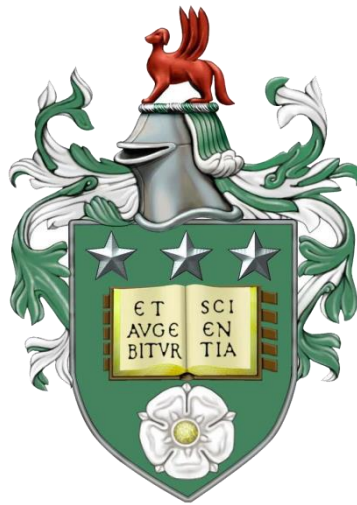# Cognitive function in cystic fibrosis and cystic fibrosis related diabetes (CFRD)

by

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The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Chapter 5:

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Chapter 7:

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Acknowledgements

Abstract

Cystic fibrosis (CF) is a complex multisystem disease caused by a gene mutation of a protein called the CF Transmembrane Conductance Regulator (CFTR). Glucose tolerance abnormalities are common in CF and the prevalence of CF related diabetes (CFRD), which shares clinical characteristics with type 1 (T1DM) and type 2 diabetes (T2DM), increases with age. Impaired glucose tolerance (IGT), T1DM and T2DM are associated with cognitive impairment relative to healthy controls. The overall aim of this thesis was to examine cognitive function in CF. Study 1 investigated the impact of CF on cognitive function, in people with CFRD (n=49), people with CF who are not diabetic (CFND, n=49) and healthy controls (n=49). Memory, attention and processing speed, and cognitive flexibility was impaired in CFRD, and to a lesser degree in CFND, relative to healthy controls. Study 2 assessed cognitive function over a 1-3 year period in people with CFRD (N=36) and found no evidence of cognitive decline despite a decline in lung function. Study 3 compared cognitive function in people with CFRD who were post transplant (CFRDTx, n=18), people with CFRD (who were not post transplant, n=18), and healthy controls (n=18). CFRD was associated with impairment in attention and processing speed, spatial working memory, cognitive flexibility and to a lesser extent verbal memory. Cognitive function did not improve post transplantation in people with CFRD. Study 4 followed up people with CFRDTx (N=8) over an 18±6 month period and found no decline in cognitive function. Taken together, the evidence presented in this thesis suggests that diabetes in CF is associated with cognitive impairment, and that maintaining glycaemic control protects against cognitive decline. The cognitive impairment observed in people with CF is of clinical significance and has implications for self care and disease management. The recent discovery that CFTR is present in the pancreas and the brain has important implications for the effects of the new CFTR potentiator and corrector therapies on cognitive function in CF.

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List of Abbreviations

4CRT	Four Choice Reaction Time
α	Alpha
ABC	ATP-binding cassette
ABI	Ankle branchial index
ABPA	Allergic Bronchopulmonary Aspergillosis
ACCORD-MIND	Action to Control Cardiovascular Risk in Diabetes- Memory in Diabetes
ADDITION	Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AGCT	Army General Classification Test
AGE	Advanced Glycation End-products
APOE-ε4	Apolipoprotein E- ε4
ASL	Airway Surface Liquid
AST	Attention Switching Task
ATP	Adenosine triphosphate
AVLT	Auditory Verbal Learning Test
AWMA	Automated Working Memory Assessment
β	Beta
B. cepacia	Burkholderia Cepacia Complex
BADS-c	Behavioural Assessment of the Dysexecutive Syndrome in Children
BAS	British Ability Scales
BBB	Blood Brain Barrier
BDI	Beck Depression Inventory
Beery VMI	Beery-Buktenica Developmental Test of Visual-Motor Integration
BMI	Body Mass Index

BNT	Boston Naming Test
BOS	Bronchiolitis Obliterans Syndrome
BOT	Brunininks-Osertesky Test of Motor Development
BVFT	Borkowski Verbal Fluency Test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAT	Children's Apperception Test
CBAVD	Congenital Bilateral Absence of the Vas Deferens
CDS	Cognitive Difficulties Scale
CELF (-R)	Clinical Evaluation of Language Fundamentals (-Revised)
CES	Center for Epidemiologic studies
CF	Cystic Fibrosis
CFFPR	Cystic Fibrosis Foundation Patient Registry
CFND	Cystic fibrosis Non-Diabetes
CFQ	Cognitive Failures Questionnaire
CFRD	Cystic Fibrosis- Related Diabetes
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CGM	Continuous Glucose Monitoring
cIMT	carotid Intima-Media Thickness
Cl-	Chloride
CLOX	Clock drawing test
CMS	Children's Memory Scale
CNS	Central Nervous System
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
COPD	Chronic Obstructive Pulmonary Disease
COppm	Carbon Monoxide Parts Per Million
COWA	Controlled Oral Word Association Test
CPT	Continuous Performance Test
CRN	Clinical Research Network
CRP	C-Reactive Protein
CRT	Choice Reaction Time

CTEQ	Cognitive Test Evaluation Questionnaire
CTOPP	Comprehensive Test of Phonological Processing
CVLT	California Verbal Learning Test
CWAT	Controlled Word Association Test
DALI	Diabetes Atorvastatin Lipid Intervention
DART	Dutch Adult Reading Test
DBP	Diastolic Blood Pressure
DCCT	Diabetes Control and Complications Trial
DI	Disposition Index
DSP	Distal Symmetrical Polyneuropathy
DSST	Digit Symbol Substitution Test
DTVP-2	Developmental Test of Visual Perception (2nd edition)
EDIC	Epidemiology of Diabetes Interventions and Complications
EMIS	Egton Medical Information Systems
ENaC	Epithelial Sodium Channel
ERCF	European Epidemiologic Registry of Cystic Fibrosis
ET2DS	Edinburgh Type 2 Diabetes Study
EVT	Expressive Vocabulary Test
F	Female
FEF_{25-75}	The average forced expiratory flow during the mid 25-75% portion of the FVC
FEV_1	Forced Expiratory Volume in 1 Second
FEV_1 %predicted	Forced Expiratory Volume in 1 Second expressed as a percentage of the predicted normal for a person of the same sex, age and height
FH	Fasting Hyperglycaemia
FPG	Fasting Plasma Glucose
FSIQ	Full Scale Intelligence Quotient
FT	Full time
FVC	Forced Vital Capacity
GABA	γ (gamma)-Aminobutyric acid
GCLC	Glutamate-Cysteine Ligase Catalytic Subunit
GDS	Global Deterioration Scale

GI	Glycaemic Index
GIT	Groninger Intelligence Test
GLUT	Glucose transporter proteins
GSH	Glutathione
GST	Glutathione S-transferase
H. influenzae	Haemophilus influenza
HADS	Hospital Anxiety and Depression Scale
HARU	Human Appetite Research Unit
HbA1c	Glycated Haemoglobin.
HDL	High Density Lipoprotein
HPA	Hypothalamic-Pituitary-Adrenal
(H)RINTB	(Halstead)Reitan-Indiana Neuropsychological Test Batteries for Children
HRQoL	Health Related Quality of Life
IFCC	International Federation of Clinical Chemistry
IGF-1	Insulin-like Growth Factor-1
IGT	Impaired Glucose Tolerance
IL	Interleukin
IQ	Intelligence Quotient
IV	Intravenous
K_{ATP}	ATP-sensitive Potassium
(K-) BNT	(Korean-) Boston Naming Test
LDL	Low Density Lipoprotein
LLT	Location Learning Test
LSEQ	Leeds Sleep Evaluation Questionnaire
M	Male
MCI	Mild Cognitive Impairment
MHVS	Mill Hill Vocabulary Scale
MMSE	Mini Mental State Examination
MoCA	Montreal Objective Cognitive Assessment
MOT	Motor Screening Test

mRNA	Messenger Ribonucleic Acid
MRSA	Methicillin Resistant *S. aureus*
NA+	Sodium
NACFC	North American Cystic Fibrosis Conference
NART	National Adult Reading Test
NEPSY II	A Developmental NEuroPSYchological Assessment
NGT	Normal Glucose Tolerance
NHANES	National Health and Nutrition Examination Survey
NIHR	National Institute for Health Research
NIS	Neuropsychological Impairment Scale
NO	Nitric Oxide
NT-proBNP	N-terminal probrain natriuretic peptide
O2-	Superoxide
OGTT	Oral Glucose Tolerance Test
OH	Hydroxyl
OTS	One Touch Stocking of Cambridge
P. aeruginosa	Pseudomonas Aeruginosa
PAL	Paired Associate Learning
PASAT	Paced Auditory Serial Addition Task
PCO_2	Pulmonary Carbon Dioxide
PE(s)	Pulmonary Exacerbation(s)
PERT	Pancreatic Enzyme Replacement Therapy
PI	Pancreatic Insufficient
PIQ	Performance Intelligence Quotient
PIS	Participant Information Sheet
PO_2	Pulmonary Oxygen
PP	Pancreatic Polypeptide
PPM	Parts Per Million
PPVT	Peabody Picture Vocabulary Test
PRM	Pattern Recognition Memory
PS	Pancreatic Sufficient

PSIQ	Pittsburgh Sleep Quality Index
PSS	Perceived Stress Scale
PT	Part Time
QoL	Quality of Life
R&D	Research and Development
RAVLT	Rey Auditory Verbal Learning Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomised Control Trial
REC	Research Ethics committee
RINTB	Reitan-Indiana Neuropsychological Test Batteries For Children
RIQ	Recruitment Information Questionnaire
ROCF	Rey-Osterrieth Complex Figure
ROS	Reactive Oxygen Species
RPM	Raven's Progressive Matrices
RTI	Reaction Time
RVIP	Rapid Visual Information Processing
RVP	Rapid Visual Processing
S. aureus	Staphylococcus aureus
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDLT	Serial Digit Learning Test
SDS	Shwachman-Diamond syndrome
SE	Standard error
SES	Socioeconomic status
SILS	Shipley Institute of Living Scale
SJUH	St James's University Hospital
SOP	Standard operating procedure
SPS-6	Stanford Presenteeism Scale-6
SRT	Simple Reaction Time
SSP	Spatial Span
STAI	State-Trait Anxiety Inventory

SWM	Spatial Working Memory
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TCS/2	Test of Cognitive Skills/Second Edition
TEA-Ch	Test of Every Day Attention For Children
TIDES	The International Depression Epidemiological Study
TLX	Task Load Index
TMT (A, B)	Trail Making Test (Part A, Part B)
TNF-α	Tumour Necrosis Factor-α
TOH	Tower of Hanoi
TOL	Tower of London
TOMAL	Test of Memory and Learning
Tx	Transplantation
VAS	Visual Analogue Scales
VBM	Voxel-Based Morphometry
VIQ	Verbal Intelligence Quotient
VLDL	Very Low Density Lipoprotein
VRM	Verbal Recognition Memory
VSLT	Visual Spatial Learning Test
VVLT	Visual Verbal Learning Test
WAIS-R	Wechsler Adult Intelligence Scale-Revised
WAIT-II	Wechsler Individual Achievement Test-II
WC	Waist Circumference
WCST	Wisconsin Card Sorting Test
WHO	World Health Organisation
WISC-R	Wechsler Intelligence Scale for Children-Revised
WJ(-R) ACH	Woodcock-Johnson (-Revised) Tests of Achievement
WMS –R/III	Wechsler Memory Scale- Revised/3rd edition
WPPSI (-III or -R)	Wechsler Preschool and Primary Scale of Intelligence (-3rd Edition or – Revised)
WRAML	Wide Range Assessment of Memory and Learning

