuretic medication	.101	.001	-.062	-.108	-.162**	.061	.121*	.180**	-.180**	-.179**	.031	.217*	-.098	-.075	-.047
Beta blocker medication	.064	-.041	-.009	-.071	-.013	.041	.010	.086	-.070	-.118*	.069	.071	.021	-.014	-.026
Anti-arrythmia medication	.088	.025	.044	-.049	-.081	.023	.090	.110	-.134*	-.162**	.034	.153**	-.082	-.064	-.016
Anti-coagulant medication	.060	.056	.041	-.081	-.097	.012	.026	.089	-.080	-.079	-.032	.140*	-.039	-.065	-.002
RVEF	-.030	-.079	.034	.089	.131*	-.035	-.035	-.101	.096	.144*	-.131*	-.099	.062	.071	.055
LVEF	-.022	-.107	.019	.108	.107	-.025	-.023	-.154**	.160**	.190**	-.113*	-.140*	.071	.092	.003
Palliation total	.097	.099	.032	-.091	-.095	.094	.111	.078	-.084	-.131*	.076	.094	-.044	.017	.061
Catheter lab total	.000	.083	-.036	-.002	-.133*	-.064	-.046	.069	-.074	-.115*	.007	.025	-.115	-.088	-.101
Medication total	.040	.063	.033	-.122*	-.108	.051	.092	.135*	-.134*	-.175**	.024	.140*	-.035	-.101	-.041

Univariate regression (screening) for factors associated with cognitive functioning in the total study sample (all groups combined)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP-W (β)	WAIS-III (β)	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NOCAT (β)	FTM (β)	TTC (β)	SDMTW (β)	SDMT-O (β)	RAVLT
Age at repair Q2	0.058	-0.03	-0.016	0.089	0.129	0.028	0.056	0.07	0.013	0.052	0.146	-0.087	0.224	0.300	0.138
Age at repair Q3	-0.112	-0.187	-0.167*	0.019	-0.088	0.09	0.193	0.103	-0.002	-0.076	0.103	0.213	0.103	0.019	0.109
Age at repair Q4	-0.03	-0.275	0.063*	-0.088	-0.159	0.013	0.077	-0.019	0.058	0.069	0.044	-0.11	0.12	0.149	0.385
Cyanosis days Q2	0.109	-0.057*	-0.007	0.045	0.07	-0.057	-0.011	0.06	-0.068	-0.083	0.095	-0.019	-0.027	0.15	0.056
Cyanosis days Q3	0.006	-0.234**	0.118*	0.205	0.028	0.023*	0.094	0.12	-0.056	-0.063*	0.068	0.179	0.021	0.114	0.141
Cyanosis days Q4	-0.101	-0.199	0.047*	0.089	-0.056	0.125*	0.334	0.14	-0.122	-0.123*	-0.034	0.007	-0.01	0.072	0.153
Current saturation Q1	0.027*	0.001	0.062	-0.035*	-0.02	0.113	0.029	0.202	-0.2	-0.21	0.05	0.151	-0.059*	-0.04	0.15
Current saturation Q2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Current saturation Q3	-0.189**	-0.232*	0.157	0.001	0.154	-0.03	-0.129	-0.075	0.082	0.036	0.115	0.042	0.199	0.088	0.121
ICU days Q2	0.08	-0.075	-0.041	0.155	-0.061	0.003	0.195	0.187	-0.107	-0.228	0.135	0.252	-0.041	-0.089	0.136
ICU days Q3	-0.121	-0.134	-0.135	0.135	-0.195	0.012	0.092	0.142	-0.129	-0.235	0.033	0.159	-0.033	-0.041	0.033
ICU days Q4	-0.019	0.036	-0.079	0.05	-0.208	0.117	0.248	0.147	-0.132	-0.166	0.086	0.181	-0.129	-0.169	-0.021
CPB minutes Q2	0.037	-0.18	-0.191	0.143	0.061	0.005**	-0.199	-0.08	0.052	0.057	-0.099	-0.068	0.121	-0.002	0.14
CPB minutes Q3	0.037	-0.21	-0.067	0.313	0.153	-0.063*	-0.158	-0.085	0.066	0.057	-0.156	-0.065	0.177	0.217	0.011
CPB minutes Q4	0.037	-0.21	-0.299	0.085	-0.121	-0.049	-0.086	-0.015	-0.02	-0.134	-0.093	0.201	0.02	0.054	-0.035
HA minutes Q2	0.227	0.013*	0.097	-0.252	0.094	0.122	-0.055	-0.058	0.00	0.056	-0.053	-0.109	0.017	0.074	-0.108
HA minutes Q3	-0.115	-0.121	0.169	-0.053	0.227	-0.093	-0.131	-0.126	0.052	0.078	-0.181	-0.05	0.203	0.214	0.026

Univariate regression (screening) for factors associated with cognitive functioning in the total study sample (all groups combined)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP-W (β)	WAIS-III (β)	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NO CAT (β)	FTM (β)	TTC (β)	SDMTW (β)	SDMT-O (β)	RAVLT
HA minutes Q4	0.031	-0.057*	0.096	-0.149	0.051	-0.035	-0.063	0.078	-0.097	-0.075	-0.121	-0.069	0.017	0.083	0.017
In hospital days Q2	-0.275*	-0.285*	0.014	0.093*	-0.059*	0.012	-0.031	0.348*	-0.35**	-0.261	0.137	-0.087	0.025	-0.058	-0.059
In hospital days Q3	-0.255	-0.293*	-0.052	0.073	0.011**	-0.226	-0.13	0.286*	-0.273*	-0.28*	-0.006	0.133	0.117**	0.123	0.163
In hospital days Q4	-0.123	-0.233	0.01	0.193	-0.016	-0.07	0.015	0.219	-0.217	-0.28*	0.081	0.196	0.083*	0.067	0.025
PANAS PA	-.058	-.217***	.163**	.165**	.260***	-.158**	-.141*	-.113*	.109	-.075	.063	.076	.249***	.266***	.167*
PANAS NA	-.023	.089	.025	-.216***	-.156**	-.053	-.081	.078	-.074	.126	-.033	-.081*	-.086	-.086	-.035
STAI	.044	.124*	-.071	-.266***	-.204***	.055	.059	.108	-.092	.057	-.104	-.014	-.088	-.118*	-.046
CESD	.011	.073	-.059	-.183**	-.174**	.022	-.022	.111	-.103	.152	-.062	-.086*	-.120*	-.135*	-.080

Note - * p<0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Univariate regression (screening) for factors associated with cognitive functioning in the ToF sample

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NOCAT (β)	TTC (β)	FTM (β)	SDMTW (β)	SDMTO (β)	RAVLT
Age	-.103	-.264*	.063	-.047	-.122	-.035	.086	.098	-.090	-.170	.061	.179*	.119	-.022	.282
Education (years)	-.020	-.269*	.324	.321**	.596	-.219	-.102	-.315**	.327**	.288	-.176	.010*	.394**	.310	.264*
Gender (Males)	.005	-.124	.131	.249*	.596	.006	.109	.091	-.130	-.193	-.011*	.301**	.092	.088	-.255
Employment	.011	-.330**	.030	.209	.145	-.070	-.028	-.007	.050	-.010	-.047	.094	.326	.153	-.091*
Arrhythmia	-.074	.084	.067	-.164	-.187	-.028	.149	.161	-.156*	-.229	.045	.217	-.139**	-.239	-.009
Hypertension	-.045	.000	.141	.024	-.117	.012	.188	-.127	.134	.153	-.024	-.076	.008	-.121	.039
NYHA	.035	.162	-.135	.056	-.184	-.015	.031	.231*	-.218*	-.319	.207*	.281	-.212	-.181	-.056
Interventions total	-.034	.040	-.003	.052	-.108	-.118	.006	.174	-.193	-.177	-.019	.054	-.083	-.073	.043
Repair total	.025	.116	-.061	.027	-.069	-.031	.030	.128	-.144	-.142	-.040	.081	-.018	-.131	-.130
Palliation before repair	-.004	-.108	.021	.003	-.025	.027	.065	.154	-.157	-.144	.059	.035*	.018	.064	.230
Yrs since last intervention	-.017	-.208	.081	-.048	.111	.018	-.066	-.050	.057	.058	.064	.049	.142	.136	.215
Post-opCNs complication	-.023	.165	.046	-.320**	-.111	-.099	-.129	.023	-.034	-.037	-.077	-.045	-.147	-.093	.025
Post-op infection	-.106	.021	-.048	.055	-.056	-.085	-.031	.108	-.142	-.189	-.019	.095	.025	-.011	-.040
Post-op VD	.008	.109	.013	-.245*	.009	-.013	.022	-.007	.003	-.132	-.090*	.241	-.092	-.075	-.096
HF clinic	-.069	-.126	.056	.016	.076	-.069	.024	.060	-.078*	-.284	.037*	.343	.062	.053	.032
ACE medication	-.065	-.015	-.112	.107	-.111	.077	.223*	.134	-.130*	-.221*	.232	.216	-.075	-.063	-.015
Diuretic medication	-.048	.041	-.207	.108	-.095	-.063	.081	.083	-.094	-.155	.209	.076	-.088	.060	.069
Beta blocker medication	.015	-.055	.146	-.031	-.027	-.077	.033	.035	-.035	-.140	-.095*	.258	-.029	-.165	.009

Univariate regression (screening) for factors associated with cognitive functioning in the ToF sample (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NOCAT (β)	TTC (β)	FTM (β)	SDMTW (β)	SDMTO (β)	RAVLT
Anti-arrythmia medication	-.043	-.079	.137	.072	.103	-.165	-.036	.015	-.038	-.189	-.092	.211	.007	.010	.071
Anti-coagulant medication	.074	.082	-.139	.096	-.167	-.020	.036	.095	-.054	-.107*	.233*	.243	-.126	-.099	-.039
RVEF	.024	-.029	-.020	-.123	.033	.060	-.002	-.004	-.035	.033	-.007	-.097	.012	.046	.054
LVEF	.008	-.094	.011	-.011	.102	.060	-.050	-.123	.162*	.231	-.182	-.151	.129	.127	.014
Palliation total	.025	-.096	.033	-.013	-.016	.046	.078	.179	-.184	-.159	.067	.018**	.001	.063	.233
Catheter lab total	-.065	.023	.054	.146	-.062	-.130	-.034	.068	-.092	-.150	-.023	.116	-.084	-.012	-.021
Medication total	-.017	.036	.040	.062	-.169	-.049	.146	.125	-.098*	-.265	.150*	.336	-.114	-.103	.041
Age at repairQ2	.002	-.253	-.242	.287	.233	-.239	-.243	.116	-.006	-.046	-.013	-.014	.165	.302	.149*
Age at repairQ3	-.192	-.282	-.291	.129	-.051	-.108	-.002	.144	-.033	-.125	.044	.140	.111	.144	.225*
Age at repairQ4	.093	-.204	.113	-.016	-.057	-.188	-.087	-.035	.102	.065	-.083	-.053	.061	.110	.319*
Cyanosis days Q2	-.329	-.750	-.025	1.886	.895	.096	-.136*	-.099	.068	.123	.131	.109	1.258	.715	-.270
Cyanosis days Q3	-.393	-1.127	.010	2.383	1.093	.008	-.175*	-.046	.030	.014	.256	.337	1.510	.994	-.194
Cyanosis days Q4	-.549	-1.141	.095	2.242	.986	.171	.059*	.000	.029	.057	.101	.250	1.455	.945	-.026
Current saturationQ1	.089	.232	-.084	-.067	-.188	.204	.086	.304	-.310	-.236	.147	.007	-.286	-.231	.025
Current saturationQ2	-.034	-.182	.152	.005	.122	-.006	-.028	.035	-.029	-.101	-.048	.202	.147	.128	.186
Current saturationQ3	-.189	-.232	.157	.001	.154	-.030	-.129	-.075	.082	.036	.115	.042	.199	.088	.121
ICU days Q2	-.124	-.389	.341	.088	.198	-.221	.030	-.065	.123	.018	.144	.276	.168	.271	.241

Univariate regression (screening) for factors associated with cognitive functioning in the ToF sample (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NO CAT (β)	TTC (β)	FTM (β)	SDMT W (β)	SDMT O (β)	RAVLT
ICU days Q3	-.231	-.360	.103	.135	-.043	-.133	.039	.030	-.009	-.138	.077	.245	.093	.170	.140
ICU days Q4	-.129	-.190	.159	.050	-.056	-.029	.196	.036	-.012	-.069	.130	.267	-.003	.042	.086
CPB minutes Q2	.056	.077	.037	.001	.056	.147	.060	-.020	.043	.169	.140	-.295	-.004	-.002	.042
CPB minutesQ3	-.002	-.335	.189	.233	.247	-.086	-.126	-.182	.230	.220	-.014	-.101	.313	.217	.171
CPB minutes Q4	-.032	-.025	.069	.213	.147	-.056	-.526	-.132	.130	.203	-.017	-.103	.013	.054	.134
HA minutes Q2	.277	.433	.035	-.257	-.411	.189	.165	-.105	.030	.160	-.027	-.220	-.447	-.241	-.193
HA minutes Q3	.106	.183	.219	-.160	-.101	-.062	-.060	-.341	.283	.346	-.189	-.195	-.125	.057	.007
HA minutes Q4	.112	.210	.079	-.218	-.272	-.029	.028	-.029	-.004	.061	-.132	-.159	-.273	-.078	-.028
In hospital Days Q2	-.133	.061	.149	-.027	-.150	-.150	.030	.196	-.246	-.141	.071	-.100	-.232	-.387	.024
In hospital days Q3	-.358	-.146	-.096	-.091	-.169	-.206	.064	.426	-.428	-.404	.182	.077	-.102	-.265	.023
In hospital days Q4	-.225	-.130	.155	.108	-.067	-.156	.115	.310	-.339	-.327	.099	.117	-.104	-.160	.075
PANAS PA	.057	-.376**	.050	.161	.150	-.227	-.116	-.110	.117	.052	-.085	.106	.241*	.222	.082
PANAS NA	-.068	.089	.008	-.301**	-.122	-.227	.004	-.010	-.011	.038	.054	-.140	-.207	-.087	.135
STAI	-.044	.157	-.112	-.344**	-.192	.016	.078	-.022	.014	.136	-.034	-.261*	-.098	-.084	.206
CESD	-.003	.109	-.006	-.250*	-.120	.155	-.007	-.024	.032	.061	.017	-.093	-.128	-.129	.071

Note - * p<0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Univariate regression (screening) for factors associated with cognitive functioning in the TGA sample

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NOCAT (β)	TTC (β)	FTM (β)	SDMT W (β)	SDMTO (β)	RAVLT
Age	-0.139	-0.191	0.103	-0.06	-.093	-.018	.044	.142	-.139	-.213	-.076	0.128	0.107	0.018	-.097
Education (years)	-0.042	-0.142	0.229*	0.27*	.496***	-.320**	-.232*	-.219	.171	.262*	-.059	-0.233*	0.291**	0.269*	.424***
Gender (Males)	-0.151	-0.053	0.094	-0.018	.080	.074	.055	.088	-.072	-.130	-.097	0.069	-0.114	-0.132	-.253*
Employment	-0.286*	-.303**	0.261*	0.218	.297*	-.182	-.136	-.005	.004	.000	-.012	-0.182	0.226*	0.239*	.102
Arrhythmia	-0.078	-0.152	0.1	-0.035	.006	-.021	-.053	-.037	.039	.011	-.041	-0.036	0.121	0.058	.036
Hypertension	-0.096	-0.022	-0.007	-0.055	.086	-.086	-.146	.145	-.179	-.203	.101	0.055	0.104	0.127	-.027
NYHA	0.008	-0.043	-0.058	-0.055	-.066	.087	.165	.086	-.072	-.100	.054	0.201	0.054	-0.005	-.064
Interventions total	0.052	0.015	-0.061	-0.108	-.168	.093	.043	.106	-.077	-.048	-.031	0.009	-0.068	-0.12	-.064
Repair total	0.035	0.041	-0.022	-0.108	-.305**	.033	-.003	.240*	-.222*	-.206	.037	0.158	-0.177	-0.233*	-.044
Palliation before repair	-0.031	0.106	-0.121	-0.125	-.207	.069	.011	.079	.120	-.120	.054	0.008	-0.25*	-0.237*	-.255*
Yrs since last intervention	-0.072	0.041	0.038	0.093	.056	-.106	-.015	-.098	.075	.005	-.028	0.066	0.072	0.091	-.051
Post-opCNs complication	0.066	0.334**	-0.106	-0.299	-.306**	.243*	.267*	.319**	-.344**	-.270*	.334**	-0.085	-0.289**	-0.239*	-.079
Post-op infection	0.058	0.16	-0.062	-0.391	-.222*	.147	.227*	.187	-.207	-.175	.184	0.039	-0.277*	-0.22	-.132
Post-op VD	0.067	0.028	0.055	-0.05	-.151	-.020	-.092	.065	-.085	-.072	.027	-0.025	-0.079	-0.055	.068
HF clinic	0.034	0.17	-0.148	-0.137	-.262*	.201	.192	.190	-.157	-.157	-.029	0.089	-0.141	-0.205	-.226*
Pacemaker	0.136	0.15	0.049	-0.083	-.164	.044	.021	.226*	-.210	-.133	.039	0.124	-0.063	-0.085	-.047