Glossary

Abluminal	Outer surface
Acinar cells	Cells of the pancreas which produce and transport enzymes that are passed into the duodenum where they assist in the digestion of food
Adenosine Triphosphate	Compound which stores energy in the cells containing adenine, ribose and three phosphate groups
Advanced Glycation End-products	Proteins or lipids that become glycated (non-enzymatic reaction) as a result of exposure to sugars (glucose, fructose, galactose). The formation of AGEs is a part of normal metabolism, but if excessively high levels of AGEs are reached in tissues and the circulation they can become pathogenic
Airway Surface Liquid	A tightly regulated liquid layer covering the luminal (apical) surface of the airway epithelium that plays a major role in protecting the lung against infection.
Albumin	A protein made by the liver.
Alpha-1 Antitrypsin Deficiency	A genetic disorder in which a person is deficient of the enzyme alpha-antitrypsin leading to healthy tissue being damaged
Alpha cells	Part of the endocrine pancreas, and produce glucagon
Allergic Bronchopulmonary Aspergillosis	Condition characterised by an exaggerated response of the immune system (a hypersensitivity response) to the fungus aspergillus
Aminoglycosides	A class of antibiotics used mainly in the treatment of aerobic gram-negative bacilli infections, although they are also effective against other bacteria including Staphylococci and Mycobacterium tuberculosis. Aminoglycosides are thought to work by inhibiting protein synthesis inside bacteria.
Amyloid	A description of proteins which have folded abnormally and then collected together. In this form they do not break down as easily as normal proteins and can build up in tissues and organs. If this build-up causes the tissues or organs to stop working properly, the resulting conditions are called amyloidosis.
Ankle Branchial Index	Ratio of blood pressure at the ankle to blood pressure in the upper arm. Compared to the arm, lower blood pressure in the leg is an indication of blocked arteries due to peripheral artery disease
Antioxidants	Molecules present in cells that prevent oxygen free radical reactions by donating an electron to the free radicals without becoming destabilized themselves. An imbalance between oxidants and antioxidants is the underlying basis of oxidative stress.

Apolipoprotein E	Type of lipoprotein (protein connected to a fat). APOE E is a major component of specific lipoproteins called very low-density lipoproteins (VLDL). A major function of VLDLs is to remove excess cholesterol from the blood and carry it to the liver for processing. Maintaining normal levels of cholesterol is essential for the prevention of cardiovascular diseases.
Apolipoprotein E- ε4	One of the 3 common polymorphisms in the APOE gene (others: ε2, ε3) which results in a single amino acid change in the APOE protein. APOE ε4 is a risk-factor gene for late onset Alzheimer's disease; however, inheriting an APOE ε4 allele does not mean that a person will definitely develop Alzheimer disease. People with one copy of the e4 allele have an increased risk and people who inherit two copies have a still higher chance.
Apoptosis	Cell death
Ascorbic acid	Vitamin C
Aspergillus Bronchitis	Chronic superficial infection of the lower airways (trachea and bronchi)
Astrocytes	The most abundant glial cells in the brain that are closely associated with neuronal synapses. They regulate the transmission of electrical impulses within the brain. Named because they are "star-shaped".
Atherogenic Dyslipidaemia	A triad of increased blood concentrations of small, dense LDL particles, decreased HDL particles, and increased triglycerides
Atherosclerosis	The build-up of fatty material inside arteries which causes them to harden. It is the leading cause of heart attacks, stroke, and peripheral vascular disease.
Atorvastatin	A cholesterol-lowering medication that blocks the production of cholesterol.
ATP-Binding Cassette	Transport system superfamily consisting of transmembrane proteins and membrane associated enzymes
ATP-sensitive Potassium Channel	Potassium channel that is inhibited by intracellular ATP and play key physiological roles in many tissues including muscle, pancreatic beta cells and the brain. In pancreatic beta cells, these channels regulate glucose-dependent insulin secretion. K_{ATP} channels couple cell metabolism to electrical activity of the plasma membrane by regulating membrane K^+ fluxes. A reduction in metabolism opens K_{ATP} channels, producing K^+ efflux, membrane hyperpolarization, and suppression of electrical activity. Conversely, increased metabolism closes K_{ATP} channels.
Atrophy	(of body tissue or an organ) waste away, especially as a result of the degeneration of cells.
Autonomic neuropathy	A group of symptoms that occur when there is damage to the nerves that manage every day body functions such as blood pressure, heart rate, sweating, bowel and bladder emptying, and digestion
Autosomal	Numbered as opposed to sex chromosomes
Beta cells	Part of the endocrine pancreas, and produce insulin
Biliary Atresia	A disorder in which inflammation develops within the bile ducts around the time of birth leading to scarring of the liver

Blood Brain Barrier	Highly selective barrier separating blood from extracellular fluid in the central nervous system. Formed by brain endothelial cells, which are connected by tight junctions, and allows passage of molecules such as water, some lipid-soluble molecules, glucose and amino acids.
Bronchiolitis Obliterans Syndrome	A form of chronic lung allograft dysfunction that affects a majority of lung transplant recipients and is the principal factor limiting long-term transplant survival. Results in inflammatory obstruction of the lungs tiniest airways (bronchioles). The bronchioles become damaged and inflamed which leads to excessive scarring that blocks the airways.
Burkholderia cepacia complex	Name for a group or "complex" of bacteria that can be found in soil and water. B. cepacia bacteria are an important cause of chronic respiratory infection among persons with cystic fibrosis and often resistant to common antibiotics.
C-Reactive Protein	A blood test marker for inflammation in the body. CRP is produced in the liver.
Calcineurin Inhibitors	Drugs which inhibit the action of calcineurin, a protein phosphatase involved in activating the T-cells of the immune system.
Carboxyhaemoglobin	A stable complex of carbon monoxide that forms in red blood cells when carbon monoxide is inhaled. Reduces capacity of the blood to deliver oxygen.
Carotenoids	Any of a class of mainly yellow, orange, or red fat-soluble pigments, including carotene, which give colour to plant parts. Carotenoids are potent antioxidants with the ability to quench singlet oxygen and other toxic oxygen species. Pancreatic insufficiency in cystic fibrosis is often associated with decreased carotenoid absorption.
Carotid Intima-Media Thickness	Measurement of the thickness of the inner two layers of the carotid artery - the intima and media, usually measured by ultrasound. Test alerts to any thickening when patients are still asymptomatic.
Catabolic State	A state of breaking down larger molecules into smaller ones within the body. For example, breaking down fats into fatty acids, proteins into amino acids, glycogen or other sugars down into glucose.
Catecholamines	Hormones produced by the adrenal glands. Included among catecholamines are epinephrine (adrenaline), norepinephrine (noradrenaline), and dopamine.
Cepacia Syndrome	B. cepacia is spread throughout the body, which causes rapid deterioration in lung function and can lead to death within weeks
Chronic Obstructive Pulmonary Disease	Group of lung conditions including emphysema (damage to the air sacs in the lungs) and chronic bronchitis long-term inflammation of the airways () that causes breathing difficulties. Occurs when lungs become inflamed, damaged and narrowed
Cognitive Reserve	The resilience of the brain to adequately function despite clinical damage
Congenital bilateral absence of the vas deferens	Condition in males where the vas deferens (tubes that carry sperm out the testes) fail to develop properly, resulting in infertility

CFTR	A member of the superfamily of ATP-binding cassette (ABC) transporters. This protein functions as a channel across the membrane of cells that produce mucus, sweat, saliva, tears, and digestive enzymes. The channel transports negatively charged particles called chloride ions into and out of cells. The transport of chloride ions helps control the movement of water in tissues, which is necessary for the production of thin, freely flowing mucus. The CFTR protein also regulates the function of other channels, such as those that transport positively charged particles called sodium ions across cell membranes. These channels are necessary for the normal function of organs such as the lungs and pancreas.
CFTR Corrector	Correctors overcome defective protein processing that normally results in the production of misfolded CFTR. This allows increased trafficking of CFTR to the plasma membrane
CFTR Gene	Provides instructions for making a protein called the cystic fibrosis transmembrane conductance regulator (CFTR). Mutations of CFTR gene result in Cystic Fibrosis.
CFTR Modulators	Small molecules that target specific defects caused by mutations in the CFTR gene. They are classified into three main groups: Potentiators, Correctors and Production correctors (or Read-through agents).
CFTR Potentiator	Potentiators increase the activity of defective CFTR at the cell surface. Potentiators can either act on gating defects or conductance defects.
Coccobacillus	A type of bacterium with a shape intermediate between cocci (spherical bacteria) and bacilli (rod-shaped bacteria)
Creatinine	A compound which is produced by metabolism of creatine and excreted in the urine. Elevated creatinine level signifies impaired kidney function or kidney disease.
Crystallised intelligence	The ability to utilise learned knowledge, experience and skills and is measured using VIQ subcomponents
Cyclosporine	Immunosuppressant medication. Used to prevent organ rejection in people who have received a liver, kidney, or heart transplant.
Cytokines	Small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names include lymphokine (cytokines made by lymphocytes), monokine (cytokines made by monocytes), chemokine (cytokines with chemotactic activities), and interleukin (cytokines made by one leukocyte and acting on other leukocytes). There are both pro-inflammatory cytokines and anti-inflammatory cytokines.
Delta cells	Part of the endocrine pancreas, and produce somatostatin (involved in the inhibition of both insulin and glucagon)
Diabetogenic	Diabetes producing
Diastolic Blood Pressure	Lowest pressure of blood when the heart relaxes between beats. A normal reading will be between 60 and 80.

Disposition Index	Product of measures of insulin sensitivity and first-phase insulin secretion. Shown to predict diabetes.
Distal Symmetrical Polyneuropathy	Umbrella term for nervous system disorders affecting the hands and feet which causes numbness, tingling, pain and weakness. Typically starts in the toes and slowly spreads proximally.
Dyslipidaemia	Characterised by the elevation of triglycerides (hypertriglyceridemia) and/or low high density lipoprotein (HDL) cholesterol in people with type 2 diabetes
Energy Homeostasis	The control of food intake and energy expenditure
Epithelial Sodium Channel	Membrane-bound ion channel that is selectively permeable to sodium (Na^+) ions. Involved in the reabsorption of sodium ions in kidney, lung, colon and sweat glands in aid of fluid homeostasis, osmolarity and blood pressure regulation.
Eosinophil	A specific type of white blood cell that protects your body against certain kinds of germs, mainly bacteria and parasites.
Euglycaemic	The condition of having a normal concentration of glucose in the blood.
exocytosis	Active transport in which a cell transports molecules (such as proteins) out of the cell via secretory vessels
F508del	The mutation F508del is the commonest cause of cystic fibrosis. It results from the deletion of Phenylalanine in position 508 of the Cystic Fibrosis Transmembrane conductance Regulator.
Fasting Hyperglycaemia	High levels of fasting plasma glucose. Observed in patients with diabetes
Fasting Plasma Glucose	Plasma glucose level after several hours of fasting and used to screen for (pre)diabetes. The World Health Organisation defines normal as below 6.1 mmol/l (110 mg/dl), impaired as between 6.1 and 6.9 mmol/l (111 mg/dl and 125 mg/dl) and diabetic as 7.0 mmol/l and above (126 mg/dl and above)
Fluid Intelligence	The ability to solve new problems, use logic in new situations, and identify patterns and relationships without prior knowledge and is measured using PIQ subcomponents.
Forced Expiratory Volume in 1 Second	Amount or volume of air exhaled during the first second of a forced breath
Forced Vital Capacity	Total amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.
γ (gamma)-Aminobutyric acid	Plays the principal role in reducing neuronal excitability throughout the nervous system and is responsible for muscle tone regulation
Glucagon	A peptide hormone, produced by alpha cells of the pancreas. It works to raise the concentration of glucose in the bloodstream
Glucocorticoids	A class of corticosteroids, which are a class of steroid hormones.
Gluconeogenesis	The biosynthesis of glucose from certain non-carbohydrate carbon substrates
Glucose Facilitation Effect	Increases in circulating glucose can facilitate cognitive function