Univariate regression (screening) for factors associated with cognitive functioning in the TGA sample (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NOCAT (β)	TTC (β)	FTM (β)	SDMT W (β)	SDMTO (β)	RAVLT
ACE medication	0.028	0.038	-0.122	-0.157	-.091	.282*	.284*	.173	-.171	-.256*	-.028	0.15	0.045	-0.027	-.071
Diuretic medication	0.059	-0.108	-0.111	-0.318**	-.240*	.016	.081	.288**	-.245*	-.216	.033	0.015	-0.013	-0.013	-.054
Beta blocker medication	-0.086	-0.137	-0.042	-0.056	.019	-.055	-.056	.014	.022	-.002	-.002	-0.069	0.197	0.078	.013
Anti-arrythmia medication	0.094	-0.024	0.002	-0.048	-.147	-.078	.021	.174	-.175	-.157	.046	0.048	0.047	0.013	-.033
Anti-coagulant medication	0.049	0.018	-0.185	-0.214	-.234*	.099	.117	.096	-.046	-.059	-.075	-0.063	-0.025	-0.082	-.063
RVEF	0.032	-0.109	0.043	0.323**	.264*	-.099	-.072	-.267*	.259*	.335**	-.147	-0.324**	0.151	0.149	.184
LVEF	-0.021	-0.123	0.021	0.251*	.175	-.153	-.088	-.300**	.289**	.315**	-.094	-0.173	0.183	0.231*	.150
Palliation total	0.187	0.019	0.03	-0.002	-.089	.033	.138	-.093	.090	.033	.013	0.002	0.028	0.105	-.187
Catheter lab total	-0.293	-0.078	-0.026	-0.116	-.073	-.097	-.169	.166	-.150	-.147	.074	0.011	-0.073	-0.103	-.015
Medication total	0.027	0.081	-0.12	-0.181	-.121	.151	.162	.178	-.165	-.182	.134	-0.047	0.028	-0.077	.100
Age at repair Q2	.029	.199*	-.165	-.206	-.098	-.009	-.200	.091	-.086	-.114	.191	-.068	-.052	-.033	-.224
Age at repair Q3	.002	.151*	.025	-.191	-.068	-.056	-.032	-.041	.037	.045	-.024	.055	-.116	-.040	-.080
Age at repair Q4	-.174	-.188*	.022	-.204	-.010	-.044	-.125	.101	-.107	-.255	.054	.216	.071	.110	-.141
Cyanosis days Q2	.011	.311*	-.285	-.266	-.220	.228	.058	.080	-.082	-.137	.176	.012	-.221	-.154	-.349**
Cyanosis days Q3	-.093	.175*	.038	-.289	-.096	-.020	.028	.074	-.078	-.091	.028	.083	-.136	-.073	-.090
Cyanosis days Q4	-.092	-.121*	-.117	-.277	-.145	.055	-.074	.149	-.135	-.251	.077	.189	.009	.029	-.306*

Univariate regression (screening) for factors associated with cognitive functioning in the TGA sample (contined)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	NO CAT (β)	TTC (β)	FTM (β)	SDMT W (β)	SDMT O (β)	RAVLT
Current saturation Q1	.154	.030	-.122	-.141	-.167	.049	-.038	-.074	.056	-.046	.001	.102	-.008	-.046	-.210
Current saturation Q2	-.016	-.003	-.049	.012	.020	.153	.145	.015	-.017	-.098	-.023	.096	-.034	-.010	-.055
Current saturation Q3	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
ICU days Q2	.048	.176	-.170	.063	-.085	.002	-.124	-.086	.104	.172	-.002	-.259	-.173	-.185	.057
ICU days Q3	-.034	.109	-.100	.036	.010	.108	-.061	-.019	.017	.027	.020	-.239	-.031	-.089	.103
ICU days Q4	.071	.115	-.110	-.216	-.196	-.061	-.063	.077	-.098	-.139	.267	-.047	-.213	-.206	-.015
CPB minutes Q2	.263*	.128	.129	-.058*	-.157*	-.116	-.122	.166	-.190	-.082	.156	.033	-.059	-.263*	.134
CPB minutes Q3	-.092*	-.187	.328	.304*	.349**	-.164	-.144	-.018	.007	-.082	-.038	.051	.257	.001	.216
CPB minutes Q4	.065**	-.112	.104	.090*	.224*	-.157	-.110	-.073	.050	.113	.018	.096	.198	-.025	.347
HA minutes Q 2	.044	.000	-.046	.163	.189	-.176	-.061	-.182	.194	.259	-.222	-.136	.025	.067	.142
HA minutes Q3	.079	.000	-.039	.041	.035	-.233	-.185	-.188	.138	.162	-.182	-.057	.025	.142	.107
HA minutes Q4	-.206	-.273	.063	.189	.239	-.313	-.194	-.058	.049	.098	-.202	-.051	.224	.177	.343
In hospital days Q2	.177	.206	-.071	-.094	-.150	.034	.056	.136	-.144	-.108	.026	.089	-.246	-.268	-.053
In hospital days Q3	.169	.206	.026	-.245	-.199	.086	.056	.067	-.025	-.019	.024	-.075	-.230	-.205	-.162
In hospital days Q4	.114	.189	-.116	-.310	-.227	.330	.405**	.317	-.312	-.263	.243	.091	-.265	-.286	-.081
PANAS PA	-0.047	-0.147	0.086	0.09	.137	-.168	-.221*	.075	-.071	-.086	.033	0.072	0.128	0.171	-.014
PANAS NA	-0.198	-0.119	0.386***	-0.121	.062	-.105	-.162	.111	-.120	-.118	.349**	-0.031	0.259*	0.124	.046
STAI	0.025	0.015	0.171	-0.141	-.041	.138	.154	.164	-.142	.034	.044	-0.121	0.037	0.035	-.012
CESD	-0.059	0.029	0.082	-0.141	-.007	.089	.013	.159	-.164	-.142	.347**	-0.105	0.06	-0.034	.003

Note - * p<0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Univariate regression (screening) for factors associated with cognitive functioning in the SV sample

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
Age	-.149	-.188	.274*	-.031	.183	.100	.044	.142	-.139	-.057	.004	.083	.127	.020	.258*
Education (years)	-.170	-.050	.333**	.211	.497***	-.129	-.232	-.219*	.171*	-.123	.092	.285*	.255*	.244	.251*
Gender (Males)	.055	.045	.121	.035	.037	.187	.055	.088	-.072	-.083	-.031	.074	-.189	-.110	-.087
Employment	.073	-.037	.127	.024	.112	.088	-.136	-.005	.004	-.088	.102	.043	.254*	.028	-.027
Arrhythmia	.067	.047	.120	.049	.040	-.118	-.053	-.037	.039	.050	-.080	-.128	.053	.014	.048
Hypertension	-.052	-.058	.054	.010	-.058	.043	-.146	.145*	-.179*	-.024	.011	-.181	-.055	.074	-.181
NYHA	.003	.189	-.102	-.079	-.175	-.036	.165	.086	-.072	.056	.028	.036	-.124	-.093	.056
Interventions total	-.025	.206	.147	.176	-.126	-.153	.043	.106	-.077	.057	.046	-.032	-.043	-.018	-.062
Repair total	.040	-.083	.068	.068	.004	-.147	-.003	.240	-.222	-.015	.180	-.142	.031	.124	-.052
Palliation before repair	.050	.161	-.119	.015	-.247*	-.084	.011	.079	-.051	.112	.233	-.337**	-.138	-.010	.051
Yrs since last intervention	-.017	-.095	-.084	-.046	.028	-.064	-.015	-.098	.075	.031	.301*	-.240	.026	.061	.121
Post-opCNs complication	.198	.043	-.390*	-.082	-.522***	.085	.267	.319**	-.344**	.452***	-.117	-.462***	-.224	-.210	-.322**
Post-op infection	.322**	.324**	-.168	-.227	-.304*	.168	.227*	.187*	-.207*	.111	.122	-.322**	-.366*	-.127	-.212
Post-op VD	.017	.107	.115	-.035	.012	-.104	-.092	.065	-.085	-.097	-.053	-.037	.020	-.179	-.154
HF clinic	.103	.124	.065	-.210	-.160	-.021	.192	.190	-.157	.028	-.139	.025	-.017	-.106	.004
Pacemaker	.277*	.095	.175	-.048	-.027	-.063	.021	.226	-.210	-.079	-.014	.052	-.115	-.195	-.059
ACE medication	.058	.101	-.120	-.137	-.242	.066	.284	.173	-.171	.003	-.088	-.053	.057	-.154	-.233
Diuretic medication	.298*	-.098	-.117	-.026	-.209	.236	.081	.288*	-.245	.414**	.063	-.202	-.158	-.135	-.098
Beta blocker medication	.326**	.058	-.155	-.010	-.095	.217	-.056	.014*	.022*	.160	.048	-.329*	-.217	-.144	-.010

Univariate regression (screening) for factors associated with cognitive functioning in the SV sample (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
Anti-arrythmia medication	.121	.029	-.027	-.041	-.117	.098	.021	.174	-.175	.303*	-.133	-.199	-.202	-.187	-.066
Anti-coagulant medication	-.034	-.127	.198	.036	.070	-.222	.117	.096	-.046	.113	-.281*	.003	.111	-.055	.048
RVEF	.003	.041	-.153	-.021	-.033	.119	-.072	-.267	.259	-.123	.113	-.080	-.099	.011	-.009
LVEF	.032	-.016	-.101	-.035	-.037	.131	-.088	-.300	.289	-.109	-.006	-.035	-.112	-.007	-.049
Palliation total	-.004	.164	-.019	-.020	-.124	-.041	.138	-.093	.090	.115	.164	-.204	.018	-.049	.177
Catheter lab total	.084	.207	-.013	.079	-.105	-.044	-.169	.166	-.150	.004	-.125	-.018	-.127	-.061	-.133
Medication total	.071	-.019	.060	-.021	-.057	-.070	.162	.178	-.165	.075	-.244	-.117	-.026	-.183	-.128
Age at repair Q2	-.107	-.263	.226	.061	.291	-.138	-.138	.069	-.016	.001	.005	-.084	.285	.169	.396
Age at repair Q3	-.116	-.187	.308	.023	.220	-.173	-.180	.090	-.032	.004	-.173	-.094	.094	-.115	.219
Age at repair Q4	-.151	.018	.224	.112	.166	-.030	-.064	-.110	.114	.201	-.125	-.323	.158	-.039	.220
Cyanosis days Q2	.035	-.151	-.202	-.111	-.260	.168	.222	.167	-.136	-.002	.175	-.216	-.115	-.109	-.170
Cyanosis days Q3	-.142	-.184	.101	.106	-.020	.018	.020	.099	-.077	.029	.067	-.211	.016	-.056	-.163
Cyanosis days Q4	.086	.004	.098	-.158	-.203	.163	.202	-.091	.140	.215	.094	-.274	-.262	-.192	-.079
Current saturation Q1	.140	.067	-.018	-.150	-.155	.130	.135	-.062*	.145	.109	-.201	.150	-.249	-.304*	.149
Current saturation Q2	.190	.030	-.143	-.245	-.224	.128	.150	.356	-.331*	.326	-.228	-.215	-.348	-.360*	.187
Current saturation Q3	.143	.025	.079	.011	.097	-.006	-.041	-.047	.097	.029	-.064	.102	-.188	-.068	.358

Univariate regression (screening) for factors associated with cognitive functioning in the SV sample (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
ICU days Q2	-.048	-.070	.155	-.063	.000	-.073	.026	-.035	.019	-.204	.117	.049	-.080	-.061	-.164
ICU days Q3	-.093	.034	.225	-.054	-.083	-.222	-.092	.133	-.222	-.026	.042	-.156	-.069	.005	-.043
ICU days Q4	-.037	.095	.162	.051	-.031	-.193	-.191	.006	-.072	-.150	.254	-.069	.013	.196	-.053
CPB minutes Q2	-.017	-.081	.285	.329*	.331	-.154	-.161	.039	-.131	.043	.059	.046	.183	.059	.261
CPB minutes Q3	.157	-.067	.072	.130	.054*	-.126	-.079	.338	-.397	.188	.249	-.285	.067	.154	.019
CPB minutes Q4	.241	.199	.163	.020	-.060	-.047	.038	.188	-.300	.209	.191	-.229	-.030	.109	.086
HA minutes Q2	-.090	-.008	.171	.170	.278	-.111	-.203	.016	-.074	.073	.166	-.094	.411**	.292	.411**
HA minutes Q3	.129	.193	.060	-.117	.040	-.095	-.074	.030	-.086	.097	.118	-.034	.094	.005	.124
HA minutes Q4	.161	.098	.032	.127	.102	.006	-.078	-.039	-.042	.238	-.035	.074	.331*	.156	.260
In hospital days Q2	-.098	.310	.064	.247	.071	-.233	-.081	-.096	.091	-.109	.283	-.036	.141	.163	.005
In hospital days Q3	.025	.241	-.010	.154	-.063	-.183	-.074	.123	-.171	-.080	.248	-.188	-.016	-.022	-.107
In hospital days Q4	-.080	.315	.067	.127	-.110	-.141	-.201	.027	-.080	-.024	.040	-.044	.168	-.032	-.004
PANAS PA	-.223	-.212	.317*	.277*	.442***	-.004	-.221	.075**	-.071	-.131	.196	.111	.364	.440	.418**
PANAS NA	.081	.231	-.128	-.148	-.228	-.150	-.162	.111	-.071	-.015	-.146	.013	-.273*	-.299*	-.086
STAI	-.006	.111	-.100	-.170	-.185	-.197	.154	.164	-.142	.044	-.039	-.074	.004	-.173	-.176
CESD	-.042	.147	-.050	-.066	-.228	-.135	.013	.159	-.164	.052	-.206	-.010	-.222	-.299*	-.094

Note - * p<0.05, **p<0.01, ***p<0.001

Univariate regression (screening) for factors associated with cognitive functioning in the SIMPLE group

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
Age	-.170	-.038	.289**	-.166	-0.069	-0.029	0.102	0.212	-0.241*	0.119	-0.112	-0.226*	-0.059	-0.1	0.016
Education (years)	-.054	-.181	.256*	.180	0.54***	-0.091	-0.164	0.311**	0.275*	-0.297**	-0.126	0.306**	0.299**	0.204	0.143
Gender (Males)	-.035	-.065	-.142	-.040	-0.025	0.346**	0.163	-0.055	0.01	-0.156	-0.135	-0.005	-0.043	-0.121	-0.274*
Employment	-.078	-.136	-.004	.235*	0.067	0.031	0.004	-0.101	0.096	-0.208	-0.112	0.128	0.116	0.01	0.015
Arrhythmia	.029	.110	-.020	-.202	-0.115	0.019	0.134	-0.002	-0.036	-0.041	0.016	-0.055	-0.149	-0.164	-0.008
Hypertension	-.119	.010	-.082	-.190	-0.172	-0.007	-0.017	0.228*	-0.235*	0.063	-0.035	-0.207	-0.014	-0.098	-0.315**
NYHA	.022	.077	.113	-.228*	-0.097	-0.008	-0.017	0.085	-0.105	0.063**	-0.058	-0.107	-0.148	-0.205	-0.077
Interventions total	.065	.145	-.013	.061	-0.155	0.061	-0.059	-0.153	0.127	-0.073	0.058	0.117	-0.156	-0.074	-0.039
Repair total	-.160	-.176	.189	.128	0.257*	0.048	-0.077	-0.18	0.179	-0.071	0.129	0.200	0.165	0.22*	0.114
Yrs since last intervention	-.112	-.158	.055	.058	0.061	0.212	0.295**	-0.035	0.035	-0.145	0.063	0.027	0.071	-0.062	-0.062
Post-op infection	-.119	-.047	-.021	.067	-0.027	-0.055	-0.093	-0.148	0.133	-0.052	-0.099	0.144	0.078	0.022	-0.01
Post-op VD	-.134	-.122	.070	.060	0.171	0.054	-0.065	-0.117	0.092	-0.023	-0.054	0.122	0.123	0.23*	0.01
HF clinic	-.061	.020	-.223*	.021	-0.035	-0.127	-0.082	-0.071	0.046	-0.059	0.12	0.03	0.019	0.001	-0.032
Pacemaker	-.115	.018	.053	.085	-0.106	-0.174	-0.095	-0.122	0.127	-0.029	-0.05	0.139	-0.043	0.11	0.003
ACE medication	.012	.084	.036	-.216*	-0.172	0.058	0.114	0.001	-0.007	-0.1	-0.065	0.139	-0.115	-0.2	-0.343**
Diuretic medication	.051	.125	.167	-.164	-0.091	-0.031	0.06	0.099	-0.159	0.228*	-0.047	-0.138	-0.152	-0.219*	-0.091

Univariate regression (screening) for factors associated with cognitive functioning in the SIMPLE group (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
Beta blocker medication	-.015	.009	.043	-.186	0.023	0.029	-0.091	0.101	-0.065	0.18	0.112	-0.107	0.049	0.077	-0.067
Anti-arrythmia medication	-.001	.067	.117	.036	-0.08	0.031	0.223*	-0.03	-0.008	-0.005	0.028	-0.018	-0.14	-0.099	0.023
Anti-coagulant medication	-.002	-.013	.149	.105	-0.05	0.036	-0.028	0.17	-0.18	0.496***	-0.085	-0.194	-0.146	-0.118	0.059
RVEF	.041	.185	.162	-.135	0.052	0.063	0.113	0.07	-0.047	0.065	-0.133	-0.039	-0.079	-0.081	-0.096
LVEF	.024	.092	.234*	-.016	0.1	0.08	0.085	-0.182	0.175	-0.16	-0.042	0.138	-0.052	-0.014	-0.083
Palliation total	.107	.051	-.128	.060	-0.178	0.169	0.243*	0.169	-0.177	-0.01	-0.035	-0.159	-0.155	-0.037	-0.029
Catheter lab total	.096	.205	-.023	.005	-0.244*	-0.154	-0.083	0.048	-0.074	0.012	0.005	-0.091	-0.179	-0.162	-0.114
Medication total	-.048	.069	.076	-.204	-0.1	0.054	-0.008	0.163	-0.16	0.187	0.011	-0.205	-0.059	-0.139	-0.152
Age at repair Q2	-.340**	-.053	.154	-.039	.287	-.127	-.165	-.198	.184	-.051	-.093	.191	-.049	.388	.290
Age at repair Q3	.171	.148	-.018	-.085	.066	-.258	-.255	-.307*	.303*	.006	-.238	.345**	-.157*	.016	.134
Age at repair Q4	-.177	-.054	.158	-.167	.088	-.192	-.216	.133	-.153	.222	-.197	-.156	.081*	.114	.112
Current saturation Q1	-.004	-.015	.103	-.003	-.130	-.016	.084	.265	-.260	.382**	.124	-.268	-.128	-.101	.010
Current saturation Q2	-.181	.003	.170	-.104	-.059	-.034	.167	.088	-.063	-.007	-.118	-.098	-.161	.023	-.172
Current saturation Q3	.119	.154	.193	.029	.069	.000	.106	.055	-.025	.032	.079	-.061	.021	.076	-.026
ICU days Q2	-.207	-.158	-.034	.161	.118	.094	.078	-.042	.005	-.011	.160	-.020	.217	.183	-.041
ICU days Q3	-.289	-.189	-.006	.126	-.050	.017	-.052	-.009	.001	-.063	.061	.012	.046	.089	-.057
ICU days Q4	-.115	-.132	.128	.171	.154	.027	.086	-.006	-.008	-.083	.156	.046	.183	.198	-.089

Univariate regression (screening) for factors associated with cognitive functioning in the SIMPLE group (continued)

	TMT-A (β)	TMT-B (β)	COWA (β)	STROOP (β)	WAIS-III	GP-D (β)	GP-ND (β)	ERROR (β)	CLR (β)	TTC (β)	FTM (β)	NO CAT (β)	SDMT W (β)	SDMT O (β)	RAVLT
CPB minutes Q2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	.222	n/a
CPB minutes Q3	.203	-.047	.076	-.177	-.018	.018	-.047	.022	-.013	.126	-.003	-.056	-.074	.031	.024
CPB minutes Q4	-.093*	-.148	.050	.092	.134	.124	-.025	-.094	.110	.021	.005	.046	.158	.130	-.028
HA minutes Q2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
HA minutes Q3	.186	.105	-.005	-.248*	-.123	.059	.087	.099	-.084	.131	.017	-.119	-.118	.009	.030
HA minutes Q4	.077	.093	.015	.123	-.024	.194	.049	-.141	.142	.020	-.010	.079	.016	.085	.016
In hospital days Q2	-.141	-.023	-.042	.054	-.105	.127	-.024	-.140	.129	-.049	.016	.066	.028	.084	-.132
In hospital days Q3	-.022	-.085	-.019	.037	-.004	.209	.002	-.051	.047	-.108	.070	.076	.112	-.049	-.097
In hospital days Q4	.125	.086	-.060	-.105	-.089	.006	-.059	.058	-.030	-.140	.095	-.028	-.026	.000	-.238
PANAS PA	-.067	-.142	.276*	.222*	.407***	-.325**	-.167	-.227*	.225*	-.211	-.143	.317*	.367**	.308**	.264*
PANAS NA	.135	.175	-.218*	-.317**	-.371	.037*	-.140	.232*	-.223*	.132	.206	-.293**	-.201	-.147	-.248*
STAI	.219*	.196	-.304**	-.429***	-.423**	.104	.079	.204	-.173	.175	.039	-.210	-.368**	-.292**	-.207
CESD	.178	.091	-.291**	-.359**	-.382***	.113	-.012	.282*	-.273*	.257*	.164	-.338**	-.265*	-.152	-.239*

Note - * p<0.05, **p<0.01, ***p<0.001

Appendix O: Univariate Screening for the SF-36 Subscales (MCS & PCS) in the Cross-Sectional Study

(a) - Univariate screening for the QoL Mental Component Summary (SF 36- MCS) score by total sample and the different structural complexity groups

Independent variables	Total group	ToF group	TGA group	SV group	Simple group
Total composite NP score	.109	-.139	-.052	.103	.309**
Age	.151	.228*	.041	.260*	.147
Education (years)	-.020	.083	-.011	-.051	-.031
Gender (Males)	.063	.053	.312**	-.014	-.075
Employment	.247***	.335**	.187	.384**	.099
Arrhythmia	.034	.181	.015	-.074	-.038
Hypertension	-.078	-.034	.081	.011	-.121
NYHA	-.055	.054	-.121	-.107	-.032
Interventions total	.073	.127	-.024	-.048	.207
Palliation before repair	.062	.070	-.067	.008	n/a
Years since last intervention	.053	.100	-.028	.167	-.061
Post-op CNS complication	.022	.141	.051	-.141	.048
Post-op infection	.115*	.118	-.008	.193	.048
Post-op ventricular dysfunction	.073	.165	.053	-.016	.106
HF clinic	.049	.108	.066	-.024	.081
Pacemaker	-.028	n/a	-.046	-.039	-.055
ACE medication	-.114*	.176	-.014	-.319*	-.167
Diuretic medication	.031	.135	.029	.048	-.060
Beta blocker medication	-.013	.066	-.117	.238	-.170
Anti-arrythmia medication	.076	.119	.049	.067	.162
Anti-coagulant medication	-.043	.043	.026	-.094	-.009
RVEF	-.072	-.237*	.031	.194	-.081
LVEF	.003	-.120	-.160	.151	.079
Palliation total	.023	.071	.107	-.058	.122
Catheter lab total	.033	-.041	-.102	-.006	.076
Medication total	-.113*	.130	-.273*	-.105	-.121
Age at repair Q2	.134	.107	-.00	-.103	.255
Age at repair Q3	.099	.035	.098	-.269	.001
Age at repair Q4	-.025	.241	.168	-.194	.207

*p0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Univariate screening for the QoL Mental Component Summary (MCS) score by total sample and the different structural complexity groups (Continued)

Independent variables	Total group	ToF group	TGA group	SV group	Simple group
Cyanosis days Q2	.101	.119	.077	.054	n/a
Cyanosis days Q3	.205**	.144	.140	.040	n/a
Cyanosis days Q4	.079	.202	.173	-.079	.093
Current saturationQ1	-.106	-.049	.102	-.253**	-.060
Current saturationQ2	.076	-.248*	.216	-.417	-.155
Current saturationQ3	-.068	n/a	n/a	-.246	-.186
ICU days Q2	-.040	.078	-.210	-.119	-.092
ICU days Q3	-.008	.200	-.066	-.280	-.097
ICU days Q4	.055	.356**	-.149	.141	-.045
CPB minutes Q2	.147*	-.012	.005	.000	n/a
CPB minutes Q3	.112	.081	.007	-.021	-.068
CPB minutes Q4	.144*	.049	.020	-.041	.074
HA minutes Q2	.056	.007	-.024	.170	n/a
HA minutes Q3	.170*	.305*	.076	.267	-.065
HA minutes Q4	.069	.014	-.094	.176	-.059
In hospital days Q2	.041	-.272*	-.186	.200	-.062
In hospital days Q3	.034	-.061	-.104	.013	.136
In hospital days Q4	.035	.101	-.172	-.027	-.059
PANAS PA	.502***	.453***	.437***	.525***	.561***
PANAS NA	-.617***	-.425***	-.568***	-.747***	-.720***
STAI	-.496***	-.417***	-.306**	-.609***	-.591***
CESD	-.748***	-.690***	-.306***	-.794***	-.768***

*p0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

(b) - Univariate screening for the QoL Physical Component Summary (PCS) score by total sample and the different structural complexity groups

Independent variables	Total group	ToF group	TGA group	SV group	Simple group
Total composite NP score	.109	.031	.234	.133	.161
Age	-.164**	-.119	-.145	-.116	-.369**
Education (years)	.185**	.152	.194	.129	.305**
Gender (Males)	.107	.077	.087	.327**	.053
Employment	.174**	.344**	.112	.219	.057
Arrhythmia	-.138*	-.284*	-.065	-.020	-.124
Hypertension	.018	.022	.168	.126	-.096
NYHA	-.460***	-.560***	-.341**	-.529**	-.555***
Interventions total	-.113*	-.232*	-.094	-.004	-.298**
Palliation before repair	-.083	-.110	-.047	.101	-.009
Years since last intervention	.163**	.254*	.105	.161	.115
Post-op CNS complication	-.050	-.012	-.083	-.048	-.083
Post-op infection	-.108	-.306**	-.046	-.049	.023
Post-op ventricular dysfunction	.054	.038	.204	.018	.048
HF clinic	-.135*	-.113	-.148	-.081	-.088
Pacemaker	-.055	n/a	-.010	-.090	-.031
ACE medication	-.156**	-.287**	-.018	-.030	-.258*
Diuretic medication	-.295***	-.360**	-.214	-.202	-.395***
Beta blocker medication	-.174**	-.276*	-.170	-.108	-.151
Anti-arrythmia medication	-.117*	-.301**	-.084	-.045	.107
Anti-coagulant medication	-.186**	-.276*	-.161	-.005	-.119
RVEF	.089	.165	.100	.053	.021
LVEF	.127*	.195	.012	.091	.081
Palliation total	-.055	-.125	.085	.136	.043
Catheter lab total	-.163**	-.132	-.174	-.159	-.208

*p0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Univariate screening for the QoL Physical Component Summary (PCS) score by total sample and the different structural complexity groups (Continued)

Independent variables	Total group	ToF group	TGA group	SV group	Simple group
Medication total	-.229***	-.390***	-.086	-.001	-.242*
Age at repair Q2	.038	.081	-.051	.094	.098
Age at repair Q3	-.035	-.020	.038	-.021	-.111
Age at repair Q4	-.228**	-.145	-.029	-.194	-.262*
Cyanosis days Q2	.042	-.207	-.131	-.244	n/a
Cyanosis days Q3	-.011	-.135	-.102	-.347*	n/a
Cyanosis days Q4	-.154	-.072	-.118	-.516***	n/a
Current saturationQ1	-.297***	-.265*	-.061	-.406**	-.203
Current saturationQ2	-.064	-.154	-.085	-.071	.057
Current saturationQ3	-.071	n/a	n/a	.058	.228
ICU days Q2	.058	-.144	.111	.063	.067
ICU days Q3	.013	-.226	.013	-.008	.024
ICU days Q4	-.059	-.088	-.023	-.043	.027
CPB minutes Q2	.134	.056	-.058	.302	n/a
CPB minutes Q3	.079	-.144	.087	.179	-.199
CPB minutes Q4	.033	-.252	.122	.130	-.018
HA minutes Q2	-.020	.187	-.079	.216	n/a
HA minutes Q3	.026	-.008	.059	.127	-.189
HA minutes Q4	-.003	.147	-.198	.255	-.028
In hospital days Q2	.039	-.130	.100	.055	.210
In hospital days Q3	.001	-.185	.031	-.074**	.280*
In hospital days Q4	-.203**	-.360**	-.051	-.326*	-.018
PANAS PA	.272***	.215	.260*	.394**	.240*
PANAS NA	-.279***	-.157	-.212	-.393**	-.337**
STAI	-.218***	.020	-.145	-.228	-.416***
CESD	-.312***	-.147	-.249*	-.408**	-.341**

*p0.05, **p<0.01, ***p<0.001, n/a- in adequate cell count to run analysis

Appendix P: Cross-Sectional Study Clinical Variables Descriptive Data

Variable (Median, Interquartile range)	ToF	TGA	SV	Simple	Total	H	r (ES)	df	p-value
Age at repair	48.0 [a] (20-71.50)	8.0 [b] (5-14)	111.0 [c] (63-226)	88.50 [a, c] (16-327)	48.00 (9.75-121)	88.298	-0.72 - 0.36	3	**<0.001**
Interventions total	2.0 [a, b] (1-3)	2.0 [a, b] (2-3)	3.0 [b] (2-4)	1.0 [c] (1-2)	2.0 (1-3)	74.01	-0.22 - 0.64	3	**<0.001**
Repairs total	1.0 [a] (1-2)	1.0 [b,c,d] (1-1)	1.0 [b,c,d] (1-1)	1 [b,c,d] (1-1)	1.0 (1-1)	41.46	0.35 – 0.43	3	**<0.001**
Palliations total	0.0 [a] (0-1)	0.0 [b,d] (0-0)	1.0 [c] (1-2)	0.0 [b,d] (0-0)	0.0 (0-1)	130.17	-0.49 – 0.88	3	**<0.001**
Catheter labs total	0.0 [a,c,d] (0-1)	1.0 [b] (1-2)	0.0 [a,c,d] (0-1)	0.0 [a,c,d] (0-1)	0.0 (0-1)	65.13	-0.57 – 0.52	3	**<0.001**
Years since last intervention	10.0 [a, b, c, d] (3-27)	25.0 [b, d] (7.25-30)	15.0 [c, d] (4-21)	10.0 [a,b,c,d] (3.25-24)	17.0 (4-26)	12.73	0.27	3	**<0.001**
Cyanosis days total	900 [a,c] (390-1747.50)	242.0 [b] (150-420)	1825.0 [a,c] (900-4310)	0.0 [d] (0-0)	322.50 (0-1095)	218.11	-0.51 – 1.01	3	**<0.001**
Current saturation	97.0 [a] (96-98)	96.50 [b] (96-97)	93.0 [c] (88-97)	98.0 [d] (97-100)	97.0 (96-98)	101.06	-0.22 – 0.56	3	**<0.001**
CPB minutes Total	115.0 [a,b,c] (77.5-160.5)	100.0 [a,b,c] (75.25-160)	109.0 [a,b,c] (80.50-143)	0.0 [d] (0-58.75)	90.0 (53-134)	109.98	0.05 – 0.70	3	**<0.001**
HA minutes total	30 [a,b,c] (24.50-39)	34.50 [a,b,c] (27.5-48.75)	30.0 [a,b,c] (15-55.50)	0.0 [d] (0-19.50)	28.0 (10-40)	81.12	0.04 – 0.64	3	**<0.001**
In hospital days	35 [a,b,c] (24.50-60)	25.50 [a,b] (20-48)	50.0 [a,c] (30-90)	12.0 [d] (8.25-20)	26.50 (15.75-50)	120.31	-0.35 – 0.83	3	**<0.001**
Co-morbidities total	1 [a] (0-1)	1.0 [b] (0-2)	1.0 [c] (0-1)	1.0 [d] (0-1)	1.0 (0-1)	4.14	n/a	3	0.247
Medication total	0.0 [a,d] (0-0.50)	1.0 [b,c,d] (0-1)	1.0 [c] (1-2)	0.0 [a, b,d] (0-1)	0.0 (0-2)	36.64	-0.23 – 0.25	3	**<0.001**
RVEF	58.0 [a,b,c] (49.50-61.50)	55.0 [a,b,c] (50.25-60)	60.0 [a,b,c] (50-62)	65.0 [d] (60-65)	50.0 (53-64)	71.82	-0.46 - -0.61	3	**<0.001**
LVEF	60.0 a (56.50-65)	64.0 a,b,d (58-67.75)	57.0a,c (50-61)	65.0 b,d (60-70)	61.0 (57-65)	50.36	-0.32 – 0.42	3	**<0.001**

Note: H= Kruskal-Wallis test statistic, ES= Effect Size, SD=Standard Deviation, RVEF = Right Ventricle Ejection Fraction, LVEF=Left Ventricle Ejection Fraction, HA = Hypothermic arrest, CPB= Cardio Pulmonary Bypass.

Interpretation key- the pair wise comparisons between the groups are indicated in the table with the help of superscripts. Groups sharing a common alphabet indicate the absence of any significant differences on that variable. The range of the effect sizes across all pairwise comparisons is presented ('r').