Glucose Transporter Proteins	Membrane proteins that facilitate the transport of glucose over a plasma membrane. Each glucose transporter isoform plays a specific role in glucose metabolism determined by its pattern of tissue expression, substrate specificity, transport kinetics, and regulated expression in different physiological conditions. In the brain, GLUT- 1 and GLUT-3 are the two main transporters.
Glutamate-Cysteine Ligase, Catalytic Subunit	An enzyme that in humans is encoded by the GCLC gene. It is the first rate-limiting enzyme of glutathione synthesis
Glutathione	A tripeptide antioxidant, produced by the liver, which is present in the fluid of the epithelial lining and is transported by CFTR. Levels of GSH are found to be decreased in people with Cystic Fibrosis due to disturbed transport across epithelial cell membrane. Deficiency leads to lowered digestion and malabsorption of fat soluble antioxidant vitamins. This in turn contributes to defective antioxidant protection which can further exacerbate oxidative stress; hence, people with Cystic Fibrosis are more susceptible to oxidative stress and lung tissue degradation.
Glutathione S-transferase	Isozymes (group of different variants of the same enzyme) responsible for the catalysis of the reactive form of glutathione into its harmless form
Glycaemic Index	Describes the blood glucose response after consumption of a carbohydrate containing test food relative to a carbohydrate containing reference food, typically glucose or white bread A value of 100 represents the standard, an equivalent amount of pure glucose.
Glycogen	A large multi-branched polymer of glucose which is accumulated in response to insulin and broken down into glucose in response to glucagon. Glycogen is mainly stored in the liver and the muscles and provides the body with a readily available source of energy if blood glucose levels decrease.
Glycolysis	The breaking down of glucose and the formation of pyruvate with the production of two molecules of ATP.
Gram-negative	A group of bacteria that do not take up the crystal violet stain used in the Gram staining method of bacterial differentiation. Gram-negative bacteria are resistant to multiple drugs and are increasingly resistant to most available antibiotics
Gram-positive	A group of bacteria that take up the crystal violet stain used in the Gram staining method of bacterial differentiation, and then appear to be purple coloured when seen through a microscope. Gram positive bacteria are more receptive to antibiotics due to the absence of the outer membrane.
Gray matter	A major component of the central nervous system, consisting of neuronal cell bodies, neuropil (dendrites and myelinated as well as unmyelinated axons), glial cells (astroglia and oligodendrocytes), synapses, and capillaries.
Glyburide	Sulphonylurea insulin secretagogue
Glycogenesis	Conversion of glucose to glycogen for storage

Glycolysis	First step in the breakdown of glucose to extract energy for cellular metabolism
Haemophilus influenza	A Gram-negative coccobacillus that can cause serious invasive disease in children and adults. The most prevalent strain is type b (Hib).
HbA1c	Glycated haemoglobin. It develops when haemoglobin, a protein within red blood cells that carries oxygen throughout your body, joins with glucose in the blood, becoming 'glycated'.
Heterozygous	Individuals who are heterozygous for a certain gene carry two different alleles.
High Density Lipoprotein	Type of cholesterol, often referred to as 'good' cholesterol
Homozygous	Individuals who are homozygous for a certain gene carry two copies of the same allele
Hydroxyl	A free radical/reactive oxygen species. Consists of one atom of hydrogen and one of oxygen and is neutral or negatively charged.
Hypercapnia	Abnormally elevated carbon dioxide (CO_2) levels in the blood
Hyperglycaemia	A condition in which an excessive amount of glucose circulates in the blood plasma. Defined by the World Health Organisation as blood glucose levels greater than 7.0 mmol/L when fasting, and greater than 11.0 mmol/L 2 hours after meals.
Hypertension	Raised blood pressure
Hyperinsulinemia	A condition in which there are excess levels of insulin circulating in the blood relative to the level of glucose. While it is often mistaken for diabetes or hyperglycaemia, hyperinsulinemia can result from a variety of metabolic diseases and conditions.
Hyperintensities	Areas of high intensity on types of magnetic resonance imaging (MRI) scans of the human brain i.e. an area that appears lighter in colour than the surrounding tissues;
Hyperlipidaemia	An abnormal increase in the levels of fats (lipids), including cholesterol, in the blood.
Hypoglycaemia	Occurs when blood glucose levels fall below 4 mmol/L i.e. too low
Hypoinsulinemia	Abnormally low concentration of insulin in the blood
Hypothalamic-Pituitary-Adrenal Axis	A complicated set of relationships and signals that exist between the hypothalamus, the pituitary gland and the adrenal, and is involved in the regulation of the immune system
Hypoxia	Reduction in oxygen supply at the tissue level, which is not measured directly by laboratory value.
Hypoxaemia	Arterial oxygen tension or partial pressure of oxygen (PaO_2) is below normal. Normal: 80-100mmHg
Idiopathic pancreatitis	Inflamed pancreas with no underlying cause
Impaired Glucose Tolerance	A pre-diabetic state of hyperglycaemia that is associated with insulin resistance and increased risk of cardiovascular pathology. The World Health Organisation defines impaired glucose tolerance as blood glucose of 7.8 mmol/L or more but less than 11.1mmol/L after a 2 hour oral glucose tolerance test.

Insulin-like Growth Factor-1	Any of several peptide hormones that function primarily to stimulate growth but that also possess some ability to decrease blood glucose levels. Hormone has a similar in structure to insulin.
Insulinopenic	A decrease in, the level of circulating insulin
Interleukin	Any of various small proteins that are produced by a variety of cell types, especially T cells and other white blood cells, and that regulate many aspects of inflammation and the immune response, including stimulating the production of white blood cells and platelets.
Ischemic	Reduction in blood supply to tissues causing a shortage of oxygen and glucose needed for cellular metabolism
Islets of Langerhans	Collection of hormone producing and secreting cells within the endocrine pancreas which are essential for the regulating of glucose metabolism
Ivacaftor	Trade name Kalydeco (developed as VX-770) is a prescription drug used to treat cystic fibrosis in people with certain mutations in the CFTR gene.
Lacunar Infarcts	Classic markers of small vessel disease revealed using MRI
Lipoprotein	Lipoproteins are responsible for carrying cholesterol and other fats through the bloodstream as little packages and are essential for the normal breakdown of these molecules.
Low Density Lipoprotein	Type of cholesterol, often referred to as 'bad' cholesterol
Lumacaftor	Developed as VX-809, is a prescription drug used to treat cystic fibrosis in people with certain mutations in the CFTR gene. ORKAMBI is a combination of lumacaftor and ivacaftor, a CFTR potentiator, indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene.
Luminal	Inner surface
Lymphocytes	A small white blood cells (leukocytes) that plays a large role in defending the body against disease and are responsible for immune responses. There are two main types: B cells and T cells. B cells make antibodies that attack bacteria and toxins while T cells attack body cells themselves when they have been taken over by viruses or have become cancerous.
Macrophages	A type of large white blood cell that ingests foreign material. It uses a process called phagocytosis to destroy and get rid of unwanted particles in the body.
Macroalbuminuria	Also known as proteinuria. A condition caused by progressive kidney disease which results in more albumin leaking into the urine
Macroangiopathy	An angiopathy (i.e. disease of blood vessels) affecting large blood vessels in the body.
Macrovascular disease	Damage to large blood vessels; cardiovascular disease, myocardial infarction, stroke, carotid, coronal or peripheral arteries
Meconium ileum	A condition where there is a bowel obstruction in babies. It occurs when the meconium in the intestine is even thicker and stickier than normal meconium, creating a blockage in a part of the small intestine called the ileum.

Messenger ribonucleic acid (mRNA)	Molecule in cells that carries codes from the DNA in the nucleus to the sites of protein synthesis in the cytoplasm (the ribosomes). Because information in DNA cannot be decoded directly into proteins, it is first transcribed, or copied, into mRNA.
Metformin	An oral antidiabetic drug for the treatment of diabetes.
Metabolic syndrome	Clinical diagnostic entity identifying those at high risk with respect to cardiovascular morbidity associated with insulin resistance.
Methicillin resistant *S. aureus*	Staphylococcus aureus (bacterium) that has developed resistance against methicillin and several other antibiotics and therefore can cause difficult-to-treat infections in humans.
Microalbuminuria	A small or moderate increase of albumin excretion in the urine
Microangiopathy	An angiopathy (i.e. disease of blood vessels) affecting small blood vessels in the body.
Microvascular disease	Damage to small blood vessels; retinopathy, neuropathy and nephropathy.
Mild Cognitive Impairment	An intermediate stage between the expected cognitive decline of normal aging and the more-serious decline of dementia. It can involve problems with memory, language, thinking and judgment that are greater than normal age-related changes.
Monocytes	Large, white blood cells, whose function is to destroy certain types of viruses and bacteria to protect the body against the development of infection.
Nephropathy	Kidney disease or damage
Nephrotoxic	Damaging or destructive to the kidneys.
Normal glucose tolerance	The World Health Organisation defines normal as a fasting plasma blood glucose as below 6.1 mmol/l (110 mg/dl), and under 7.8 mmol/L after a 2 hour oral glucose tolerance test.
Normoxic	Normal levels of oxygen in tissue or blood
Neuroglycopenia	A shortage of glucose (glycopenia) in the brain, usually due to hypoglycaemia. Glycopenia affects the function of neurons, and alters brain function and behaviour.
Neutrophil	Most abundant type of white blood cell
Oxidative Stress	As a consequence of the body constantly reacting with oxygen (e.g. breathing and as cells produce energy), highly reactive molecules are produced within cells known as free radicals/reactive oxygen species. Oxidative stress occurs when there is an imbalance between the production of free radicals and the ability of the body to counteract or detoxify their harmful effects through neutralisation by antioxidants. Oxidative stress is linked with ageing, diabetes, Alzheimer's disease, and Parkinson's disease
Pancreatic Enzyme Replacement Therapy	Therapy whereby patients take capsules containing digestive (pancreatic) enzymes needed to digest food and absorb its nutrients
Pancreatic Insufficiency	Inability to properly digest food due to a lack of digestive enzymes made by the pancreas. Can lead to fat malabsorption, malnutrition and fat-soluble vitamin deficiencies.

Pancreatic Polypeptide	A 36 amino acid peptide produced and secreted by PP cells of the pancreas which are primarily located in the Islets of Langerhans. Secretion is stimulated in response to hypoglycaemia, ingestion of food, or "sham" feeding (food is chewed, but not swallowed).
Pancreatic Sufficient	Enough exocrine pancreatic function to allow normal digestion without enzyme supplements i.e. able to absorb fat through normal intestinal absorption
Peripheral Neuropathy	Encompasses all disorders that result in injury to nerves within the peripheral nervous system.
Phagocytosis	Process by which certain living cells called phagocytes ingest or engulf other cells or particles.
Polyol Pathway	A two-step metabolic pathway in which glucose is reduced to sorbitol, which is then converted to fructose.
Presenteeism	The practice of coming to work despite illness, injury, anxiety, etc., often resulting in reduced productivity.
Proliferative retinopathy	A developed form of retinopathy whereby new but weak blood vessels begin to form on the retina to help restore blood supply
Pro-oxidant	Induces oxidative stress, by generating reactive oxygen species and inhibiting antioxidants
Pseudomonas aeruginosa	Strains of gram-negative bacteria that are widely found in the environment. Pseudomonas aeruginosa is the key bacterial agent of cystic fibrosis lung infections, and the most important pathogen in progressive and severe cystic fibrosis lung disease.
Pulmonary Exacerbation	Intermittent episodes of acute worsening of symptoms associated with a decline of lung function (e.g. cough, sputum production)
Reactive Oxygen Species	Chemically reactive chemical species containing oxygen. Examples include peroxides, superoxide, and hydroxyl radical. When the level of Reactive Oxygen Species exceeds the defence mechanisms, a cell is said to be in a state of oxidative stress.
Recessive	Relating to or denoting heritable characteristics controlled by genes which are expressed in offspring only when inherited from both parents.
Repagalinide	An antidiabetic. It works to lower blood glucose by stimulating the release of insulin from the pancreas gland.
Retinopathy	A complication of diabetes, caused by high blood glucose levels damaging the back of the eye (retina). It can cause blindness if left undiagnosed and untreated.
Rosiglitazone	Thiazolidinedione insulin sensitizer
Shwachman-Diamond syndrome	A rare congenital disorder characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, skeletal abnormalities, and short stature. It is the second most common cause of inherited pancreatic insufficiency after cystic fibrosis.
somatic neuropathy	Nerve damage, usually affecting the feet and legs; causing pain, numbness, or a tingling feeling. Also called peripheral neuropathy or distal sensory polyneuropathy.

Staphylococcus aureus	A gram-positive, round-shaped bacterium frequently found in the nose, respiratory tract, and on the skin. It is the most prevalent organism infecting the respiratory tract of children with cystic fibrosis, and remains the second most prevalent organism in adults with cystic fibrosis. During early childhood, infections are associated with pulmonary inflammation and decline in FEV_1, but their clinical significance in adults with CF is poorly characterized.
Sulphonylureas	Class of oral (tablet) medications that control blood sugar levels in patients with type 2 diabetes by stimulating the production of insulin in the pancreas and increasing the effectiveness of insulin in the body.
Superoxide	Also known by hyperoxide. Product of the one-electron reduction of dioxygen (oxygen gas). With one unpaired electron, the superoxide ion is a free radical/ reactive oxygen species. Superoxide radicals can attack susceptible biological targets, including lipids, proteins, and nucleic acids.
Systolic blood pressure	Highest pressure of blood when your heart beats and pushes the blood round your body. A normal reading will be between 90 and 120.
Tacrolimus	An immunosuppressive drug used mainly after organ transplantation to lower the risk of organ rejection. It blocks the action of certain blood cells (e.g., T lymphocytes) that can cause the body to reject the transplanted organ.
Theory of Mind	Ability to attribute and understand mental states of oneself and others
Thiazolidinediones	Also known as glitazones. A group of oral anti-diabetic drugs designed to treat patients with type 2 diabetes. Classed as oral hypoglycaemic drugs along with biguanides, they work by targeting insulin resistance - a core physiologic defect in those with type 2 diabetes. By reducing the body's resistance to insulin, the hormone is allowed to work more effectively at improving blood glucose control. Glitazones also help lower blood pressure and improve lipid metabolism by increasing levels of HDL cholesterol and reducing LDL levels.
Townsend score	A measure of material deprivation based on a participant's postcode. The score is calculated from rates of unemployment, household overcrowding, non car- and non home ownership in an area.
Triglycerides	Store fat that your body can use for energy.
Tumour Necrosis Factor-α	A cell signalling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction.
Vitamin E Deficiency	α-tocopherol(T) <300 ug/dL
Voxel-based morphometry	A neuroimaging analysis technique that allows investigation of focal differences in brain anatomy, using the statistical approach of statistical parametric mapping.
White matter	Composed of bundles of myelinated nerve cell projections (or axons), which connect various gray matter areas (the locations of nerve cell bodies) of the brain to each other, and carry nerve impulses between neurons

Chapter 1

Overview of cystic fibrosis, aetiology, management and psychosocial issues

1.1 Cystic fibrosis

Cystic fibrosis (CF) is one of the most common autosomal recessive diseases affecting Caucasians (O'Riordan, Robinson, Donaghue, & Moran, 2008). In the UK, the carrier frequency is 1 in 25 (Schram, 2012) with an incidence of 1 in 2500 live births (Cystic Fibrosis Trust, 2015). With improved life expectancy, there are now over 10,000 people with CF in the UK with a larger number of adults than children (Cystic Fibrosis Trust, 2015b; Simmonds, 2013). In 2015, the median life expectancy of someone with CF was 45.1 years (Cystic Fibrosis Trust, 2015) and 40 years and over has been used as an arbitrary threshold for defining a person with CF as old (Simmonds, 2013). Despite significant improvements in treatment, approximately two lives are lost to CF each week (Cystic Fibrosis Trust, 2013). Recurrent respiratory tract infections and progressive respiratory failure remains the most common cause of morbidity and mortality in this patient group (Rosenblatt, 2009).

1.1.1 Aetiology of CF

CF is a complex multisystem disease resulting from a gene mutation on the long arm of Chromosome 7 (at q31.2; Kerem et al., 1989). The mutation results in defective production and function of a 1480 amino acid protein called the CF transmembrane conductance regulator (CFTR). The widespread presence of CFTR throughout the body explains the multisystem nature of the disease which affects many organs including the lungs, gastrointestinal tract, and pancreas.

This protein functions as a cyclic AMP-dependent chloride channel, a bicarbonate channel and as a modulator of epithelial sodium (ENaC) and other ion channels (Ooi & Durie, 2012). In the lung (see Figure 1.1), defective CFTR leads to abnormal acidification, dehydration of airway surface liquid (ASL) and abnormally thick sticky mucus (Brennan, Geddes, Gyi, & Baker, 2004; T. S. Cohen & Prince, 2012). The resulting abnormality in ASL and mucocilliary clearance leads to a predisposition to infections (viral, fungal and bacterial) and a reduction in innate beta (β)-defensins activity (Ntimbane et al., 2009). CFTR is a driver of chloride-bicarbonate exchange (Kenny et al., 2014) and the defect in this key process influences mucus properties and reduces innate bacterial killing.

a)

Paracellular pathway

Mucous layer

Airway surface liquid

NaC

Cl- Cl-

H2O

Apical membrane

Na+   Inhibition

Cystic Fibrosis transmembrane conductance regulator

Cl-   Na+ K+ Cl-

Basolateral membrane

Na+
Na/K ATPase

H2O /Cl-   **Normal airway epithelium**

In CF, defective CFTR causes reduced fluid production. Enhanced sodium absorption through Na+ channels and basolateral Na/K ATPase pumps results in increased fluid absorption. The volume of airway surface liquid is reduced (i.e. it is drier), which leads to mucus in the airways to be more viscid (sticky). This in turn causes ciliary clearance to be impaired i.e. small hairs on the surface of the airways do not beat in a coordinated fashion so that mucus is not moved up and out of the lungs. This results in bacterial infection.

b)

Mucous layer

ASL   Bacteria

Cl-

Na+

-ve

Defective CFTR

Cl- Cl-   Na+ K+ Cl-

Na+ Na+
Na/K ATPase

H2O /Cl-   **Cystic fibrosis airway epithelium**

Figure 1.1 Airway epithelium: a) Normal airway epithelium and b) cystic fibrosis airway epithelium (reproduced with permission from cfmedicine.com)

Bacterial colonisation and infection triggers a sustained neutrophilic inflammatory response (González Jiménez, Díaz Martín, Arias-Llorente, & Bousoño García, 2015) and activation of macrophages, eosinophils, monocytes and lymphocytes (Ntimbane et al., 2009). This results in the production and release of reactive oxygen species (free radicals) such as superoxide (O2-) and hydroxyl (OH) which can result in oxidative stress. The elevation of pro-inflammatory cytokines, particularly interleukins (IL-1β, IL-6 and IL-8), tumour necrosis factor-α (TNF-α), and potent neutrophilic chemo-attractants leads to pro-oxidant production, tissue damage and cell apoptosis (Elizur, Cannon, & Ferkol, 2008).

Glutathione (GSH) is a tripeptide antioxidant which is present in the fluid of the epithelial lining (Hudson, 2001) and is transported by CFTR (Gould, Min, Martin, & Day, 2012). Levels of GSH are found to be decreased in people with CF due to disturbed transport across epithelial cell

membranes (Ntimbane et al., 2009). This GSH deficiency leads to lowered digestion and malabsorption of fat soluble antioxidant vitamins such as vitamin E, carotenoids, and ascorbic acid (Galli et al., 2012). This in turn contributes to defective antioxidant protection which can further exacerbate oxidative stress. Hence, people with CF are more susceptible to oxidative stress and lung tissue degradation.

The CFTR protein is also expressed in both the brain and pancreas, including endocrine β cells which store and release insulin (Guo et al., 2014; Guo, Su, McNutt, & Gu, 2009). Abnormal production and regulation of insulin secretion through defective CFTR and pancreatic damage results in a high prevalence of abnormal glycaemic control and CF related diabetes (CFRD). There is little data on the role and impact of defective CFTR in the brain although there is some suggestion that there is an abnormally high rate of Chiari malformations[1] in people with CF compared to the general population (Needleman, Panitch, Bierbrauer, & Schidlow, 2000).

The diagnosis of CF is based on clinical assessment, the presence of two CF causing mutations and/or at least two positive sweat chloride tests (>60 mmol/L; Fanen, Wohlhuter-Haddad, & Hinzpeter, 2014). In people with less severe mutations, the sweat test result may be between 30 and 60 mmol/L. Males are usually infertile due to congenital bilateral absence of the vas deferens (CBAVD; Sosnay et al., 2011). CF carriers show higher than expected incidence of idiopathic pancreatitis and male infertility (Cohn, 2005).

1.1.2   Class of CF gene mutation and gene modifiers

There is variable phenotypic expression in CF (Kerem & Kerem, 1995) which is influenced by the class of gene mutation, gene modifier genes and environmental exposure. The CF gene was identified in 1989 (Riordan et al., 1989) and since then a further 2008 different mutations have been identified (Cystic Fibrosis Mutation Database Statistics, 2016) although the majority are rare.

Mutations can be categorised into 7 different classes depending on the type of CFTR protein dysfunction (see Figure 1.2; De Boeck & Amaral, 2016). Variation in levels of CFTR activity, which arise as a function of class of mutation, result in differing levels of disease severity (Welsh & Smith, 1993; Zielenski, 2000). However, not all mutations result in clinical symptoms. There is a correlation between the severity of defective CFTR and the degree of sweat chloride dysfunction (Hamosh & Corey, 1993). It is proposed that 0-10% of normal functioning CFTR results in the spectrum of CF phenotype from male infertility to multisystem involvement (Sosnay et al., 2011).

Individuals who have milder mutations tend to be diagnosed in adolescence and have better nutritional status due to being pancreatic sufficient[2] (Rodman et al., 2005). Sometimes, diagnosis can be as late as adulthood (Nick & Rodman, 2005) and those diagnosed in adulthood are classified as having atypical CF (Kerem & Kerem, 1995).