Appendix Q: Correlation Matrix for the WCST-64 Scores

	WCST- total number of error	WCST- Conceptual level response (CLR)	WCST- NO of categories completed	WCST- Trials to complete 1st category (TTC)	WCST- failure to maintain set (FTM)
WCST- total number of error	-				
WCST-Conceptual level response	-.973**	-			
WCST- NO of categories completed	-.863**	.869**	-		
WCST- Trials to complete 1st category	.345**	-.353**	-.404**	-	
WCST- failure to maintain set	.085	-.066	-.408**	-.019	-

Note- **p<0.01

Appendix R: Multiple Hierarchical Regression Analysis to Identify Factors Associated with Cognitive Functioning (Sub-Group Analysis)

Multivariate regression models for the ToF group

Regression model for TMT-B test in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.229	.199	.229	7.618		**.000****
	Age					-.257	.014
	Education (Yrs)					-.271	.009
	Employment					-.267	.010
2		.225	.216	.026	2.651		.108
	Age					-.225	**.031**
	Education (Yrs)					-.253	.014
	Employment					-.155	.206
	Positive affect					-.203	.108
**p<0.01							

Regression model for SDMT- Written scores in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.155	.145	.155	14.533		**<0.001**
	Education (Yrs.)					.394	**<0.001**
2		.177	.156	.021	2.028		.158
	Education (Yrs.)					.397	**<0.001**
	Arrhythmias					-.146	.158
3		.209	.178	.032	3.086		.083
	Education (Yrs.)					.373	**<0.001**
	Arrhythmias					-.128	.212
	Positive affect					.181	.083

Regression model for Stroop test in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.146	.124	.146	6.687		**.002****
	Education (Yrs)					.293	**.007****
	Gender (Males)					.210	.050
2		.269	.230	.122	6.367		**.003****
	Education (Yrs)					.312	**.003****
	Gender (Males)					.221	.030
	Post-op CNS complication					-.183	.110
	Post-op Ventricular dysfunction					-.226	.051
3		.321	.256	.052	1.872		.142
	Education (Yrs)					.267	.010
	Gender (Males)					.159	.130
	Post-op CNS complication					-.167	.138
	Post-op Ventricular dysfunction					-.229	.047
	Depression					-.025	.848
	Anxiety					-.141	.269
	Negative affect					-.122	.324
**p<0.01							

Regression model for WCST-Error in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.099	.088	.099	8.672		**.004****
	Education (Yrs)					-.315	**.004****
2		.139	.117	.040	3.652		.060
	Education (Yrs)					-.294	**.007****
	NYHA					.202	.060
**p<0.01							

Regression model for WCST-Conceptual level responses in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.107	.096	.107	9.472		**.003****
	Education (Yrs)					.327	**.003****
2		.152	.107	.045	1.336		.269
	Education (Yrs)					.324	**.004****
	NYHA					-.127	.308
	Arrhythmias					-.061	.596
	HF clinic					-.085	.484
3		.164	.084	.012	.361		.781
	Education (Yrs)					.316	**.006****
	NYHA					-.158	.234
	Arrhythmias					-.056	.666
	HF clinic					-.100	.466
	ACE medication					-.067	.616
	LVEF					.066	.582
	Medication total 0 vs. all					.134	.385
**p<0.01							

Regression model for WCST-Failure To Maintain score in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.144	.111	.144	4.327		**.007****
	Education (Yrs)					-.008	.938
	Gender (Males)					.341	**.002****
	Age					.234	.032
2		.163	.107	.019	.851		.431
	Education (Yrs)					.005	.960
	Gender (Males)					.372	**.001*****
	Age					.227	.038
	Palliation total 0 vs. all					-.440	.359
	Palliation before repair					.533	.270
3		.198	.133	.035	3.245		.076
	Education (Yrs)					-.038	.727
	Gender (Males)					.302	.011
	Age					.234	.031
	Palliation total 0 vs. all					-.567	.236
	Palliation before repair					.627	.191
	Anxiety					-.208	.076
**p<0.01							

Regression model for WCST-No. of categories completed in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.049	.025	.049	2.020		.140
	ACE medication					-.214	.082
	Anti-coagulant medication					-.017	.889

Regression model for WCST- Trials to complete first set in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.000	-.013	.000	.009		.923
	Gender (Males)					-.011	.923
2		.045	.007	.044	1.789		.174
	Gender (Males)					-.030	.789
	NYHA					.217	.067
	HF clinic					-.023	.844
3		.069	.020	.025	2.034		.158
	Gender (Males)					-.026	.819
	NYHA					.223	.058
	HF clinic					.110	.464
	Post-operative ventricular dysfunction					-.208	.158
4		.146	.064	.076	2.167		.099
	Gender (Males)					-.039	.727
	NYHA					.222	.099
	HF clinic					.208	.215
	Post-operative ventricular dysfunction					-.167	.255
	Medication total 0 vs. all					-.006	.972
	Anti-coagulant medication					.216	.174
	Beta-blocker medication					-.284	.046

Regression model for GP- Non dominant in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.103	.068	.103	2.948		.038
	Cyanotic days Q2					-.011	.934
	Cyanotic days Q3					.094	.482
	Cyanotic days Q4					.334	.014
2		.132	.087	.029	2.576		.113
	Cyanotic days Q2					-.024	.855
	Cyanotic days Q3					.053	.693
	Cyanotic days Q4					.293	.031
	ACE medication					.176	.113

Regression model for RAVLT scores in ToF

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.083	.060	.083	3.550	.033*	.033
	Education (Yrs.)					.275	**.013****
	Employment					-.118	.281
2		.243	.192	.159	5.266	**.002****	**.002****
	Education (Yrs.)					.367	**0.001**
	Employment					-.128	.216
	Age at repair Q2					.188	.125
	Age at repair Q3					.175	.156
	Age at repair Q4					.486	**<0.001**
**p<0.01							

Multivariate regression models for the TGA group

Regression model for TMT-A in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.082	.070	.082	6.933		.010
	Employment					-.286	.010
2		.161	.116	.079	2.360		.078
	Employment					-.272	.014
	CPB minutes Q2					.274	.040
	CPB minutes Q 3					-.044	.738
	CPB minutes Q 4					.048	.714

Regression model for TMT-B in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.092	.080	.092	7.859		**.006****
	Employment					-.303	**.006****
2		.289	.241	.197	5.130		**.001****
	Employment					-.293	**.004****
	CNS complication					.278	**.008****
	Age at repair Q2					.237	.040
	Age at repair Q3					.208	.070
	Age at repair Q4					-.088	.446
3		.352	.279	.063	2.311		.084
	Employment					-.327	**.002****
	CNS complication					.284	**.008****
	Age at repair Q2					.128	.537
	Age at repair Q3					.367	.147
	Age at repair Q4					.090	.738
	Cyanosis days Q2					.224	.281
	Cyanosis days Q3					-.140	.598
	Cyanosis days Q4					-.196	.475
**p<0.01							

Regression model for COWA in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.112	.089	.112	4.875		.010
	Employment					.210	.054
	Education (Yrs)					.246	.025
2		.291	.263	.179	19.174		**<0.001**
	Employment					.238	.016
	Education(Yrs)					.278	**.005****
	Negative affect					.425	**<0.001**
**p<0.01							

Regression model for STROOP in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.073	.061	.073	6.122		.016
	Education (Yrs)					.270	.016
2		.161	.116	.088	2.634		.056
	Education (Yrs)					.241	.026
	CPB minutes Q2					-.057	.664
	CPB minutes Q3					.281	.032
	CPB minutes Q4					.081	.530
3		.277	.207	.116	3.860		.013
	Education (Yrs)					.152	.151
	CPB minutes Q2					-.057	.650
	CPB minutes Q3					.311	.014
	CPB minutes Q4					.110	.388
	RVEF					.206	.119
	LVEF					.117	.332
	Diuretic medication					-.111	.373

Regression model for WAIS-III in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.314	.296	.314	17.608		**<0.001**
	Education (Yrs)					.476	**<0.001**
	Employment					.261	**.007****
2		.316	.289	.002	.219		.641
	Education (Yrs)					.459	**<0.001**
	Employment					.254	.010
	Heart failure clinic					-.048	.641
3		.535	.475	.219	5.485		**<0.001**
	Education (Yrs)					.353	**<0.001**
	Employment					.191	.029
	Heart failure clinic					-.055	.565
	CPB minutes Q2					-.156	.133
	CPB minutes Q3					.241	.026
	CPB minutes Q4					.254	.017
	Repair surgeries total					-.168	.074
	Post-op CNS complication					-.131	.160
	Post-op infection					-.074	.414
4		.584	.510	.050	2.678		.054
	Education (Yrs)					.322	**.001****

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
	Employment					.192	.027
	Heart failure clinic					.048	.629
	CPB minutes Q2					-.143	.154
	CPB minutes Q3					.281	**.009****
	CPB minutes Q4					.307	**.004****
	Repair surgeries total					-.142	.124
	Post-op CNS complication					-.153	.094
	Post-op infection					-.063	.473
	Diuretic medication					.115	.311
	Anti–coagulant medication					-.215	.043
	RVEF					.209	.046
**p<0.01							

Regression model for GP dominant hand in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.102	.091	.102	8.890		**.004****
	Education (Yrs)					-.320	**<0.001**
2		.146	.124	.044	3.943		.051
	Education (Yrs)					-.297	**.006****
	Post-op CNS complication					.210	.051
3		.206	..175	.060	5.789		.019
	Education (Yrs)					-.229	.035
	Post-op CNS complication					.251	.019
	ACE medication					.257	.019
**p<0.01							

Regression model for GP non-dominant hand in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.054	.042	.054	4.434		.038
	Education (Yrs)					-.232	.038
2		.189	.122	.135	2.437		.042
	Education (Yrs)					-.122	.276
	In hospital days Q2					.050	.681
	In hospital days Q3		.			.048	.701
	In hospital days Q4					.302	.029
	Post-op CNS complication					.181	.117
	Post-op infection					.046	.701
3		.237	.163	.048	4.556		.036
	Education (Yrs)					-.074	.504
	In hospital days Q2					.07	.538
	In hospital days Q3					.030	.806
	In hospital days Q4					.238	.083
	Post-op CNS complication					.234	.043
	Post-op infection					.047	.688
	ACE medication					.240	.036
4		.258	.174	.020	1.944		.168
	Education (Yrs)					-.050	.654
	In hospital days Q2					.071	.548

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
	In hospital days Q3					.014	.911
	In hospital days Q4					.205	.137
	Post-op CNS complication					.222	.054
	Post-op infection					.078	.509
	ACE medication					.239	.036
	Positive affect					-.150	.168

Regression model for SDMT-Oral in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.120	.097	.120	5.261		**.007****
	Education (Yrs)					.252	.021
	Employment	.				.220	.044
2		.288	.207	.167	2.780		.017
	Education (Yrs)					.105	.348
	Employment		.			.162	.126
	CPB minutes Q2					-.046	.717
	CPB minutes Q3					.246	.052
	CPB minutes Q4					.237	.065
	Post – op CNS complication					-.122	.245
	Repair surgeries total					-.174	.123
	Palliation before repair					-.201	.063
3		.359	.276	.071	7.754		**.007****
	Education (Yrs)					.055	.613
	Employment					.184	.071
	CPB minutes Q2					-.059	.624
	CPB minutes Q3					.267	.029
	CPB minutes Q4					.201	.102
	Post – op CNS complication					-.115	.251
	Repair surgeries total					-.173	.110
	Palliation before repair					-.253	.017
	LVEF					.279	**.007**
**p<0.01							

Regression model for SDMT-Written in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.127	.104	.127	5.579		**.005****
	Education (Yrs)					.275	.012
	Employment	.				.205	.058
2		.237	.185	.110	3.570		.018
	Education (Yrs)					.172	.116
	Employment		.			.178	.087
	Palliation before repair					-.184	.089
	Post-op CNS complication					-.201	.067
	Post-op infection					-.154	.161

3		.340	.286	.103	11.395		**.001****
	Education (Yrs)					.184	.074
	Employment					.201	.040
	Palliation before repair					-.205	.044
	Post-op CNS complication					-.205	.046
	Post-op infection					-.168	.105
	Negative affect					.324	**.001****
**p<0.01							

Regression model for RAVLT in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.248	.229	.248	12.727		**<0.001**
	Education (Yrs)					.429	**<0.001**
	Gender (Males)	.				-.263	.010
2		.251	.221	.002	.210		.648
	Education (Yrs)					.411	**<0.001**
	Gender (Males)		.			-.258	.012
	HF clinic					-.049	.648
3		.268	.229	.018	1.803		.183
	Education (Yrs)					.375	**.001****
	Gender (Males)					-.262	.010
	HF clinic					-.030	.780
	Palliation before repair					-.140	.183
4		.322	.256	.054	1.910		.136
	Education (Yrs)					.326	**.004****
	Gender (Males)					-.271	**.007****
	HF clinic					-.006	.957
	Palliation before repair					-.111	.300
	Cyanotic days Q2					-.244	.044
	Cyanotic days Q3					-.057	.641
	Cyanotic days Q4					-.210	.088
5		.347	.273	.025	2.701		.105
	Education (Yrs)					.322	**.004****
	Gender (Males)					-.257	.010
	HF clinic					.003	.980
	Palliation before repair					-.114	.282
	Cyanotic days Q2					-1.507	.136
	Cyanotic days Q3					-.053	.958
	Cyanotic days Q4					-1.203	.233
**p<0.01							

Regression model for WCST-Error in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.147	.125	.147	6.649		**<0.001**
	Post-op CNS complication					.301	**.006****
	Repair surgeries					.215	.045
2		.264	.204	.117	2.901		.028
	Post-op CNS complication					.310	**.004****
	Repair surgeries		.			.150	.179

	RVEF					-.076	.579
	LVEF					-.20	.089
	Diuretic medication					.096	.452
	Pacemaker					.088	.435
**p<0.01							

Regression model for WCST-Conceptual level responses in TGA

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.156	.134	.156	7.119		.001**
	Repair surgeries					-.194	.068
	Post-op CNS complications					-.328	**.003****
2		.255	.205	.099	3.283		.025
	Repair surgeries					-.138	.213
	Post-op CNS complications					-.342	**.001****
	Diuretic medication		.			-.072	.555
	RVEF					.123	.364
	LVEF					.197	.102
**p<0.01							

Regression model for WCST-No of Categories completed in TGA

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.069	.057	.069	5.762		.019
	Education (Yrs)					.262	.019
2		.128	.105	.059	5.201		.025
	Education (Yrs)					.235	.031
	Post-op CNS complication					-.244	.025
3		.314	.257	.186	4.951		**.001****
	Education (Yrs)					.119	.257
	Post-op CNS complication					-.301	**.004****
	RVEF					.222	.060
	LVEF					.128	.260
	ACE Medication					-.180	.089
**p<0.01							

Regression model for WCST- Failure to maintain set score in TGA

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	β	*Sig.*
1		.054	.042	.054	4.467		.038
	Education (Yrs)					-.233	.038
2		.131	.109	.077	6.849		.011
	Education (Yrs)					-.168	.129
	RVEF					-.285	.001**
**p<0.01							

Regression model for WCST-Trials to complete first category score in TGA

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.112	.100	.112	9.806		**.002****
	Post-op CNS complication					.334	**.002****
2		.231	.200	.119	5.876		**.004****
	Post-op CNS complication					.299	**.005****
	Negative affect					.271	.043
	Depression					.104	.446
**p<0.01							

Multivariate regression models for the SV group

Regression model for WAIS-III in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.247	.235	.247	20.680		**.009****
	Education (Yrs)					.497	.012
2		.524	.465	.277	5.523		**<0.001**
	Education (Yrs)					.344	**.001**
	Post-op CNS complication					-.351	**.001**
	Post-op infection					-.152	.125
	Palliation before repair					-.221	.023
	CPB minutes Q2					.222	.061
	CPB minutes Q3					.118	.314
	CPB minutes Q4					.000	1.000
3		.589	.530	.065	8.805		**.004****
	Education (Yrs)					.290	**.003****
	Post-op CNS complication					-.293	**.003****
	Post-op infection					-.201	.035
	Palliation before repair					-.209	.023
	CPB minutes Q2					.177	.112
	CPB minutes Q3					.201	.081
	CPB minutes Q4					.009	.933
	Positive affect					.293	**.004****
**<0.01							

Regression model for TMT-A in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.103	.089	.103	7.271		**.009****
	Post-op infection					.322	**.009****
2		.253	.203	.149	3.994		.012
	Post-op infection					.296	.014
	Pacemaker					.235	.051
	Diuretic medication					.260	.052
	Beta-blocker medication					.045	.754
**p<0.01							

Regression model for TMT-B in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.105	.091	.015	7.395		**.008****
	Post-operative infection					.324	**.008****
**p<0.01							

Regression model for COWA in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.165	.138	.165	6.112		**.004****
	Education (Yrs)					.302	.012
	Age					.233	.051
2		.238	.200	.073	5.864		.018
	Education (Yrs)					.237	.045
	Age					.172	.141
	Post-op CNS complications					-.287	.018
3		.267	.218	.029	2.377		.128
	Education (Yrs)					.203	.082
	Age					.167	.149
	Post-op CNS complications					-.247	.044
	Positive affect					.181	.128
**P<0.01							

Regression model for Stroop-word score in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.090	.045	.090	2.016		.121
	CPB minutes Q2					.329	.032
	CPB minutes Q3					.130	.393
	CPB minutes Q4					.020	.893
2		.147	.090	.056	3.966		.051
	CPB minutes Q2					.271	.074
	CPB minutes Q3					.193	.206
	CPB minutes Q4					.017	.909
	Positive affect					.257	.051

Regression model for Grooved pegboard-non dominant hand score in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.068	.053	.068	4.611		.036
	Post-operative infection					.261	.036

Regression model for WCST-Error score in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.167	.154	.167	12.622		**.001****
	Education (Yrs)					-.409	**.001****
2		.225	.200	.058	4.621		.035
	Education (Yrs)					-.379	**.001****

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
	Hypertension					.242	.035
3		.362	.320	.138	6.470		**.003****
	Education (Yrs)					-.272	.015
	Hypertension					.158	.144
	Post-op CNS complication					.344	.003
	Post-op infection					.164	.125
4		.443	.374	.080	2.738		.052
	Education (Yrs)					-.221	.045
	Hypertension					.135	.198
	Post-op CNS complication					.352	**.002****
	Post-op infection					.175	.093
	Current saturation Q1					.046	.708
	Current saturation Q2					.323	**.009****
	Current saturation Q3					.128	.314
5		.458	.370	.016	.796		.456
	Education (Yrs)					-.234	.036
	Hypertension					.117	.272
	Post-op CNS complication					.308	**.009****
	Post-op infection					.153	.159
	Current saturation Q1					.012	.924
	Current saturation Q2					.320	.010
	Current saturation Q3					.136	.289
	Diuretic medication					.086	.513
	Beta-blocker medication					.077	.530
6		.468	.369	.009	.953		.333
	Education (Yrs)					-.214	.059
	Hypertension					.116	.275
	Post-op CNS complication					.281	.020
	Post-op infection					.156	.151
	Current saturation Q1					-.024	.862
	Current saturation Q2					.305	.015
	Current saturation Q3					.115	.376
	Diuretic medication					.067	.615
	Beta-blocker medication					.090	.465
	Positive affect					-.111	.333
**p<0.01							

Regression model for WCST-Conceptual level responses score in SV

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.173	.160	.173	13.170		**.001****
	Education (Yrs)					.416	**.001****
2		.231	.206	.058	4.66		.035
	Education (Yrs)					.387	**.001****
	Hypertension					-.242	.035
3		.410	.371	.180	9.143		.029
	Education (Yrs)					.263	.014
	Hypertension					-.147	.156

	Post-op CNS complication					-.383	**.001****
	Post-op infection					-.203	.049
4		.496	.434	.086	3.225		**<0.001**
	Education (Yrs)					.213	.042
	Hypertension					-.117	.239
	Post-op CNS complication					-.384	**<0.001**
	Post-op infection					-.205	.039
	Current saturation Q1					.030	.800
	Current saturation Q2					-.303	.010
	Current saturation Q3					-.085	.479
5		.505	.434	.009	.964		.330
	Education (Yrs)					.222	.035
	Hypertension					-.108	.278
	Post-op CNS complication					-.361	**.001****
	Post-op infection					-.179	.081
	Current saturation Q1					.036	.761
	Current saturation Q2					-.306	**.009****
	Current saturation Q3					-.088	.465
	Beta-blocker medication					-.100	.330
**P<0.01							

Regression model for WCST-Trials to complete first category score in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.205	.192	.205	16.203		**<0.001**
	Post-op CNS complication					.452	**<0.001**
2		.321	.287	.116	5.220		**.008****
	Post-op CNS complication					.327	**.005****
	Diuretic medication					.271	.019
	Anti-arrhythmic medication					.201	.067
**P<0.001							

Regression model for WCST-Failure to maintain set score in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.091	.076	.091	6.228		.015
	Yrs. Since last operation					.301	.015
2		.159	.132	.068	5.031		.028
	Yrs. Since last operation					.284	.018
	Anti-coagulant medication					-.262	.028

Regression model for WCST-No categories completed score in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.081	.067	.081	5.560		.021
	Education (Yrs)						.021
2		.372	.331	.291	9.283		**<0.001**
	Education (Yrs)					.161	.138
	Palliation before repair					-.269	.012
	Post-op CNS complication					-.357	**.001****

	Post-op infection					-.220	.040
3		.398	.347	.026	2.514		.118
	Education (Yrs)					.176	.104
	Palliation before repair					-.264	.013
	Post-op CNS complication					-.315	**.006****
	Post-op infection					-.177	.103
	Beta-blocker medication					-.172	.118
**p<0.01							

Regression model for RAVLT in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.115	.086	.115	4.011		.023
	Age					.229	.062
	Education (Yrs)					.221	.072
2		.288	.214	.174	3.534		.012
	Age					.217	.065
	Education (Yrs)					.140	.238
	Post-op CNS infection					-.229	.059
	HA minutes Q2					.429	.003
	HA minutes Q3					.149	.283
	HA minutes Q4					.248	.077
3		.360	.281	.072	6.398		.014
	Age					.207	.066
	Education (Yrs)					.089	.437
	Post-op CNS infection					-.161	.172
	HA minutes Q2					.384	**.006****
	HA minutes Q3					.157	.237
	HA minutes Q4					.262	.051
	Positive affect					.290	.014
**p<0.01							

Regression model for SDMT-written score in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.109	.080	.109	3.784		.028
	Education (Yrs)					.214	.084
	Employment					.213	.087
2		.312	.241	.203	4.289		.028
	Education (Yrs)					.140	.227
	Employment					.172	.131
	HA minutes Q2					.361	.011
	HA minutes Q3					.141	.302
	HA minutes Q4					.282	.041
	Post-op infection					-.315	**.007****
3		.358	.279	.046	4.047		**.004****

	Education (Yrs)					.172	.133
	Employment					.104	.368
	HA minutes Q2					.322	.020
	HA minutes Q3					.078	.566
	HA minutes Q4					.236	.081
	Post-op infection					-.312	**.006**
	Negative affect					-.233	.049
**p<0.01							

Regression model for SDMT-Oral score in SV

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.138	.096	.138	3.259		.027
	Current saturation Q1					-.304	.037
	Current saturation Q2					-.360	.013
	Current saturation Q3					-.068	.645
2		.184	.115	.046	1.653		.200
	Current saturation Q1					-.194	.212
	Current saturation Q2					-.286	.057
	Current saturation Q3					-.006	.967
	Negative affect					-.105	.565
	Depression					-.146	.416

Multivariate regression models for the Simple group

Regression model for TMT-A in Simple group

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.222	.172	.222	4.442		**.001****
	Age at repair Q2					-.300	.019
	Age at repair Q3					.177	.147
	Age at repair Q4					-.171	.163
	CPB minutes Q3					.165	.122
	CPB minutes Q4					-.004	.973
2		.233	.173	.011	1.135		.290
	Age at repair Q2					-.268	.040
	Age at repair Q3					.179	.144
	Age at repair Q4					-.172	.159
	CPB minutes Q3					.150	.162
	CPB minutes Q4					-.005	.966
	Anxiety					.113	.290
**p<0.01							

Regression model for COWA in Simple group

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.227	.207	.227	11.862		**<0.001**
	Age					.427	**<0.001**

	Education (Yrs)					.403	**<0.001**
2		.276	.249	.050	5.489		.022
	Age					.414	**<0.001**
	Education (Yrs)					.417	**<0.001**
	HF clinic					-.224	.022
3		.298	.263	.022	2.483		.119
	Age					.419	**<0.001**
	Education (Yrs)					.395	**<0.001**
	HF clinic					-.175	.084
	LVEF					.158	.119
4		.374	.307	,076	2.267		.070
	Age					.400	**<0.001**
	Education (Yrs)					.343	.001**
	HF clinic					-.237	.023
	LVEF					.117	.238
	Positive affect					.027	.844
	Negative affect					.157	.309
	Anxiety					-.218	.139
	Depression					-.175	.332
**p<0.01							

Regression model for Stroop-Colour Word in Simple group

Block	***Predictor Variables***	***R^2***	***Adjusted R^2***	***ΔR^2***	***ΔF***	**β**	***Sig.***
1		.055	.044	.055	4.776		.032
	Employment					.235	.032
2		.081	.058	.025	2.245		.138
	Employment					.179	.117
	NYHA					-.169	.138
3		.144	.101	.064	2.950		.058
	Employment					.126	.266
	NYHA					-.156	.163
	HA minutes Q3					-.206	.066
	HA minutes Q4					.111	.313
4		.190	.138	.045	4.376		.040
	Employment					.131	.239
	NYHA					-.069	.554
	HA minutes Q3					-.236	.033
	HA minutes Q4					.138	.202
	ACE medication					-.233	.040
5		.319	.237	.130	3.523		.011
	Employment					.063	.553
	NYHA					-.003	.978
	HA minutes Q3					-.184	.083
	HA minutes Q4					.185	.076
	ACE medication					-.195	.069
	Positive affect					-.148	.301
	Negative affect					-.025	.872
	Anxiety					-.371	.019
	Depression					-.111	.556

Regression model for WAIS-III in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.291	.283	.291	33.708		**<0.001**
	Education (Yrs)					.540	**<0.001**
2		.317	.292	.026	1.517		.226
	Education (Yrs)					.506	**<0.001**
	Cathlab intervention total					-.015	.891
	Repairs total					.158	.123
3		.423	.378	.106	4.720		**.004****
	Education (Yrs)					.440	**<0.001**
	Cathlab intervention total					-.011	.909
	Repairs total					.115	.235
	Positive affect					.098	.448
	Anxiety					-.185	.171
	Depression					-.092	.514
**p<0.01							

Regression model for GP dominant hand score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.120	.109	.120	11.182		**.001****
	Gender (Males)					.346	**.003****
2		.222	.193	.102	5.272		**.007****
	Gender (Males)					.300	.063
	Positive affect					-.387	**.002****
	Negative affect					-.188	.116
**p<0.01							

Regression model for GP non-dominant hand score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.133	.111	.133	6.204		**.003****
	Yrs since last operation					.273	.010
	Total no. of palliations					.216	.041
2		.206	.176	.073	7.334		**.008****
	Yrs since last operation					.313	**.003****
	Total no. of palliations					.216	.034
	Anti-arrythmia medication					.273	**.008****
**p<0.01							

Regression model for WCST-error score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.097	.086	.097	8.793		**.004****
	Education					-.311	
2		.143	.122	.046	4.238		.039
	Education					-.302	.004**
	Hypertension					.216	.039
3		.285	.239	.141	5.136		**.003****
	Education					-.260	.011
	Hypertension					.253	.011
	Age at repair Q2					-.226	.055
	Age at repair Q3					-.367	.002
	Age at repair Q4					.029	.807
4		.332	.261	.048			.155
	Education					-.227	.027
	Hypertension					.253	.011
	Age at repair Q2					-.171	.153
	Age at repair Q3					-.362	**.002**
	Age at repair Q4					.044	.715
	Positive affect					.025	.854
	Negative affect					-.024	.875
	Depression					.262	.140
**p<0.01							

Regression model for WCST-conceptual level response score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.100	.078	.100	4.493		.014
	Age					-.166	.144
	Education (Yrs)					.218	.055
2		.138	.106	.039	3.582		.062
	Age					-.122	.284
	Education (Yrs)					.225	.045
	Hypertension					-.201	.062
3		.275	.219	.137	4.855		**.004****
	Age					.024	.857
	Education (Yrs)					.221	.037
	Hypertension					-.265	.010
	Age at repair Q2					.210	.081
	Age at repair Q3					.359	**.003****
	Age at repair Q4					-.077	.603
4		.322	.240	.047	1.709		.172
	Age					-.002	.989
	Education (Yrs)					.181	.091
	Hypertension					-.260	.013
	Age at repair Q2					.156	.200
	Age at repair Q3					.355	**.003****
	Age at repair Q4					-.077	.599

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
	Positive affect					-.006	.966
	Negative affect					.029	.852
	Depression					-.252	.161
**p<0.01							

Regression model for WCST-No. of categories completed score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.110	.088	.110	5.011		**.009****
	Age					-.138	.221
	Education (Yrs)					.258	.023
2		.252	.204	.142	4.935		**.003****
	Age					-.008	.951
	Education (Yrs)					.254	.018
	Age at repair Q2					.191	.113
	Age at repair Q3					.368	**.003****
	Age at repair Q4					-.074	.621
3		.347	.277	.095	3.624		.017
	Age					-.043	.730
	Education (Yrs)					.182	.081
	Age at repair Q2					.103	.381
	Age at repair Q3					.365	**.002****
	Age at repair Q4					-.084	.555
	Positive affect					.128	.339
	Negative affect					-.093	.531
	Depression					-.147	.393
**p<0.01							

Regression model for WCST-trials to complete first category score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.088	.077	.088	7.909		**.006****
	Education (Yrs)					-.297	**.006****
2		.138	.117	.050	4.724		.033
	Education (Yrs)					-.223	.043
	NYHA					.236	.033
3		.217	.167	.079	2.631		.056
	Education (Yrs)					-.143	.199
	NYHA					.211	.055
	Current saturation Q1					.302	.010
	Current saturation Q2					-.011	.929
	Current saturation Q3					.056	.631
4		.364	.306	.147	8.771		**<0.001**
	Education (Yrs)					.423	.423
	NYHA					.019	.019
	Current saturation Q1					.108	.108
	Current saturation Q2					.900	.900
	Current saturation Q3					.329	.329

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	β	*Sig.*
	Diuretic medication					.219	.219
	Anti-coagulant medication					.000	**<0.001**
5		.380	.314	.016	1.886		.174
	Education (Yrs)					-.071	.487
	NYHA					.326	.035
	Current saturation Q1					.169	.127
	Current saturation Q2					-.025	.815
	Current saturation Q3					.101	.350
	Diuretic medication					-.178	.232
	Anti-coagulant medication					.416	**<0.001**
	Depression					.131	.174
**p<0.01							

Regression model for RAVLT score in Simple group

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	β	*Sig.*
1		.075	.064	.075	6.641		.012
	Gender (Males)					-.247	.012
2		.159	.138	.084	8.055		**.006****
	Gender (Males)					-.224	.019
	Hypertension					-.291	**.006****
3		.190	.160	.032	3.121		.081
	Gender (Males)					-.237	.021
	Hypertension					-.149	.252
	ACE medication					-.228	.081
4		.245	.186	.055	1.869		.142
	Gender (Males)					-.229	.028
	Hypertension					-.148	.260
	ACE medication					-.204	.116
	Positive affect					.077	.589
	Negative affect					-.070	.662
	Depression					-.117	.537
**p<0.01							

Regression model for SDMT written score in Simple group

Block	*Predictor Variables*	*R^2*	*Adjusted R^2*	*ΔR^2*	*ΔF*	β	*Sig.*
1		.089	.078	.089	8.042		**.006****
	Education (Yrs)					.299	**.006****
2		.215	.175	.126	4.225		**.008****
	Education (Yrs)					.304	**.004****
	Age at repair Q2					.387	**.002****
	Age at repair Q3					.043	.724
	Age at repair Q4					.206	.103
3		.285	.220	.070	2.490		.067
	Education (Yrs)					.244	.022
	Age at repair Q2					.299	.016
	Age at repair Q3					.030	.798
	Age at repair Q4					.180	.146
	Positive affect					.192	.186
	Anxiety					-.220	.152
	Depression					.131	.404
**p<0.01							

Regression model for SDMT oral score in Simple group

Block	*Predictor Variables*	R^2	*Adjusted* R^2	ΔR^2	ΔF	β	*Sig.*
1		.069	.046	.069	2.983		.056
	Repairs surgery total					.143	.246
	Post-op ventricular dysfunction					.162	.188
2		.108	.074	.039	3.524		.064
	Repairs surgery total					.117	.338
	Post-op ventricular dysfunction					.167	.168
	Diuretic medication					-.200	.064
3		.176	.124	.068	3.243		.044
	Repairs surgery total					.071	.554
	Post-op ventricular dysfunction					.166	.162
	Diuretic medication					-.153	.151
	Positive affect					.192	.168
	Anxiety					-.103	.485

Appendix S: Visual Representation of the Irregular Distribution of Residuals in Regression Analysis

Figure 1 - Scatter plot of the distribution of the residuals on the RAVLT multivariate regression analysis for the total sample