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[1] structural defects in the cerebellum where the lower part of the brain pushes down into the spinal canal
[2] Enough exocrine pancreatic function to allow normal digestion without enzyme supplements
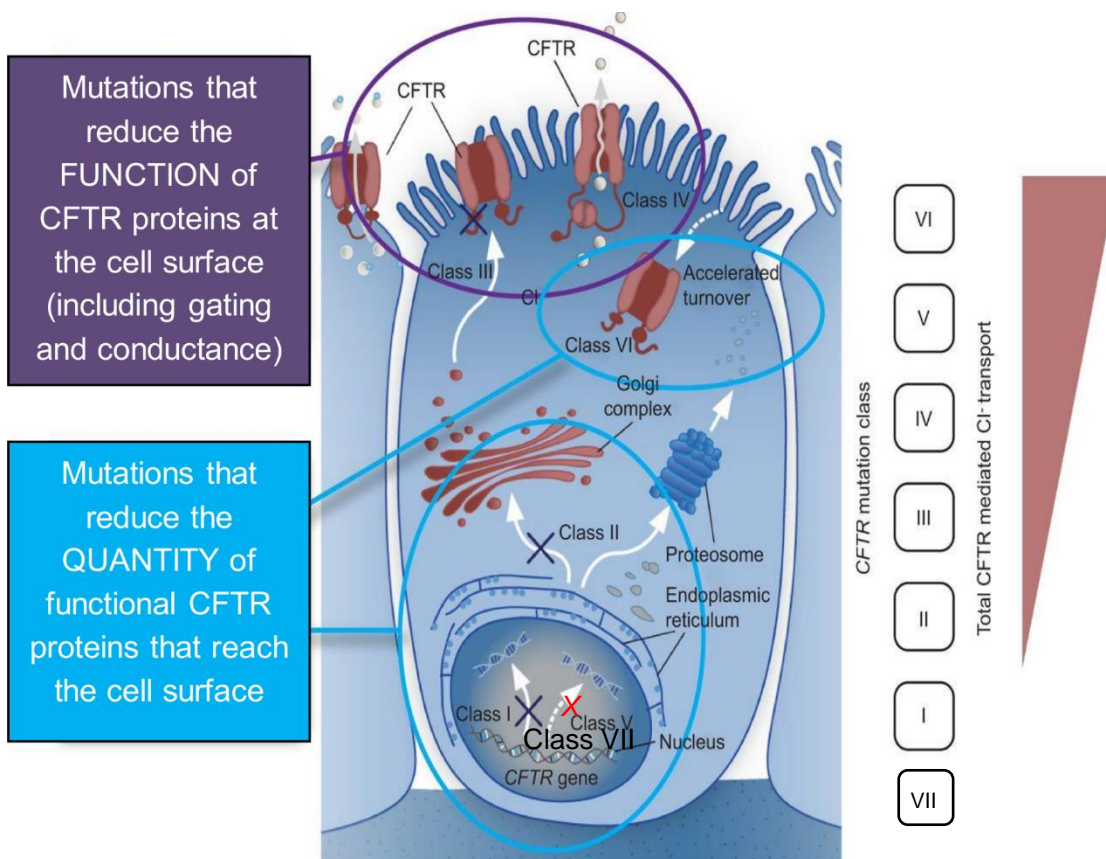
Figure 1.2 The seven classes of CFTR mutations which cause qualitative and quantitative changes in CFTR production and function (adapted from Derichs, 2013, p59)

Individuals with class I-III mutations are more likely to be diagnosed with CF at an early age (<1 year) and have pancreatic insufficiency (PI[3]; Simmonds, 2013). Interestingly, having a class IV or V mutation in combination with one from classes I-III does not result in PI (Castellani et al., 2008). In these cases, the class IV or V mutation is phenotypically dominant. It is presumed there is enough functional CFTR from the class IV or V mutation to sustain PS and thus compensate for class I-III mutations (Zielenski, 2000). However, not all identified mutations belong to a specific class and some mutations have characteristics of more than one class (Bell, De Boeck, & Amaral, 2015). Phenotypic expression and severity can differ even if individuals have the same genotypes (Ntimbane et al., 2009). Hence, CF is a wide spectrum disease. It is suggested that environmental factors and gene-gene interaction can influence disease progression, although the exact mechanism remains unclear.

1.1.2.1 **Class I**

These mutations cause defective protein production due to a premature stop codon causing premature termination of CFTR production (Zielenski, 2000). The absence or presence of

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[3] Inability to properly digest food due to a lack of digestive enzymes made by the pancreas. Can lead to fat malabsorption, malnutrition and fat-soluble vitamin deficiencies.

minimal functioning chloride channels, results in a more severe phenotype. Across European countries, the percentage of people with CF heterozygous for class I mutations varies between less than 5% to nearly 35% (De Boeck, Zolin, Cuppens, Olesen, & Viviani, 2014). In the UK, approximately 12% of people with CF are heterozygous for these class mutations.

1.1.2.2 **Class II**

This class of mutation causes defective trafficking of CFTR so that the protein cannot be expressed at the apical surface membrane (Zielenski, 2000). The protein is retained in the endoplasmic reticulum due to defective folding and is consequently degraded intracellularly. A small quantity of partially functioning CFTR may reach the apical surface membrane (Thursfield & Davies, 2012) but will have a class II and VI defect. Drugs such as lumacaftor and VX661 (i.e. correctors) can help stabilise class II mutations and allow increased membrane expression (Fraser-Pitt & O'Neil, 2015).

The most common mutation in the UK is the class II mutation F508del, (Castellani et al., 2008; Waugh et al., 2012) which accounts for 70% of alleles. Worldwide, 90% of CF sufferers have at least one copy of F508del, with approximately 50% being homozygous (Thursfield & Davies, 2012). The F508del mutation results from a phenylalanine being absent in the amino acid position 508 (Brennan et al., 2004). Class II mutations result in severe phenotypic expression (Zielenski, 2000).

1.1.2.3 **Class III**

This class of mutation causes defective CFTR regulation (Zielenski, 2000). Unlike class II mutations, trafficking of CFTR is normal such that CFTR can reach the apical surface of epithelial cells. However, defective opening (and closing) of chloride channels results in improper movement of chloride in and out of the cell. Five percent of the worldwide CF population have a class III mutation, with the most common mutation being G551D (Thursfield & Davies, 2012). Drugs such as ivacaftor (also known as Kalydeco or VX-770 i.e. potentiators), have recently been approved by NHS England and introduced as routine treatment for class III mutations (Ramsey et al., 2011). Ivacaftor rectifies the CFTR protein throughout the body and affords significant clinical improvement.

1.1.2.4 **Class IV**

These mutations are less severe and tend to be associated with milder phenotypic expression and PS (Zielenski, 2000). Class IV mutations are associated with reduced conductance. The CFTR protein is able to reach the apical surface membrane (as in class III mutations), but is defective in terms of the passage of chloride ions through the channel.

1.1.2.5 **Class V**

These mutations are associated with reduced synthesis of CFTR (Zielenski, 2000). CFTR is able to traffic and function correctly at the apical surface, however there is a reduced amount of CFTR protein. Like class IV, these mutations are less severe and tend to be associated with milder phenotypic expression and PS (Zielenski, 2000).

1.1.2.6 **Class VI**

These mutations are associated with decreased stability of CFTR (Zielenski, 2000). While CFTR is functional and present at the apical membrane, it is unstable and results in an increased turnover at the cell surface due to the truncation of the C-terminus of CFTR. Mutations belonging to this class are associated with severe disease presentation (Zielenski, 2000); however, they are relatively rare (Derichs, 2013).

1.1.2.7 **Class VII**

In 2016, De Boeck and Amaral proposed a new classification of CFTR mutation. The original class I mutations were divided into two new classes. Class I mutations are characterised by lack of CFTR protein and the new class (VII) are associated with no mRNA transcription[4]. Having class VII mutations results in people having severe CF disease. Class I mutations can be rescued with therapy (by rescuing synthesis), but those from class VII cannot be rescued at all.

1.1.2.8 **Gene modifiers**

Various gene modifiers which influence disease expression have been identified. For example, the p.Arg117His (R117H) mutation is affected by intragenic modification. The poly-T tract is present in all CFTR genes and presents in one of three forms; 5T, 7T or 9T. Having R117H and 5T results in a disease-causing mutation while R117H and 7T has variable expression (Tsui & Dorfman, 2013). F508del and R117H in combination with 5T, results in the individual having an elevated or borderline sweat test, moderate lung disease, PS and male infertility.

Other genetic modifiers which have been proposed are polymorphisms in the GSH pathway (de Lima Marson, Bertuzzo, Ribeiro, & Ribeiro, 2014) and various modifier loci in various chromosomes (F. A. Wright et al., 2011). The transport of GSH is modulated by CFTR, and polymorphisms of GSH, Glutamate-Cysteine Ligase Catalytic Subunit (GCLC) and Glutathione S-transferase (GST), have been shown to influence the severity of CF disease (de Lima Marson, Bertuzzo, Secolin, Ribeiro, & Ribeiro, 2013). There is a genome wide association and linkage in a locus on chromosome 20 (20q13.2) and 11 (11p13) intergenic region which causes differences in the severity of lung disease (F. A. Wright et al., 2011).

1.2 **Cystic fibrosis and lung function**

In people with CF, there is a poor correlation between genotype and lung function (Bell et al., 2015) which even varies in people homozygous for the F508del mutation (Kristidis et al., 1992). This likely reflects environmental and immunological influences (Schaedel et al., 2002). Differences in exposure to pathogens and treatments between CF centres may also play an important role.

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[4] Molecules in the cell that convey genetic codes from DNA to the ribosome (cell structures that makes protein)

1.2.1 Assessment of lung function

The measurement of lung function is a key physiological parameter used to monitor people with CF. When assessing lung function, forced expiratory volume in 1 second (FEV_1) is considered the best measure compared to forced vital capacity (FVC; Kerem et al., 2014). FEV_1 is an important predictor of survival in CF (Liou et al., 2010) and has resulted in the development of predictive categories (see Table 1.1 below). FEV_1%predicted[5] is negatively associated with age (Kerem et al., 2014), with the largest decline occurring between 12 and 20 years.

Table 1.1 Lung function category definitions based on FEV_1 % predicted

Severity of lung disease categories	FEV_1 % predicted
Mild	≥70%
Moderate	40-69%
Severe	≤ 40%

There remains significant intra and inter variability in FEV_1 in individuals, irrespective of gender (Liou et al., 2010). The median fall in FEV_1 is between 1 and 3% each year although this can be significantly greater in some people. There is a strong correlation between individual and cross-sectional population changes in FEV_1 up to the age of 15, after which there is growing disparity between individuals (Liou et al., 2010). As individuals with CF are living longer, the number of people with FEV_1 ≤40% predicted has increased.

1.2.2 Factors influencing lung function decline

There are several factors which may influence lung function decline in people with CF.

1.2.2.1 Pulmonary Exacerbations (PEs)

Pulmonary exacerbations (PEs; acute lung infection and/or inflammation) are of clinical significance as they are associated with a decline in FEV_1, reduced quality of life (QoL), and increased mortality (Bradley, Blume, Balp, Honeybourne, & Elborn, 2013; Sanders, Bittner, Rosenfeld, Redding, & Goss, 2011). There is no universal definition of a PE and symptoms differ depending on lung disease severity (Abbott et al., 2009). Commonly reported symptoms include fatigue and an increase in pulmonary symptoms such as coughing and sputum production (i.e. thicker, darker). Although PEs usually resolve following intravenous (IV) antibiotics, FEV_1 does not always return to baseline i.e. pre infection level (Sanders et al., 2010). Consequently, the greater the frequency of annual PEs, the greater the decline in lung function (Sanders et al., 2011).