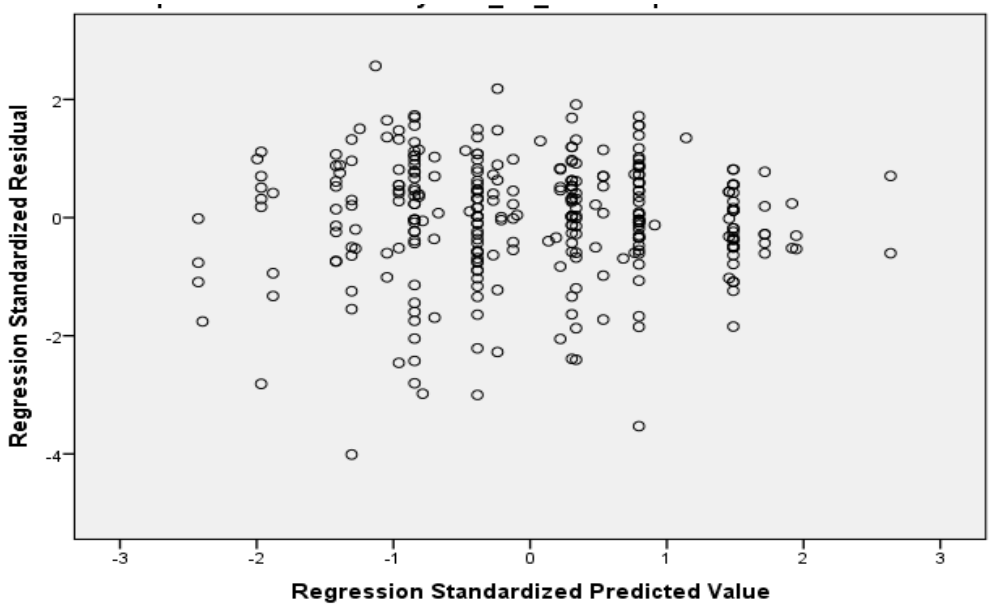
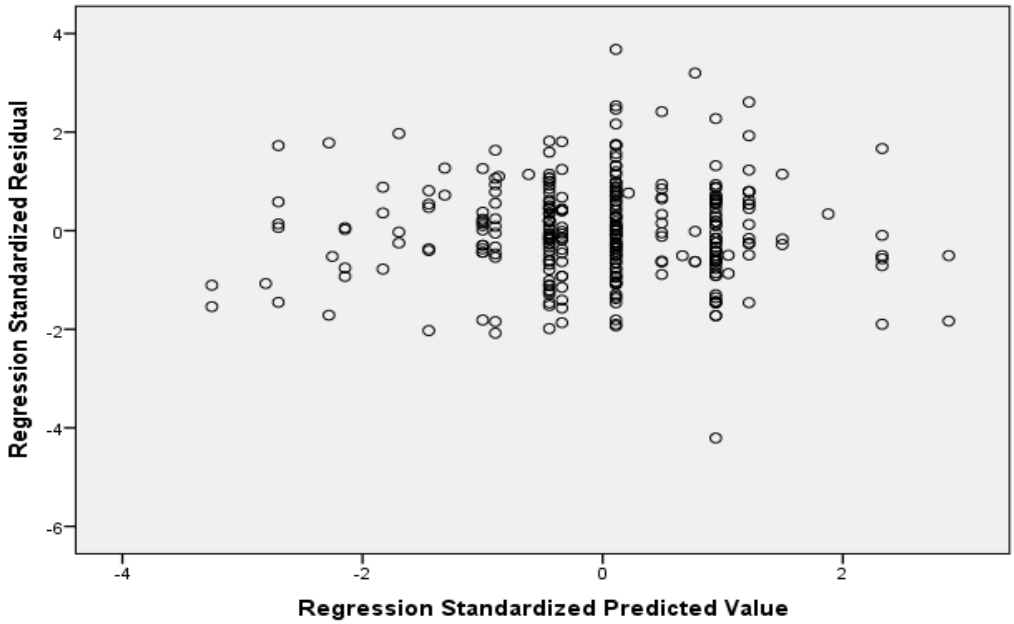


Figure 2- Scatter plot of the distribution of the residuals on the SDMT-Oral subtest multivariate regression analysis for the total sample



Appendix T: Follow-Up Study Information Sheet

University College London Hospitals NHS
NHS Foundation Trust

Consultants:
Dr Shay Cullen
Dr Fiona Walker
Prof Philipp Bonhoeffer
Prof John Deanfield

Surgeons:
Mr Victor Tsang
Ms Carin van Doorn
Mr Martin Kostolny

Clinical Nurse Specialists:
Ruth Brooks
Marie Francis
Fiona Kennedy
Kerry Romer

GUCH Office
The Heart Hospital
16-18 Westmoreland Street
London W1G 8PH
Tel: 020 7573 8808
Nurses: 020 7573 8872
Fax: 020 7573 8807
Email: guch.dept@uclh.org
Website: www.uclh.org

UCLH Project ID number : 08/0326

CONFIDENTIAL
INFORMATION SHEET (Version 3-11/11)

Quality of life in GUCH patients, follow-up

Investigators:	Professor Stanton Newman, Professor John Deanfield, Dr Shay Cullen, Jan Stygall, Fiona Kennedy, Marie Francis, Nathalie Picaut, Theodora Fteropoulli, Manavi Tyagi.
Contact details:	GUCH Unit, Heart Hospital, 16-18 Westmoreland St., London W1G 8PH Tel: 020 7573 8889

You are being invited to take part in a follow-up research study. Before you decide it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

Although various studies have been conducted into the quality of life of children with congenital heart disease very little has been carried out with adults with congenital heart disease. Moreover, there is little research examining how further treatment and disease progression affects the quality of life of GUCH patients. In order to better plan our services to support long term care we would find it extremely valuable to have an understanding of how congenital heart disease affects quality of life. Therefore, we in the GUCH Unit at the Heart Hospital, UCLH, and the Health Services Research Group at City University would like to find out how your heart condition affects your life and your functioning in the longer term, after your initial assessment.

The information you give us will then be used to improve the long-term care of adults with congenital heart disease.

Why have I been chosen?

You are being asked to take part in this follow-up study because you have a diagnosis of congenital heart disease and you have participated in the first phase of the study, about 2 years ago. Approximately, 220 patients will take part in this study over the next year.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. Your contribution to the first phase of this study will also remain unaffected.

What is involved in the study?

If you agree to take part in this study you will be asked to attend the Heart Hospital on the same day of your next outpatient appointment. The same procedure applies as in the first phase of the study. During the research appointment a researcher will take you through some questionnaires aimed to find out how your heart condition has impacted upon your life. The full appointment will take approximately 45mins.

What are the possible benefits of taking part?

Whilst there are no immediate benefits for people participating in this study, it is hoped that this work will contribute to improving the long-term care of adults with congenital heart disease.

Confidentiality of records

We also need permission to access your medical records, which relate directly to this study. All the information we obtain will be strictly confidential. City University will overview the collection, storage and handling of the data and Professor Newman, in his capacity of chief investigator, will be responsible for security and access to the data. Only study investigators (named above) will have access to the data. The information collected during the study, with exception of your name, will be stored and analysed confidentially in a computer. No identifiers on the data held by computer will enable a third party to link the data to you. A study ID number, assigned to you during the first phase of the study will appear on all data including medical information and questionnaires. All data will be kept strictly confidential and secured under lock and key in City University. The data will be stored for 5 years after the study has been completed. The results of this study may be published within the medical literature, however, no personal details will be revealed. Copies of the publications will be available to you from the researchers. A report of the findings of the follow-up research will be sent to all interested participants in approximately 3½ years from the start of the study.

Comments or concerns during the study

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions either at your appointment or on 020 7040 0871/0878. If you remain unhappy and wish to complain formally you can do this through

the Complaints Manager, UCLH, 2nd Floor West, 250, Euston Road, London NW1 2PQ. Please quote the UCLH project number at the top of this information sheet.

Ethics Committee Review

All proposals for research using human subjects are reviewed by an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Ethics Committee and NRES Committee London – Bentham in Ethics of Human Research.

Thank you for taking the time to read this. If you decide to take part you will be given a copy of this information sheet and a signed consent form to keep.

Appendix U: Follow-Up Study Consent Form

University College London Hospitals NHS
NHS Foundation Trust

GUCH Office
[redacted]
Tel: [redacted]
Nurses: [redacted]
Fax: [redacted]
Email: [redacted]
Website: www.uclh.org

UCLH Project ID number: 08/0326

CONFIDENTIAL
CONSENT FORM (Version 3-11/11)

Quality of life in GUCH patients, follow-up

Investigators:	Professor Stanton Newman, Professor John Deanfield, Dr Shay Cullen, Fiona Kennedy, Nathalie Picaut, Theodora Fteropoulli, Manavi Tyagi.
Contact details:	[redacted] Tel: [redacted]

Please read the following statements and initial box

1. I confirm that I have read and understand the information sheet (version 3-11/2011) for the above study and have had the opportunity to ask questions. ☐

2. I confirm that I have had sufficient time to consider whether or not I want to be included in the study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

4. I understand that data collected during the study, may be looked at by individuals from UCLH NHS Foundation Trust, from regulatory authorities or from the NHS Trust, Where it is relevant to my part in this research, I give permission for these individuals to have access to my records. ☐

5. I agree to take part in the above study. ☐

Continued on next page/

UCLH Project ID number: 08/0326

CONFIDENTIAL
CONSENT FORM (Version 3-11/11)

Signed: _____ Date: _____

Full name in block letters: _____

Signed (investigator): _____ Date: _____

Full name in block letters: _____

Comments or concerns during the study.

If you have a concern about any aspect of this study you should speak to the researchers who will do their best to answer your questions either at your appointment or on (telephone number yet to be provided). If you remain unhappy and wish to complain formally you can do this through the Complaints Manager, UCLH, 2nd Floor West, 250, Euston Road, London NW1 2PQ. Please quote the UCLH project number at the top of this consent form.

1 form for patient
1 to be kept as part of the study documentation
1 to be kept with hospital notes

Appendix V: NP Test Battery Follow-Up Study

Neuropsychological assessment Checklist (Follow-up):

Patient ID:
Date:

Task	Tick/Cross	Comments
Trail Making A		
Trail Making B		
Cowa		
Stroop: C		
Stroop: C-W		
Grooved Pegboard		
WCST		
Rey		
Symbol Written		
Symbol Oral		

Any additional comments

Researcher's Signature.....

GUCH Cognitive Coding

Patient ID

Trail making and Digit Symbol

Trial Making C
To Nearest Second
S S S

Trial Making D
To Nearest Second
S S S

Cowa

COWA B
(No. generated)

COWA D
(No. generated)

COWA T
(No. generated)

Stroop

Stroop C:
time to nearest second
S S S

Stroop C Correct
(number correct)

Stroop CW (2nd Stroop)
Time to nearest second
S S S

Stroop CW Correct
(2nd Stroop no. correct

Grooved Peg Board

Grooved Peg Board
Dom Time
S S S

Grooved Peg Board
Dom Drops

Grooved Peg Board
N/Dom Time
S S S

Grooved Peg Board
N/Dom Drops
S S

Wisconsin Card Sorting Task

WCST Correct (number of correct)