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[5] FEV_1%predicted: FEV_1 expressed as a percentage of the predicted normal for a person of the same sex, age and height

Gender

There is a slower rate of lung function decline in men which may relate to females having lower baseline values (Corey, Edwards, Levison, & Knowles, 1997; Kerem et al., 2014). The chronology in the decline in lung function is also associated with age and gender. In addition, the greatest drop in lung function occurs earlier in males (14-15 years) than females (15-16years; Liou et al., 2010). However, not all studies have found a gender difference which may reflect variation in intensity of treatment at CF centres (Schaedel et al., 2002).

1.2.2.3 **Nutritional and pancreatic status**

Kerem et al. (2014) reported a 6 fold increase in severe lung disease in individuals who had poor body mass index (BMI; classed as either underweight or overweight/obese) compared to those with a normal BMI. It was also estimated that the chances of developing severe lung disease is doubled in people who are PI compared to those who are PS. Individuals who are PS tend to have better and slower decline in lung function, compared to those who are PI (Kristidis et al., 1992; Schaedel et al., 2002).

1.2.3 Pulmonary infection

People with CF are susceptible to numerous pulmonary infections. These include *Staphylococcus aureus* (*S. aureus*), *Haemophilus influenza* (*H. influenzae*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Burkholderia cepacia complex* (*B. cepacia*), viruses and fungal infections.

1.2.3.1 **Staphylococcus aureus**

The most prevalent respiratory pathogen during childhood in people with CF is the gram-positive bacteria *S. aureus* (Goss & Muhlebach, 2011). *S. aureus* has gained more attention in recent years due to the increase in prevalence of methicillin resistant *S. aureus* (MRSA). *S. aureus* is associated with increased inflammation in the lower airways of children with CF (Sagel et al., 2009) and decline in lung function (Pillarisetti et al., 2011). The clinical significance of *S. aureus* is unknown in adults with CF (Ahlgren et al., 2015).

1.2.3.2 **Haemophilus influenzae**

H. influenzae is a gram-negative coccobacillus, and commonly affects the airway tract of infants with CF (King, 2012). In people with CF, the nontypeable strain is the most common cause of the majority of respiratory infections, which are often recurrent and chronic (Cardines et al., 2012).

1.2.3.3 **Pseudomonas aeruginosa**

P. aeruginosa is a common gram-negative, rod-shaped bacterium. As people with CF get older, there is an increased risk of their lungs being colonised with *P. aeruginosa* with over 80% of individuals being chronically infected by adulthood (Etherington, Hall, Conway, Peckham, & Denton, 2008; Muhdi et al., 1996). Chronic infection is often defined as the 'persistent presence of *P. aeruginosa* for at least six consecutive months' (Pressler et al., 2011, pgS76). *P.*

aeruginosa is the most common pathogen in CF and is associated with poorer survival, increased hospitalisation and a more rapid progression of lung disease (Zemanick et al., 2015). An intermittent stage precedes chronic *P. aeruginosa colonisation*, and eradication therapy following the identification of new isolates can be effective in delaying chronic *P. aeruginosa* colonisation (Kenny et al., 2014).

Individuals with CF who have chronic *P. aeruginosa* have, on average, a 13% lower FEV_1 than individuals who do not have *P. aeruginosa* (Kerem et al., 2014). Pancreatic status can also influence the degree to which colonisation of chronic *P. aeruginosa* has a negative effect on lung function (Schaedel et al., 2002); FEV_1 is lower in those who are PI.

Epithelial cells have also been shown to have greater adherence to *P. aeruginosa* than control cells (Gibson, Burns, & Ramsey, 2003). This is particularly evident in people who are homozygous F508del (Zar, Saiman, Quittell, & Prince, 1995). It has been postulated that CFTR is a receptor for *P. aeruginosa* infection and involved in bacterial clearance from the epithelium (Campodonico, Gadjeva, Paradis-Bleau, Uluer, & Pier, 2008). Thus, the susceptibility of being colonised with *P. aeruginosa* is influenced by genotype.

1.2.3.4 Burkholderia cepacia complex

B. cepacia is a group of organisms that comprises at least 17 species (previously known as genomovars) which are gram-negative and phenotypically similar, but genotypically distinct (Alexander et al., 2008). These species are present in approximately 3-5% of people with CF (Weill & Patel, 2013). People with CF often experience a steady decline in pulmonary function following colonisation and infection of *B. cepacia* (Boehler, 2003). A minority of people can develop "cepacia syndrome"[6] with a rapidly progressive necrotising pneumonia[7].

1.2.3.5 Viral infections

Viral infections may be an important trigger for PEs (Walk et al., 2012). Symptoms in the upper airways are signs of the presence of viruses (Wat et al., 2008). Significant declines in clinical status (FEV1, FVC, Shwachman score[8]) have been observed in people with CF following the presence of viral infections (Wat & Doull, 2003). It has been suggested that bacterial infections may be facilitated by respiratory viral infections and can be associated with worse outcome (Etherington et al., 2014; Flight et al., 2014).

1.2.3.6 Fungal species

There are a wide range of different fungal species found in the expectorated sputum of people with CF (Middleton, Chen, & Meyer, 2013). The most common pathogen is aspergillus fumigatus

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[6] B. cepacia is spread throughout the body, which causes rapid deterioration in lung function and can lead to death within weeks

[7] Pneumonia which is characterised by the development of necrosis (premature death of cells in living tissue) within infected lung tissue

[8] Shwachman and Kulczycki (1958); first score to assess the severity of CF disease based on general activity, physical examination, nutrition and radiology findings

which is associated with the development of allergic bronchopulmonary aspergillosis (ABPA)[9] and aspergillus bronchitis[10] (Shoseyov, Brownlee, Conway, & Kerem, 2006).

1.3 Cystic fibrosis, pancreatic dysfunction and insufficiency

In people with CF, there is a strong correlation between genotype and phenotypic expression of pancreatic dysfunction (Simmonds, 2013). However, there are still discrepancies as to whether some gene mutations are classed as mild or severe in relation to pancreatic dysfunction (Schaedel et al., 2002). The pancreas is a dual function organ with both exocrine and endocrine functions.

1.3.1 Exocrine function of the pancreas in CF

The exocrine pancreas produces and secretes digestive enzymes from acinar cells. These secretions are high in bicarbonate and play a key role in the digestion of carbohydrate, protein and fat in the intestine. Defective CFTR expression results in an abnormality of secretions flowing into the pancreaticobiliary ducts (Laguna, Nathan, & Moran, 2010). Precipitation and ductal destruction occurs due to the reduction in fluid volume and increase in protein concentration. This viscous cycle compromises normal blood flow and leads to ischemic damage, atrophy, fibrosis and fatty infiltration of the exocrine pancreas.

In people with CF, damage to the pancreas begins in utero (de Solís, Merino Torres, Mascarell Martínez, & Piñón Sellés, 2007). Intestinal malabsorption occurs early; as young as 7 weeks (Littlewood, Wolfe, & Conway, 2006). Acinar development is abnormal and there is progressive reduction of connective tissue as people with CF age (Couper et al., 1992).

Although people with CF may be classified as PS, there is large variation in enzyme secretory/acinar function between individuals, with acinar secretory function ranging from normal (albeit decreased compared to healthy non-CF controls) to severely impaired (Durie & Forstner, 1989). Individuals with CF who have exocrine function within the normal limits are less likely to show long term pancreatic deterioration compared to those with severely impaired function (Couper et al., 1992). However, a proportion of people with CF with impaired acinar function will develop PI as they age. Eighty five percent of people with CF suffer from exocrine PI (Wilschanski & Novak, 2013) and will require pancreatic enzyme replacement therapy (PERT; Littlewood et al., 2006).

1.3.2 Endocrine function of the pancreas in CF

The islets of Langerhans are made up of a collection of hormone producing and secreting cells essential for the regulating of glucose metabolism (see Figure 1.3). There are approximately 1 million islets which make up 1-2% of pancreas and receive 10-15% of the pancreatic blood flow. β cells produce insulin and make up approximately 70% of cells within the islets. CFTR has a significant role in the normal function of pancreatic β-cells (J. Robinson, Yates, Harper, & Kelly,

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[9] Condition characterised by an exaggerated response of the immune system (a hypersensitivity response) to the fungus aspergillus
[10] Chronic superficial infection of the lower airways (trachea and bronchi)

2014). Alpha (α) cells produce glucagon and make up 20% of the human islet cells. Somatostatin is involved in the inhibition of both insulin and glucagon and is produced by delta cells. These cells make up less than 10% of the islets. Pancreatic polypeptide (PP) cells make up less than 5% of islet cells and affect pancreatic secretion, amongst other effects.
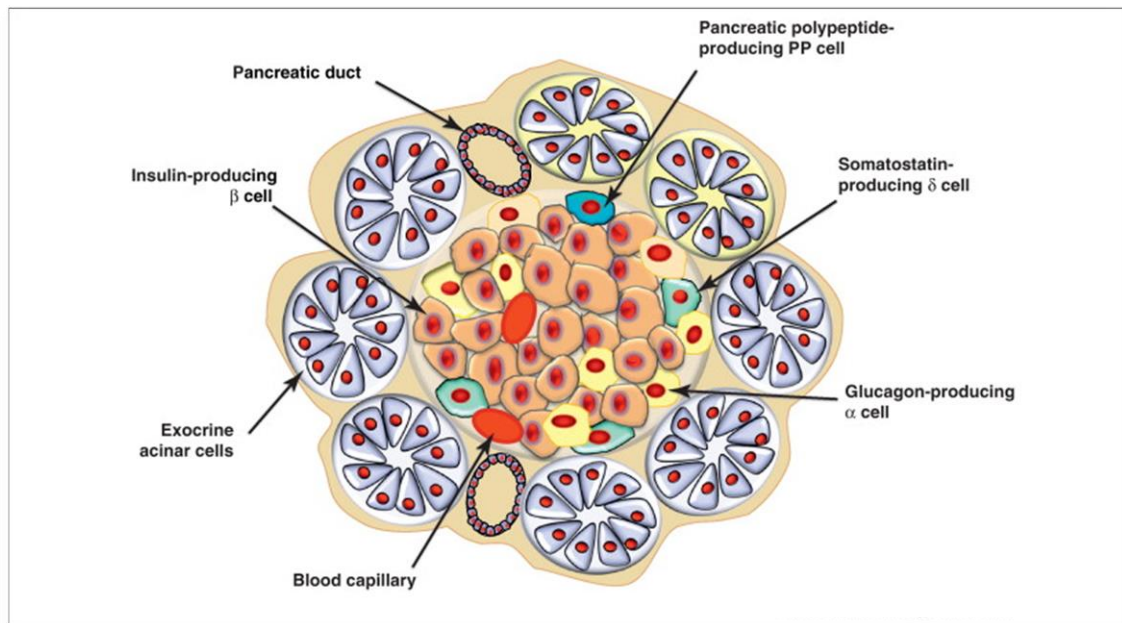
Figure 1.3 Organisation of cells within the endocrine pancreas in a healthy pancreas

During childhood, there is often adequate function in the islets of Langerhans in people with CF to avoid development of diabetes even in the presence of severe PI. However, functional endocrine pancreatic abnormalities are present in early life (Costa et al., 2005; Laguna et al., 2010). Although there is no difference in the volume density of endocrine tissue between CF and healthy pancreas, the number of islets of Langerhans are already qualitatively reduced (Löhr et al., 1989). The remaining islets appear disorganised and strangled by deposits of fatty infiltration (Meacham et al., 1993). Immunohistochemistry has shown that not all endocrine cells are involved equally in pancreatic destruction (Meacham et al., 1993). There is as much as a 50% reduction in β cell mass, minimal change in the volume of secreting glucagon α cells, and an increase in the secretion of somatostatin. The pancreas can still function adequately with this reduction in β cell mass for some time, as mass doesn't always correlate with the degree of decreased β cell function (Laguna et al., 2010). Nevertheless, β cell function (as measured by Disposition Index; DI) is reduced in people with CF when compared to controls (Merjaneh, He, Long, Phillips, & Stecenko, 2015). These destructive processes further disrupt the architecture of the islets of Langerhans which leads to progressive loss of endocrine β, α, PP cells and an increase in somatostatin secretion. As a result, the prevalence of glucose intolerance and diabetes increases as people with CF age.

1.3.3 Animal models of CF disease

Animal models have been used to better understand the pathophysiology of the CF pancreas.

1.3.3.1 Mouse/murine models of CF disease

Shortly after the discovery of CFTR, the first CF mouse models were developed (Snouwaert et al., 1992) and were considered 'knockout' mice due to not producing any detectable amounts of CFTR mRNA which results in total loss of function. Since then at least 14 mouse models have been developed with varying degrees of organ pathology which are observed in humans with CF (Fisher, Zhang, & Engelhardt, 2011). Mouse models do not produce spontaneous CF human lung disease and the mouse pancreas does not have the same structure and development of the human pancreas; the mouse pancreas develops after birth with maturation. Nevertheless, mouse models have led to the discovery that CFTR is present in the exocrine pancreas (Wilschanski & Novak, 2013). Rat models have shown CFTR is also expressed within the pancreatic islet (Boom et al., 2007). CFTR is present and in high abundance in pancreatic islet cells, CFTR conductance is measured in β cells, it is involved in exocytosis and potentiates glucagon secretion (Edlund, Huhn, Flostrum-Tullberg, & Eliasson, 2010).

1.3.3.2 Ferret and pigs models of CF

More recent research has been undertaken in CF animal models using ferrets and pigs as they more closely mimic the physiological and anatomical features of CF in humans (Wilschanski & Novak, 2013). Newborn pig CF models demonstrate similar clinical, electrophysiological and pathological findings as new born humans with CF; defective chloride transport, meconium ileus, exocrine pancreatic dysfunction and focal biliary cirrhosis (Rogers et al., 2008). However, the prevalence of meconium ileus[11] is 100% in newborn CF piglets but only 15% in human newborns. Severe exocrine pancreas damage is already apparent in CFTR$^{-/-}$ pigs and they rapidly develop PI post meconium ileus surgery. In contrast, CFTR$^{F508del/F508del}$ pigs have less severe exocrine pancreas damage (Ostedgaard et al., 2011). This suggests that the specific CFTR genotype might somewhat influence the degree of pancreatic destruction.

In ferret CF models, the lung anatomy and cell biology including defective airway chloride transport is similar to that of humans (Wilschanski & Novak, 2013). They also develop several pathological dysfunctions associated with human CF disease including meconium ileus, pancreatic and liver disease, severely impaired nutrition and a predisposition in the early postnatal period to lung infections (Sun et al., 2010).

Recent research using ferret animal models has provided insight into the role of CFTR on insulin secretion. The CF ferret has a relatively normal pancreas at birth with only mild ductal dilatation. As the animal grows there is progressive inflammation and fibrosis within the pancreas (Keiser & Engelhardt, 2011). The presence of reduced insulin secretion in the kit (young ferret) model

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[11] A condition where there is a bowel obstruction in babies. It occurs when the meconium in the intestine is even thicker and stickier than normal meconium, creating a blockage in a part of the small intestine called the ileum.

suggests that impaired glucose handling is not just a reflection of organ damage but reflects a primary abnormality in CFTR.

Studies on cultured islets from mice have demonstrated the role of CFTR in regulating glucose stimulation of insulin production, and that defects in insulin secretion can be reversed with a CFTR corrector (Guo et al., 2014). Increased insulin secretion and even reversal of CFRD has been reported in a handful of people receiving ivacaftor for treatment of the G551D (class III) mutation (Bellin et al., 2013; Hayes, McCoy, & Sheikh, 2014).

1.4 Cystic fibrosis and glucose tolerance abnormalities

People with CF have variable glucose tolerance which worsens over time (Sterescu et al., 2010) and is exacerbated by infection, gastrointestinal abnormalities and diet (O'Riordan et al., 2008). The oral glucose tolerance test (OGTT) is the gold standard to diagnose glucose tolerance abnormalities and diabetes mellitus in healthy people and those with CF (Cystic Fibrosis Trust Diabetes Working Group, 2004). The OGTT is usually performed annually in people with CF from the age of 10 years (A. M. Moran, Pillay, Becker, & Acerini, 2014). Table 1.2 shows the fasting and OGTT result categories.

Table 1.2 World Health Organisation (WHO) criteria for normal, impaired and diabetic glucose tolerance

Glucose Tolerance	Fasting Blood Glucose values (mmol/L)	2 hour OGTT blood glucose Values (mmol/L)*
Normal	< 5.6	< 7.8
Impaired	5.6 - 6.9	7.8 - 11.0
Diabetes	≥7.0	≥ 11.1

Venous plasma glucose 2 hours after ingestion of 75g oral glucose load

Impaired glucose tolerance (IGT) is common in people with CF. It occurs in 10-65% of cases (Mohan et al., 2009) and increases with age (Lanng, Hansen, Thorsteinsson, & Koch, 1995; Lanng, Thorsteinsson, Erichsen, Nerup, & Koch, 1991). It is the result of abnormal insulin production, regulation, pancreatic damage and insulin resistance (Sterescu et al., 2010). An individual's glucose tolerance and OGTT results can fluctuate significantly from year to year from diabetic to normal. Figure 1.4 shows results from 1540 OGTTs performed in people with CF between 1995 and 2009. People with CF can fluctuate between hypoglycaemia and diabetic OGTT before irreversible diabetes develops. Furthermore, a diabetic OGTT does not necessarily reflect a diagnosis of CFRD as in some people the glucose profile is normal. The diagnosis must be confirmed with elevated glucose on either pre or post prandial blood glucose profile monitoring or continuous glucose monitoring (CGM; Peckham, 2009).

Hypo <3.6mmol/L	Normal 3.7 - <7.8mmol/L	IGT >7.8 - 11.1mmol/L	DM OGTT >11.1mmol/L
5.5%	60.2%	23.4%	10.9%
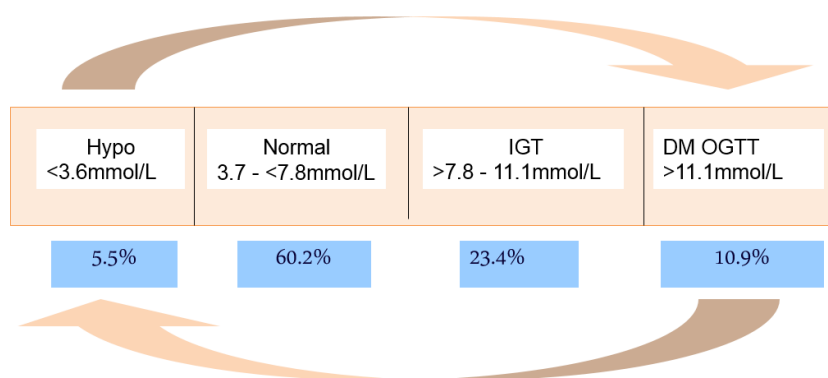
Figure 1.4 Results from 1540 OGTTs performed in people with cystic fibrosis (CF) between 1995 and 2009 at the Leeds adult CF Unit

During an OGTT, people with CF often demonstrate higher glucose levels at all time points (30, 60, 90 and 120 minutes), compared to healthy controls (Holl, Heinze, Wolf, Rank, & Teller, 1995). This elevated post-prandial glycaemia is characteristic of people with CF, even in those with normal fasting plasma glucose (FPG) levels (Holl et al., 1997). For individuals with CF with normal glucose tolerance (NGT), basal insulin secretion is maintained which allows normal FPG levels (Holl et al., 1997). The elevated post-prandial glycaemia observed in individuals with CF irrespective of glucose tolerance status can be explained by the kinetics of insulin secretion. Compared to healthy controls, people with CF have a delayed insulin secretion in response to a glucose load (Holl et al., 1995). Healthy controls achieve peak insulin secretion at 30 minutes, whereas people with CF who have NGT achieve it at 60 minutes, and at 90 minutes in people with CF who have IGT or CFRD. Delayed onset of insulin secretion may be explained by reduced sensitivity in β cells to an influx of glucose due to the downregulation of glucose transporters. This reduced sensitivity causes the first phase insulin secretion to be impaired in people with CF. Despite a consistent finding that insulin secretion is delayed, research has shown that basal (long acting) insulin secretion is maintained, at least in the short term (Kelly & Moran, 2013).

1.4.1   Hypoglycaemia

Hypoglycaemia (low blood glucose levels) can be experienced by all people with CF irrespective of glucose tolerance and mild hypoglycaemia is relatively common even in people without CFRD (A. M. Moran et al., 2014). Individuals can suffer from fasting, spontaneous or reactive hypoglycaemia, which is thought to be caused by delayed insulin secretion. Reactive hypoglycaemia is experienced when postprandial blood glucose levels are <2.8mmol/L. In a sample of 129 children and adults with CF without confirmed diabetes, fasting hypoglycaemia was detected in 14% and reactive hypoglycaemia in 15% of 188 OGTTs (Battezzati et al., 2007). It was suggested that hypoglycaemia occurred in these individuals as a consequence of the inability to suppress insulin secretion.

It has also been noted that individuals who are PI suffer from defective glucagon secretion which may also contribute to hypoglycaemia (Moran, Diem, Klein, Levitt, & Robertson, 1991). Individuals with CF can recover from insulin-induced hypoglycaemia as there is an increased catecholamine response to counteract defective glucagon secretion. It is important to note than

none of the patients in the study by Battezzati et al. (2007) who were experiencing fasting hypoglycaemia had any symptoms or reported any symptoms, even when blood glucose levels were as low as 1.9mmol/L. Moreover, people who experienced reactive hypoglycaemia were asymptomatic too. It is thought that this lack of hypoglycaemia awareness may be explained by neuroglycopenia (shortage of glucose in the brain, usually due to hypoglycaemia).

1.4.2 Factors influencing insulin sensitivity

Fluctuations in insulin sensitivity can occur as a result of various factors (Sterescu et al., 2010). For example, sex hormones can induce insulin resistance transiently, particularly during adolescence (Moreau et al., 2008).

1.4.2.1 Pulmonary exacerbations (PEs)

Episodes of PEs are associated with metabolic stress (Sc, Shoseyov, Kerem, & Zangen, 2010) and have been shown to influence insulin sensitivity. Research has shown that PEs may unmask insidious abnormalities in glucose homeostasis, even in individuals who have NGT (Sc et al., 2010). During an PE, glucose levels can increase before returning to normal once in a steady state (Battezzati et al., 2011). Albeit only transient, glucose levels may worsen enough to alter the glucose tolerance status of an individual. Hence, during a PE, glucose levels in individuals with NGT can reach or approximate diabetic levels (Sc et al., 2010).