WCST perseverative Errors

Rey Memory Test

Memory List 1
No. of correct

Memory List 2
No. of correct

Memory List 3:
No. of correct

Memory List 4
No. of correct

Memory List 5:
No. of correct

Memory List 6:
No of correct

Memory List 7:
No of correct

Symbol Digit

Symbol Digit Written

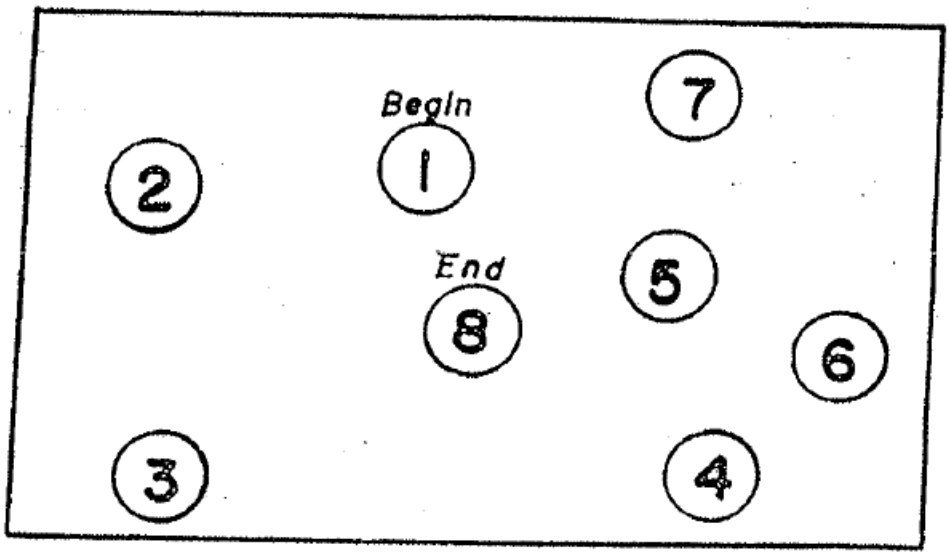
Symbol Digit Oral

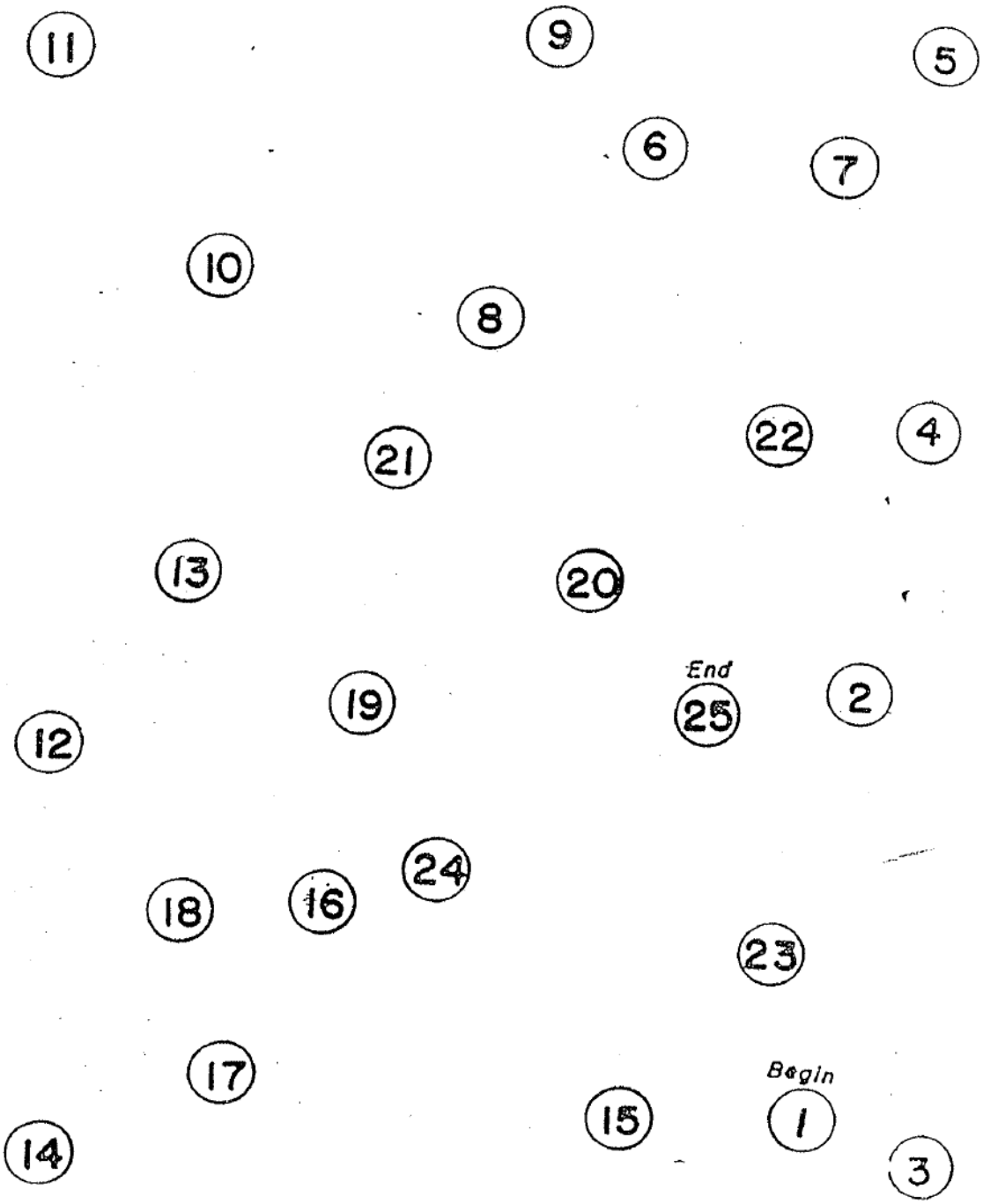
comments

TRAIL MAKING

Part: C

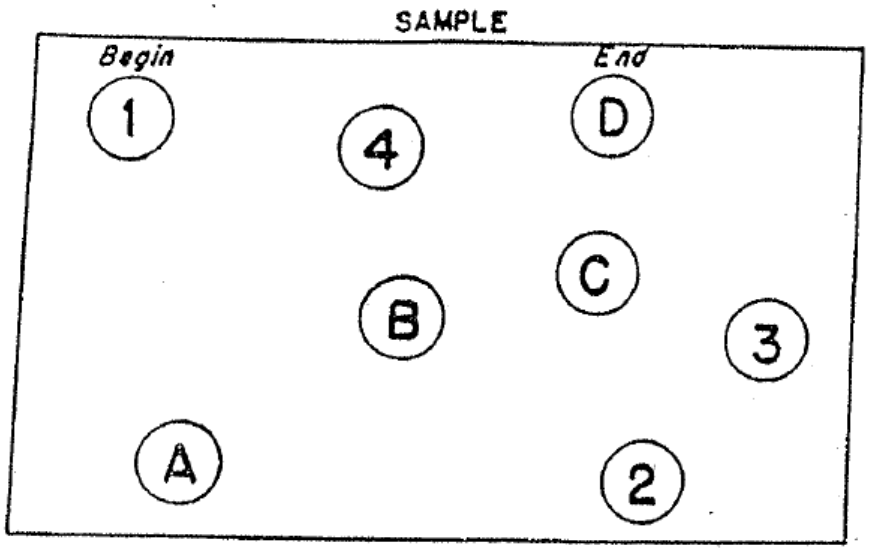
SAMPLE

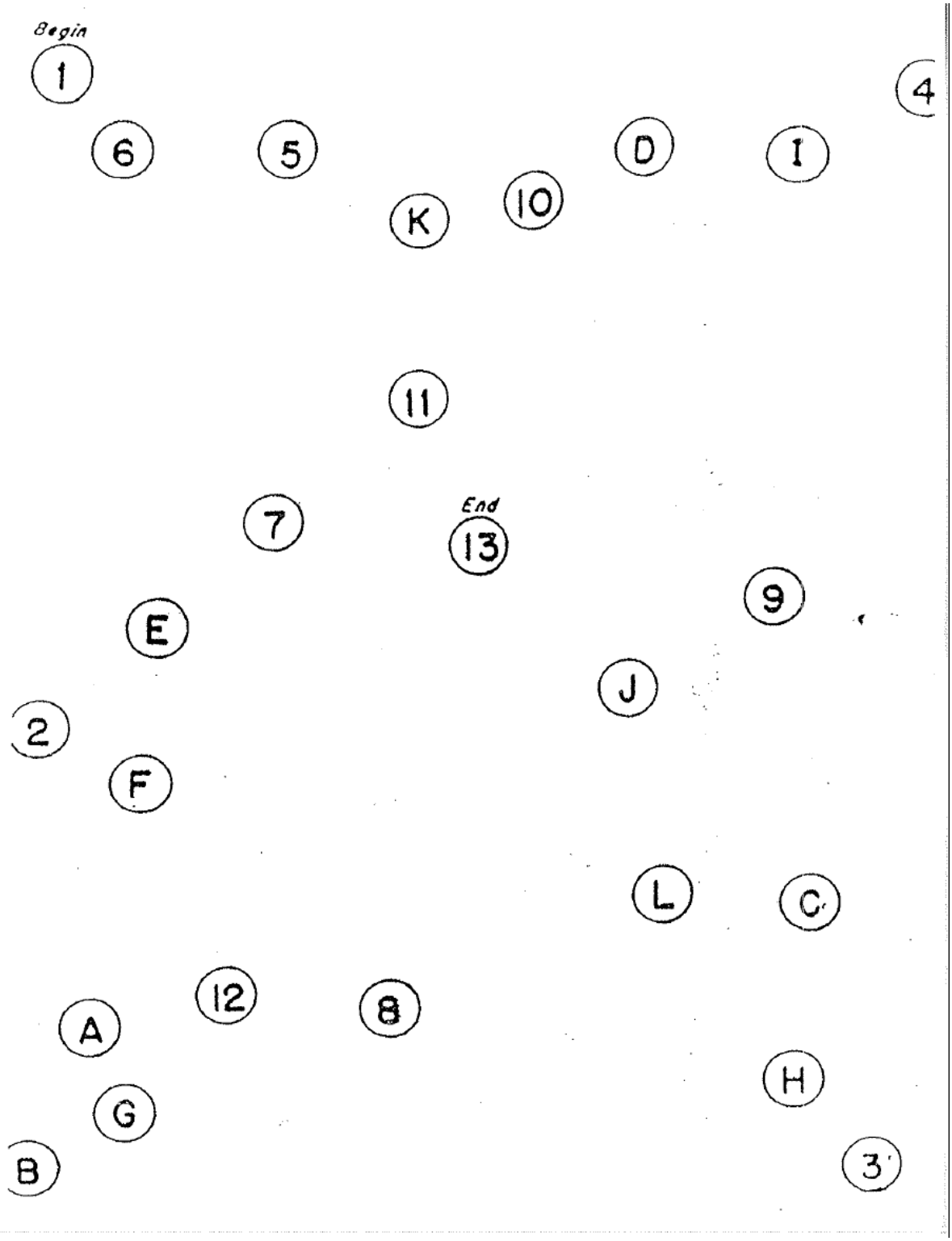



11
9
5
6
7
10
8
22
4
21
13
20
End
25
2
19
12
24
18
16
23
17
Begin
1
15
14
3

TRAIL MAKING

Part D




Begin
1
4
6
5
D
I
K
10
11
End
7
13
9
E
J
2
F
L
C
12
8
A
H
G
B
3

PATIENT ID: | | | |

TIME: | S | E | T |

COWA

Practice. Give me some words you can think of that begin with the letter C excluding proper nouns, numbers and the same word with different suffix.

Now I will be timing you.

Give as **many** words as you can think of that begin with the letter:- **(Time for 1 minute each letter).**

B D T

Form C Responses – Color Task

1 BLUE_____	29 RED_____	57 TAN_____	85 RED_____
2 GREEN_____	30 GREEN_____	58 RED_____	86 TAN_____
3 TAN_____	31 TAN_____	59 TAN_____	87 RED_____
4 RED_____	32 BLUE_____	60 BLUE_____	88 TAN_____
5 GREEN_____	33 GREEN_____	61 TAN_____	89 BLUE_____
6 BLUE_____	34 BLUE_____	62 RED_____	90 GREEN_____
7 GREEN_____	35 TAN_____	63 GREEN_____	91 RED_____
8 BLUE_____	36 GREEN_____	64 RED_____	92 BLUE_____
9 RED_____	37 TAN_____	65 BLUE_____	93 RED_____
10 BLUE_____	38 BLUE_____	66 TAN_____	94 TAN_____
11 TAN_____	39 GREEN_____	67 RED_____	95 GREEN_____
12 RED_____	40 BLUE_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 GREEN_____	69 RED_____	97 BLUE_____
14 GREEN_____	42 RED_____	70 TAN_____	98 RED_____
15 BLUE_____	43 BLUE_____	71 BLUE_____	99 BLUE_____
16 TAN_____	44 GREEN_____	72 TAN_____	100 RED_____
17 GREEN_____	45 TAN_____	73 GREEN_____	101 GREEN_____
18 RED_____	46 RED_____	74 TAN_____	102 RED_____
19 TAN_____	47 TAN_____	75 BLUE_____	103 BLUE_____
20 RED_____	48 GREEN_____	76 TAN_____	104 TAN_____
21 TAN_____	49 TAN_____	77 BLUE_____	105 BLUE_____
22 RED_____	50 RED_____	78 GREEN_____	106 GREEN_____
23 GREEN_____	51 BLUE_____	79 RED_____	107 BLUE_____
24 RED_____	52 RED_____	80 GREEN_____	108 RED_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 BLUE_____
26 BLUE_____	54 RED_____	82 RED_____	110 TAN_____
27 GREEN_____	55 TAN_____	83 GREEN_____	111 BLUE_____
28 TAN_____	56 BLUE_____	84 BLUE_____	112 GREEN_____

Form C-W Responses – Color-Word Task

1 RED_____	29 BLUE_____	57 BLUE_____	85 TAN_____
2 BLUE_____	30 TAN_____	58 TAN_____	86 RED_____
3 GREEN_____	31 GREEN_____	59 RED_____	87 GREEN_____
4 BLUE_____	32 RED_____	60 GREEN_____	88 BLUE_____
5 RED_____	33 BLUE_____	61 TAN_____	89 TAN_____
6 TAN_____	34 GREEN_____	62 RED_____	90 GREEN_____
7 BLUE_____	35 BLUE_____	63 GREEN_____	91 RED_____
8 RED_____	36 GREEN_____	64 BLUE_____	92 TAN_____
9 TAN_____	37 RED_____	65 GREEN_____	93 BLUE_____
10 GREEN_____	38 TAN_____	66 TAN_____	94 GREEN_____
11 BLUE_____	39 BLUE_____	67 BLUE_____	95 RED_____
12 RED_____	40 RED_____	68 GREEN_____	96 TAN_____
13 TAN_____	41 BLUE_____	69 RED_____	97 RED_____
14 BLUE_____	42 TAN_____	70 BLUE_____	98 GREEN_____
15 GREEN_____	43 RED_____	71 RED_____	99 RED_____
16 RED_____	44 TAN_____	72 GREEN_____	100 BLUE_____
17 TAN_____	45 BLUE_____	73 BLUE_____	101 RED_____
18 GREEN_____	46 RED_____	74 TAN_____	102 BLUE_____
19 BLUE_____	47 GREEN_____	75 GREEN_____	103 TAN_____
20 RED_____	48 BLUE_____	76 BLUE_____	104 GREEN_____
21 TAN_____	49 TAN_____	77 RED_____	105 RED_____
22 GREEN_____	50 GREEN_____	78 TAN_____	106 TAN_____
23 BLUE_____	51 RED_____	79 GREEN_____	107 BLUE_____
24 GREEN_____	52 TAN_____	80 RED_____	108 TAN_____
25 TAN_____	53 GREEN_____	81 TAN_____	109 RED_____
26 BLUE_____	54 TAN_____	82 BLUE_____	110 BLUE_____
27 TAN_____	55 BLUE_____	83 GREEN_____	111 GREEN_____
28 RED_____	56 RED_____	84 BLUE_____	112 TAN_____

TIME: S E T

PATIENT ID: | | |

Grooved Pegboard

Dominant Hand

Number of drops _____ Total ___

Time _____

Non-Dominant Hand

Number of drops _____ Total ___

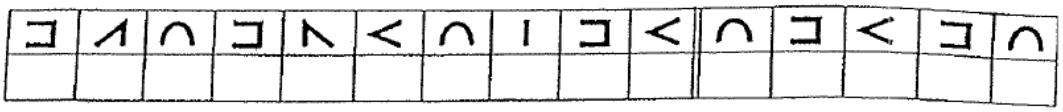
Time _____

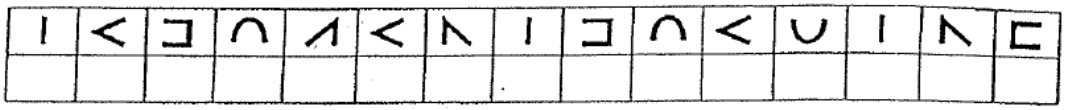
CATEGORY SEQUENCE: C F N C F N

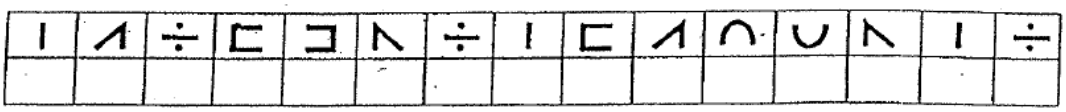
___ 1. C F N O	___ 17. C F N O	___ 33. C F N O	___ 49. C F N O
___ 2. C F N O	___ 18. C F N O	___ 34. C F N O	___ 50. C F N O
___ 3. C F N O	___ 19. C F N O	___ 35. C F N O	___ 51. C F N O
___ 4. C F N O	___ 20. C F N O	___ 36. C F N O	___ 52. C F N O
___ 5. C F N O	___ 21. C F N O	___ 37. C F N O	___ 53. C F N O
___ 6. C F N O	___ 22. C F N O	___ 38. C F N O	___ 54. C F N O
___ 7. C F N O	___ 23. C F N O	___ 39. C F N O	___ 55. C F N O
___ 8. C F N O	___ 24. C F N O	___ 40. C F N O	___ 56. C F N O
___ 9. C F N O	___ 25. C F N O	___ 41. C F N O	___ 57. C F N O
___ 10. C F N O	___ 26. C F N O	___ 42. C F N O	___ 58. C F N O
___ 11. C F N O	___ 27. C F N O	___ 43. C F N O	___ 59. C F N O
___ 12. C F N O	___ 28. C F N O	___ 44. C F N O	___ 60. C F N O
___ 13. C F N O	___ 29. C F N O	___ 45. C F N O	___ 61. C F N O
___ 14. C F N O	___ 30. C F N O	___ 46. C F N O	___ 62. C F N O
___ 15. C F N O	___ 31. C F N O	___ 47. C F N O	___ 63. C F N O
___ 16. C F N O	___ 32. C F N O	___ 48. C F N O	___ 64. C F N O

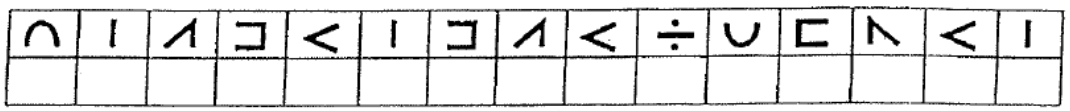
BOOK	BOOK	BOOK	BOOK	BOOK	BOWL	BOOK
FLOWER	FLOWER	FLOWER	FLOWER	FLOWER	DAWN	FLOWER
TRAIN	TRAIN	TRAIN	TRAIN	TRAIN	JUDGE	TRAIN
RUG	RUG	RUG	RUG	RUG	GRANT	RUG
MEADOW	MEADOW	MEADOW	MEADOW	MEADOW	INSECT	MEADOW
HARP	HARP	HARP	HARP	HARP	PLANE	HARP
SALT	SALT	SALT	SALT	SALT	COUNT	SALT
FINGER	FINGER	FINGER	FINGER	FINGER	POOL	FINGER
APPLE	APPLE	APPLE	APPLE	APPLE	SEED	APPLE
CHIMNEY	CHIMNEY	CHIMNEY	CHIMNEY	CHIMNEY	SHEEP	CHIMNEY
BUTTON	BUTTON	BUTTON	BUTTON	BUTTON	MEAL	BUTTON
LOG	LOG	LOG	LOG	LOG	COAT	LOG
KEY	KEY	KEY	KEY	KEY	BOTTLE	KEY
RATTLE	RATTLE	RATTLE	RATTLE	RATTLE	PEACH	RATTLE
GOLD	GOLD	GOLD	GOLD	GOLD	CHAIR	GOLD

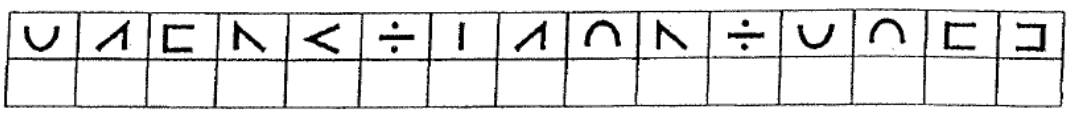
1	2	3	4	5	6	7	8	9

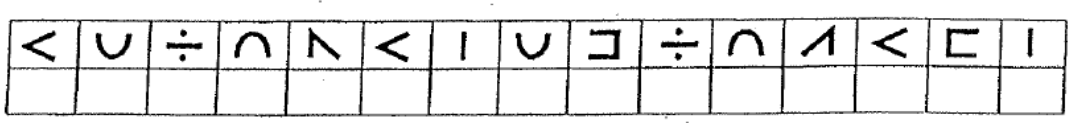


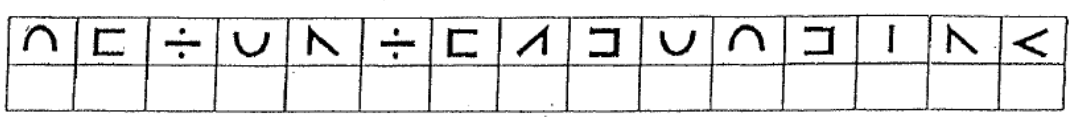


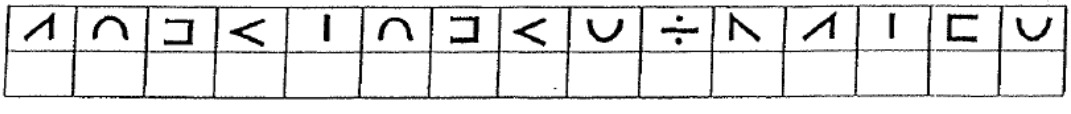












Appendix W: Follow-Up Study Missing Data

Variables	% of missing data
Demographic variables	
Employment	2.7
Age	2.7
Marital Status	2.7
Living Status	2.7
Psychosocial variables	
PANAS_PA_1	2.7
PANAS_NA_1	2.7
PANAS_PA_2	3.4
PANAS_NA_2	2.7
PANAS_PA_3	2.7
PANAS_NA_3	2.7
PANAS_NA_4	2.7
PANAS_NA_5	2.7
PANAS_PA_4	2.7
PANAS_PA_5	2.7
PANAS_NA_6	2.7
PANAS_PA_6	2.7
PANAS_NA_7	2.7
PANAS_PA_7	2.7
PANAS_NA_8	2.7
PANAS_PA_8	2.7
PANAS_PA_9	2.7
PANAS_NA_9	2.7
PANAS_PA_10	2.7
PANAS_NA_10	2.7
STAI_1	2.7
STAI_2	2.7
STAI_3	2.7
STAI_4	2.7
STAI_5	2.7
STAI_6	2.7
CESD10_1	2.7
CESD10_2	2.7
CESD10_3	3.4
CESD10_4	2.7
CESD10_5	2.7
CESD10_6	2.7
CESD10_7	2.7
CESD10_8	2.7
CESD10_9	2.7
CESD10_10	2.7
NP variables	
TMT C	0
TMT D	0

Variables	% of missing data
COWA B	0
COWA D	0
COWA T	0
Stroop C Correct	0
Stroop W Correct	0
GP Dominant Time	0
GP Non Dominant Time	0
RAVLT TRIAL 1	0
RAVLT TRIAL 2	0
RAVLT TRIAL 3	0
RAVLT TRIAL 4	0
RAVLT TRIAL 5	0
RAVLT TRIAL 6	0
RAVLT TRIAL 7	0
Symbol Digit Written	0
Symbol Digit Oral	0
WCST Errors	0
WCST Conceptual Level	0
WCST No. Categories	0
WCST Trials1stCategory	0
WCST Failure to Maintain Set	0
Clinical variables	
HF Clinic	2.7
Arrhythmias	2.7
Hypertension	2.7
ACE medication	2.7
Diuretic medication	2.7
Beta-Blocker medication	2.7
Anti-arrhythmia medication	2.7
Anticoagulant medication	2.7
Interventions Total	2.7
Current Saturation	2.7
In Hospital Days	2.7
Co Morbidities Total	2.7
Medication Total	2.7

Note- PANAS- Positive And Negative Affect Scale, STAI- State and Trait Anxiety Inventory, CESD- Centre for Epidemiologic Study Depression Scale, TMT- Trail Making Test, COWA- Controlled Oral Word Association Test, RAVLT- Rey Auditory Verbal Learning Test, WCST- Wisconsin Card Sorting Test, HF- Heart Failure, ACE- angiotensin-converting-enzyme

Appendix X: Follow-Up Study Kolmogorov-Smirnov Test Results

Kolmogorov-Smirnov for demographic variables (Follow-up data)

Variables	Kolmogorov-Smirnov test statistic	
	Statistic	p value
Age	.146	**<0.001**
Marital Status	.443	**<0.001**
Living Status	.402	**<0.001**
Total Years in Education	.205	**<0.001**
Employment	.491	**<0.001**
Occupation Category	.205	**<0.001**

Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution.

Kolmogorov-Smirnov for the Neuropsychological test scores (raw scores) (Follow-up data)

Variables	Kolmogorov-Smirnov test statistic	
	Statistic	p value
Trail making C	.148	**<0.001**
Trail making D	.218	**<0.001**
Controlled Oral Word Association letter B	.083	**.011**
Controlled Oral Word Association letter D	.066	.096
Controlled Oral Word Association letter T	.070	.063
Stroop word no correct	.250	**<0.001**
Peg dominant hand time	.225	**<0.001**
Peg Non-dominant hand time	.222	**<0.001**
RAVLT Trial 1	.147	**<0.001**
RAVLT Trial 2	.110	**<0.001**
RAVLT Trial 3	.114	**<0.001**
RAVLT Trial 4	.158	**<0.001**
RAVLT Trial 5	.136	**<0.001**
RAVLT Trial 6	.163	**<0.001**
RAVLT Trial 7	.135	**<0.001**
Symbol digit written	.075	.035
Symbol digit oral	.057	.200
Wisconsin card sort Errors	.188	**<0.001**
Wisconsin card sort Conceptual Level	.176	**<0.001**
Wisconsin card sort No. Categories	.233	**<0.001**
Wisconsin card sort Trials1stCategory	.397	**<0.001**
Wisconsin card sort Failure Maintain	.376	**<0.001**

Interpretation key- A significant ($p<0.001$) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution; RAVLT- Rey Auditory Verbal Learning Test

Kolmogorov-Smirnov results for the psychosocial variables (Scaled scores) (Follow-up data)

Variables	Kolmogorov-Smirnov test statistic	
	Statistic	p value
Physical component summary	.184	**<0.001**
Mental component summary	.135	**<0.001**
PANAS- Positive affect	.090	.004
PANAS- Negative affect	.182	**<0.001**
Sum STAI	.123	**<0.001**
Sum CESD-10	.129	**<0.001**

Interpretation key- A significant (p<0.001) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution. PANAS- Positive and Negative Affect Scale, STAI- State and Trait Anxiety Inventory, CESD-Center for Epidemiological Studies Depression Scale.

Kolmogorov-Smirnov for NP and mood change scores (Follow-up data-used in the multiple hierarchical regression analysis in follow-up study)

Variables	Kolmogorov-Smirnov test statistic	
	Statistic	p value
NP variables change scores		
TMT-A	.129	**<0.001**
COWA	.076	.031
GP-DOMINANT	.128	**<0.001**
GP-NON-DOMINANT	.221	**<0.001**
RAVLT	.064	.200
SDMT-ORAL	.088	.006
Mood variables change scores		
PANAS-PA	.052	.200
PANAS-NA	.110	**<0.001**
STAI	.112	**<0.001**
CESD-10	.131	**<0.001**

Interpretation key- A significant (p<0.001) Kolmogorov-Smirnov statistic is indicative of a non-normal distribution; TMT- Trail Making Test, COWA- Controlled Oral Word Association test, GP- Grooved Pegboard, RAVLT- Rey Auditory Verbal Learning Test, SDMT- Symbol Digit Modalities Test, PANAS- Positive and Negative Affect Scale, STAI- State and Trait Anxiety Inventory, CESD-Center for Epidemiological Studies Depression Scale.

Appendix Y: Differences between Responders and Non-Responders on Follow-Up Study

Sample characteristics	Responders	Non-responders	Test statistic	Sig.
Demographic variables				
Age (mean, SD)	33.78 (11.38)	32.73(10.01)	f(1,308)=1.851	0.391
Total years of education (mean, SD)	13.56(2.98)	13.26(2.72)	f(1,308)=2.620	0.365
Gender (N %)			$X^2(1)=.185$	0.731
Males	84(54.9%)	90(57.3%)		
Females	69(45.1%)	67(42.7%)		
Marital status (N %)			$X^2(1)=4.165$	0.053
Married/in a relationship	69(45.1%)	89(56.7%)		
Single/divorced/widowed	84(54.9%)	68(43.3%)		
Ethnicity (N %)			$X^2(1)=2.169$	0.159
White-British	134(87.6%)	128(81.5%)		
Others	19(12.4%)	29(18.5%)		
Living status (N %)			$X^2(1)=.320$	0.053
Cohabiting	127(83.0%)	89(56.7%)		
Alone	26(17.0%)	68(43.3%)		
Employment status (N %)			$X^2(1)=1.139$	0.329
Employed	109(71.2%)	103(65.6%)		
Unemployed/studying	44(28.8%)	54(34.4%)		
Clinical variables				
Post-op CNS complication (N%)			$X^2(1)=1.26$	0.345
No	146(95.4%)	145(92.4%)		
Yes	7(4.6%)	12(7.6%)		
Post-op infection (N%)			$X^2(1)=.277$	0.602
No	117(76.5%)	116(73.9%)		
Yes	36(23.5%)	41(26.1%)		
HF clinic (N%)			$X^2(1)=.065$	0.882
No	125(81.7%)	130(82.8%)		
Yes	28(18.3%)	27(17.2%)		
Arrhythmia (N%)			$X^2(1)=.155$	0.701
No	111(72.5%)	117(74.5%)		
Yes	42(27.5%)	40(25.5%)		
Hypertension (N%)			$X^2(1)=.088$	0.853
No	138(90.2%)	140(89.2%)		
Yes	15(9.8%)	17(10.8%)		
Pacemaker (N%)			$X^2(1)=.645$	0.463
No	143(93.5%)	150(95.5%)		
Yes	10(6.5%)	7(4.5%)		

Sample characteristics	Responders	Non-responders	Test statistic	Sig.
ACE (N%)			$X^2(1)=.025$	0.891
No	121(79.1%)	123(78.3%)		
Yes	32(20.9%)	34(21.7%)		
Diuretic medication (N%)			$X^2(1)=3.584$	0.072
No	141(92.2%)	134(85.4%)		
Yes	12(7.8%)	23(14.6%)		
Beta-blockers (N%)			$X^2(1)=.041$	0.88
No	128(83.7%)	130(82.8%)		
Yes	25(16.3%	27(17.2%)		
Anti-arrhythmia medication (N%)				
No	134(87.6%)	140(89.2%)	$X^2(1)=.191$	0.724
Yes	19(12.4%)	17(10.8%)		
Anti-coagulant medication (N%)			$X^2(1)=.069$	0.895
No	114(74.5%)	119(75.8%)		
Yes	39(25.5%)	38(24.2%)		
NYHA			$X^2(1)=2.713$	0.12
Class 1	139(90.8%)	133(84.7%)		
Class 2+3+4	14(9.2%)	24(15.3%)		
Repair age in months (Mean, SD)	122.84(187.587)	112.9(167.972)	f(1,308)=0.159	0.624
Interventions total (Mean, SD)	2.29(1.376)	2.39(1.334)	f(1,308)=0.216	0.513
Repair total (Mean, SD)	1.16(0.73)	1.2(0.696)	f(1,308)=0.004	0.618
Palliations total (Mean, SD)	0.46(0.787)	0.48(0.852)	f(1,308)=0.967	0.884
Catheter lab total (Mean, SD)	0.67(1.039)	0.71(0.968)	f(1,308)=0.038	0.682
Yrs. Since last operation (Mean, SD)	15.82(12.625)	16.51(11.998)	f(1,308)=0.635	0.621
Cyanotic days (Mean, SD)	1249.93(2621.231)	1317.94(2745.12)	f(1,308)=0.742	0.824
Current saturation (Mean, SD)	95.97(4.253)	95.83(5.424)	f(1,308)=0.399	0.811
ICU days (Mean, SD)	5.73(5.667)	5.71(6.167)	f(1,308)=0.106	0.97
CPB minutes (Mean, SD)	96.05(77.762)	96.22(74.137)	f(1,308)=0.023	0.985
HA minutes (Mean, SD)	31.73(26.952)	29.31(25.36)	f(1,308)=0.949	0.416
Hospital days (Mean, SD)	38.43(32.288)	42.87(67.578)	f(1,308)=0.732	0.463
Co-morbidities (Mean, SD)	0.967(1.05)	0.955(1.10)	f(1,308)=0.146	0.923
Medications total (Mean,	0.94(1.26)	0.97(1.34)	f(1,308)=0.479	0.856

Sample characteristics	Responders	Non-responders	Test statistic	Sig.
SD)				
LVEF (Mean, SD)	61.1(8.51)	60.96(8.469)	f(1,308)=0.402	0.882
RVEF (Mean, SD)	57.93(7.41)	57.11(9.511)	f(1,308)=4.672	0.402
Cognition measures				
TMT-A (Mean, SD)	0.62(1.42)	0.81(1.72)	f(1,308)=5.642	0.463
TMT-B (Mean, SD)	0.63(1.41)	0.80(1.92)	f(1,308)=5.472	0.363
COWA (Mean, SD)	-0.61(1.02)	-0.73(1.06)	f(1,308)=0.502	0.291
Stroop-CW (Mean, SD)	-0.09(1.30)	-0.49(1.62)	f(1,308)=6.824	0.019
GP-Dominant (Mean, SD)	0.92(1.84)	1.03(1.65)	f(1,308)=0.145	0.583
GP-Non-dominant (Mean, SD)	0.74(1.35)	0.73(1.35)	f(1,308)=0.311	0.973
WCST-error (Mean, SD)	0.50(1.08)	0.68(1.22)	f(1,308)=4.168	0.18
WCST-Conceptual level (Mean, SD)	-0.48(1.07)	-0.65(1.22)	f(1,308)=4.421	0.181
WCST- no. Categories (Mean, SD)	-0.44(1.09)	-0.61(1.19)	f(1,308)=1.724	0.178
Trial to complete 1st (Mean, SD)	0.23(2.62)	0.16(1.57)	f(1,308)=0.175	0.77
Failure to maintain (Mean, SD)	-0.02(0.83)	0.13(1.02)	f(1,308)=5.111	0.132
RAVLT (Mean, SD)	0.58(0.92)	0.47(1.03)	f(1,308)=1.222	0.292
SDMT-Written (Mean, SD)	0.26(1.50)	-0.02(1.58)	f(1,308)=0.019	0.099
SDMT-Oral (Mean, SD)	0.45(1.55)	0.38(1.52)	f(1,308)=0.138	0.678
WAIS-III	98.38(15.02)	95.44(15.76)	f(1,308)=0.66	0.095

Note- NYHA- New York Health Association, CPB-Cardo pulmonary bypass, HA-Hypothermic Arrest, ICU-intensive Care Unit, CNS- Central Nervous System, LVEF-Left Ventricle Ejection Fraction, RVEF- Right Ventricle Ejection Fraction, TMT- Trail Making Test, COWA- Controlled Oral Word Association test, GP- Grooved Pegboard, WCST- Wisconsin Card Sorting Test, RAVLT- Rey Auditory Verbal Learning Test, SDMT- Symbol Digit Modalities Test

Appendix Z: Univariate Screening for Factors Associated with Cognitive Change Scores in the Follow-Up Study

	COWA Change score	TMT-A Change score	GP-Dom Change score	GP Non-Dom Change score	RAVLT Change score	SDMT-O Change score
Age	-0.06	-0.077	0.015	-0.089	0.095	0.068
Education (years)	0.189*	-0.223**	0.017	-0.006	0.227**	0.127
Gender (Males)	0.02	0.033	0.013	0.051	-0.028	0.064
Employment	-0.046	0.016	-0.007	0.13	0.083	0.174*
Arrhythmia	0.02	0.098	0.07	-0.108	0.044	-0.046
Hypertension	-0.032	0.023	0.074	-0.015	0.079	0.021
NYHA	-0.022	0.178*	0.241**	-0.038	0.103	-0.071
Interventions total	-0.046	0.269**	0.187*	-0.087	-0.154	-0.134
Repair total	-0.104	0.08	0.156	0.003	-0.121	0.01
Palliation before repair	0.008	0.144	0.066	0.057	-0.033	-0.139
Years since last intervention	0.113	-0.161*	-0.006	0.191*	0.115	0.09
Post-op CNS complication	0.125	0.09	0.006	0.104	-0.134	-0.039
Post-op infection	0.077	0.155	0.054	-0.072	0.024	0.048
Post-op ventricular dysfunction	-0.103	0.079	0.131	-0.031	-0.01	-0.037
HF clinic	0.004	0.188*	0.089	-0.196*	-0.043	-0.041
Pacemaker	-0.118	0.205*	0.052	-0.089	-0.09	-0.087
ACE medication	-0.037	0.055	0.211**	0.044	-0.045	-0.099
Diuretic medication	-0.172*	0.092	0.031	0.095	-0.13	-0.115

	COWA Change score	TMT-A Change score	GP-Dom Change score	GP Non-Dom Change score	RAVLT Change score	SDMT-O Change score
Beta blocker medication	-0.011	0.177*	0.01	-0.019	-0.008	0.007
Anti-arrythmia medication	-0.04	0.205*	0.098	0.034	-0.018	-0.036
Anti-coagulant medication	-0.046	0.246**	-0.019	-0.028	0.017	-0.167*
RVEF	0.014	-0.106	-0.196*	0.029	-0.013	0.054
LVEF	-0.019	-0.228**	-0.17*	0.018	0.137	-0.013
Palliation total	0.015	0.108	0.048	-0.008	-0.113	-0.172*
Catheter lab total	-0.024	0.156	0.092	-0.042	0.009	-0.067
Medication total	-0.005	0.21*	0.043	0.048	-0.012	-0.035
Age at repair Q3	-0.157	0.039*	-0.026	0.074	-0.031	-0.034
Age at repair Q4	-0.193	-0.055	-0.162	-0.061	0.067	0.014
Cyanosis days Q2	0.065	-0.065	0.039	0.159	0.07	-0.027
Cyanosis days Q3	0.035	0.083	-0.041	-0.002	0.063	-0.05
Cyanosis days Q4	0.067	0.195	0.049	0.048	0.06	-0.158
Current saturationQ1	0.075	0.223*	-0.009	0.06	0.028	-0.01
Current saturationQ2	0.035	-0.053	0.049	0.091	0.198*	0.056
Current saturationQ3	-0.002	0.014	0.053	-0.025	-0.077	0.089
ICU days Q2	0.163	0.111	-0.163	-0.179	0.018	-0.046
ICU days Q3	0.054	0.154	-0.017	-0.01	0.007	-0.14
ICU days Q4	0.154	0.2	0.1	-0.082	0.144	-0.069

	COWA Change score	TMT-A Change score	GP-Dom Change score	GP Non-Dom Change score	RAVLT Change score	SDMT-O Change score
CPB minutes Q2	0.028	0.052	-0.109	-0.019	-0.011	0.034
CPB minutes Q4	0.116	0.234	0.079	0.093	-0.05	-0.061
HA minutes Q2	-0.112	0.03	-0.109	-0.111	-0.063	0.128
HA minutes Q3	-0.12	0.116	-0.09	-0.057	-0.061	0.142
HA minutes Q4	-0.068	0.207	0.015	0.062	0.008	0.059
In hospital days Q2	0.083	-0.048	0.006	-0.066	0.063	0.045
In hospital days Q3	0.05	-0.074	-0.087	-0.166	-0.001	-0.033
In hospital days Q4	-0.058	0.236*	0.138	-0.188	0.01	-0.071
PANAS PA	-0.076	-0.055	0.06	0.014	0.068	0.016
PANAS NA	0.01	-0.055	-0.008	-0.051	-0.091	-0.01
STAI	-0.049	-0.066	0.101	-0.041	-0.033	0.021
CESD	0.083	-0.121	-0.075	-0.033	-0.092	-0.09

***P<0.05, **P<0.01;** NYHA- New York Health Association, CNS- Central Nervous System, HF-Heart Failure, ACE-angiotensin converting enzyme, , LVEF- Left Ventricular Ejection Fraction, RVEF- Right Ventricular Ejection Fraction, ICU-Intensive Care Unit, HA-Hypothermic Arrest, ACE-Angiotensin Converting Enzyme,; PANAS= Positive and Negative Scale, STAI= State and Trait Anxiety Inventory, CESD= Centre for Epidemiology Short Depression Scale,

Appendix AA: Published Study Paper