The increase in glucose levels during a PE can be explained by the ability of β cells to function sufficiently to secrete first phase insulin, albeit delayed in the response to a glucose load. But, second phase insulin secretion cannot be sustained in stressful conditions as insulin resistance is induced. Elevation of blood glucose levels into diabetic tolerance may depend on the level of destruction to the endocrine cells of an individual (Widger et al., 2012). Periods of heightened prolonged glycaemia during PE, even in individuals who have NGT, may have a negative impact upon the health of a person with CF (e.g. lung function), questioning the need for insulin during these episodes in some people.

1.4.2.2 Pancreatic insufficiency (PI)

PI is seen as a risk factor for worsening glucose tolerance (Sterescu et al., 2010). People with CF who are PI are somewhat insulinopenic (exhibiting a decrease in, the level of circulating insulin; Widger et al., 2012). There is a significant reduction in insulin secretion in response to a glucose load, compared to healthy controls, even in individuals who have NGT (Yung et al., 2002). Furthermore, there is a gradual decease in glucose-induced insulin secretion as glucose tolerance worsens. This is in addition to the underlying gene defect which predisposes people with CF to develop glucose tolerance abnormalities. But, as people who are NGT experience β cell dysfunction, this highlights the insidious nature of glucose intolerance onset.

1.5 Cystic Fibrosis related diabetes (CFRD)

People with CF are predisposed to developing CFRD, an important and common complication of CF (Laguna et al., 2010). This unique form of diabetes is caused by anatomical and functional

pancreatic abnormalities (Meacham et al., 1993) and defective CFTR function (Guo et al., 2014). It is neither type 1 (T1DM) nor type 2 (T2DM) diabetes mellitus (Konrad et al., 2013).

1.5.1   Similarities and differences between CFRD, T1DM and T2DM

Chronic hyperglycaemia characterises all forms of diabetes (Brennan et al., 2004). However, there are clear differences between T1DM, T2DM and CFRD. T1DM is characterised by the specific auto-immune destruction of β cells in the islets of Langerhans causing absolute insulin deficiency. T2DM is characterised by a combination of insulin deficiency and severe insulin resistance. CFRD is caused by severe, but not complete insulin deficiency, and variable insulin resistance. Table 1.3 shows the similarities and differences between these three forms of diabetes as reported in Moran, Becker, et al., (2010).

Table 1.3 Similarities and differences between type 1 and 2 diabetes mellitus and cystic fibrosis related diabetes (As reported by Moran, Becker, et al., 2010)

	Type 1 diabetes mellitus (T1DM)	Type 2 diabetes mellitus (T2DM)	Cystic fibrosis related diabetes (CFRD)
Peak Age of Onset	Childhood, Adolescence	Mid- to late Adulthood	20-24 years
Usual BMI	Normal	Obese	Normal to underweight
Insulin Deficiency	Complete	Partial, Variable	Severe but not complete
Insulin Resistance	Usually modest	Severe	Usually modest, variable with infection
Autoimmune Aetiology	Yes	No	No
Ketones	Yes	Rare	Rare
HbA1c	Related to mean blood glucose	Related to mean blood glucose	Unpredictable relation to mean blood glucose
Usual Treatment	Insulin	Oral Agents, Insulin	Insulin
Microvascular Complications	Yes	Yes	Yes
Macrovascular Complications	Yes	Yes	No
Metabolic Syndrome Features	No	Yes	No
Cause of Death	Cardiovascular	Cardiovascular	Lung Disease

Both T1DM and CFRD share the characteristic of insulin deficiency caused by the destruction of β cells. However, CFRD is not a β cell specific autoimmune disease. In individuals with T1DM, only the β cells are destroyed which results in complete absence of insulin production. In contrast, people with CF experience whole islet destruction caused by fibrosis and fatty infiltration of the pancreas and thus have reduced glucagon and PP secretions too. Ketoacidosis[12] is rare in CFRD, but a common feature in T1DM indicating individuals with CFRD have some basal insulin secretion (Ali, 2009).

In contrast to T1DM, and similar to T2DM, individuals with CFRD have some functioning islet cells. As mentioned previously, people with CF have up to 50% loss of β cell mass; this loss in mass is similar to those individuals with T2DM (Couce, O'Brien, Moran, Roche, & Butler, 1996). Like individuals with T2DM, people with CFRD also experience deposits of islet amyloid within the β cells which can impair insulin secretion and the sensitivity of islet cells to glucose (Brennan et al., 2004). Islet amyloid deposition is also found in individuals with CF without CFRD and thus it is unknown whether amyloid is a consequence of β cell dysfunction or contributes to the development of CFRD (Couce et al., 1996). The latter may have support as islet amyloid can be cytotoxic to β cells, thus causing impairment to the endocrine function (Laguna et al., 2010). There are also differences between T2DM and CFRD. Whereas insulin resistance in T2DM is caused by obesity, insulin resistance varies in individuals with CFRD due to inflammation, infection and medication use at various stages of their life (Waugh et al., 2012). However, obesity is becoming more common in CF (Hanna & Weiner, 2015; Panagopoulou, Fotoulaki, Nikolaou, & Nousia-Arvanitakis, 2014) and may start to have an impact.

1.5.2   Factors influencing the development of CFRD

Based on recent research showing that CFTR is expressed in β cells and plays an essential role in insulin secretion (Guo et al., 2014), people with CF are predisposed to developing glucose tolerance abnormalities due to the underlying gene defect. Several important risk factors have been identified as to whether people with CF will develop CFRD.

1.5.2.1   Gene mutation and CFRD

There is an association between the different gene classes and developing CFRD. The European Epidemiologic Registry of CF (ERCF) indicates individuals who are homozygous or compound heterozygous for mutations belonging to class I, II or III are more likely to develop CFRD than those who are homozygous for, or carry at least, one mutation from class IV or V (Koch et al., 2001). Twenty two percent of people whose mutations belonged to either class II or III had diabetes compared to less than 2% with mutations belonging to class IV or V. A study by the ERCF showed there is a greater prevalence of CFRD in individuals who are genotypic homozygous for class II mutations e.g. F508del, than class IV mutations (Brennan et al., 2004).

A longitudinal (1996–2005) study found that there is a high incidence of CFRD in the UK, and that an individual's CFTR mutation independently increases the risk of CFRD (Adler, Shine,

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[12] Complication of diabetes caused by a lack of insulin the body. The body is unable to use glucose for energy and therefore body tissue is broken down as an energy source

Chamnan, Haworth, & Bilton, 2008). CFRD was significantly more likely to develop in those who carry mutations belonging to either class I or II, than class III or IV. This can be explained as individuals who carry I, II or III mutations are more likely to be PI. Individuals who are PS are less likely to develop CFRD (Schaedel et al., 2002), due to having less pancreatic damage.

1.5.2.2 **Age and CFRD**

Increasing age has been identified as an important risk factor. There are differences in the prevalence of CFRD and age of onset between countries (Waugh et al., 2012). This difference may be explained by the variations in the practice of screening, diagnosis and management of CFRD not only within the UK, but also between the UK and other European countries and the USA respectively.

In the UK, after the age of 10, there is a 5% increase in the prevalence of CFRD per year (Wickens-Mitchell, Gilchrist, McKenna, Raffeeq, & Lenney, 2014). This indicates CFRD develops across the lifespan in those with CF (W. Kent et al., 2013). Twenty four percent of people with CF in the UK have developed CFRD by the age of 20 years (Wickens-Mitchell et al., 2014), with the mean age of CFRD onset 21 years old (Lek & Acerini, 2010). Hence, during transition from paediatric to adult CF centres, a crucial stage in the lives of people living with CF, about a fifth will have already developed CFRD (Middleton et al., 2014). After the age of 20, the prevalence increases by 9.3% per year (Lanng, Thorsteinsson, Nerup, & Koch, 2000), and by the age of 40 years, the prevalence can be as high as 50% (Moran et al., 2009); this may be an effect of survivor bias.

In the UK, CF centres do not distinguish between those cases with and without fasting hyperglycaemia (FH). Nevertheless, younger people with CF tend to have diabetes without FH (Moran et al., 2009). The chance of developing FH increases with age. In the study by Moran et al., (2009), between the ages of 30-39 years, approximately half of the 115 people studied had FH, and this proportion rose to approximately two thirds of the people over 40 years. This increase in the proportion of people with FH due to longevity is supported by the findings of Schwarzenberg et al., (2007).

1.5.2.3 **Gender**

As well as genotype and increasing age, gender has also been identified as an important risk factor for developing CFRD. Research has found that females are more at risk of developing diabetes, and at an earlier age than males (Marshall et al., 2005). This may be partly explained by earlier pubertal development in females and the resulting increase in insulin resistance during this time. Based on people registered in the UK with CF, females are up to 60% more likely to develop CFRD than males, with advancing age also increasing this risk by 2-3% (Adler et al., 2008). Thus, the higher prevalence of CFRD in females cannot be explained solely by earlier pubertal development. After the age of 40 years, this gender bias disappears; again possibly due to survivor bias.

Although the majority of research supports increasing age, and being female as risk factors for developing CFRD, some research has suggested that this is not always the case (Kent et al.,

2013; Moran et al., 2009; Tofe et al., 2005). This discrepancy may be explained by the sample included in these studies, the differences in screening and diagnostic practices between centres, or possibly the advocated use of aggressive treatment with oral corticosteroids in some CF centres; another risk factor for CFRD. Kent et al., (2013) found no gender difference in the age of onset of CFRD over a 10 year period; however, the proportion of females with PS in the sample is not reported. Tofé et al., (2005) found no gender difference between those who had CFRD compared to those who did not (i.e. NGT or IGT). However, as the mean age of all participants was 20.7 years and only 18% had developed CFRD, it may be that a proportion of the 62% who were NGT and homozygous or heterozygous for F508del, were yet to develop CFRD.

1.5.3 Treatment for cystic fibrosis related diabetes

For individuals with T1DM and T2DM, the treatment aims are to relieve or avoid prolonged periods of hyperglycaemia and acute metabolic complications, and to prevent long term microvascular[13]and macrovascular[14] complications. These treatment aims apply to people with CFRD but also include the maintenance of lung function and nutritional status. Treatment is personalised to the individual depending on their symptoms, ability to achieve glycaemic control and capability to adhere to treatment (O'Riordan et al., 2008).

1.5.3.1 Achieving glycaemic control

The glycaemic goals are the same for those with CFRD as with T1DM and T2DM. Although glycaemic control is individualised in those with CFRD (Costa et al., 2005), the effect of such tight control on long term lung function, maintenance of weight and prevention of microvascular complications is unknown (Onady & Stolfi, 2013). Nevertheless, reducing the occurrences of hyperglycaemia has a positive effect on reducing respiratory pathogens.

Despite people with CFRD being recommended to adhere to the glycaemic goals of individuals with T1DM and T2DM, how they achieve these goals differs. The treatment for those with CFRD is altered due to their different requirements to maintain health and their low risk of cardiovascular disease. The main difference is that people with CFRD do not restrict their nutritional intake. People with CF are usually prescribed a high calorie, high protein, high salt and high fat diet as poor nutritional status is detrimental to overall health (Brennan et al., 2004). As the prevalence of obesity is increasing in the CF population, people receive individual dietary advice. Like people with T1DM, the only recommended therapy for people with CFRD is insulin (O'Riordan et al., 2008). For those with T2DM, treatment varies depending on glycaemic control but can involve insulin, oral agents and/or diet restrictions (usually calorie).

1.5.3.2 Oral Agents

Oral agents for the treatment of T2DM include insulin secretagogues (e.g. sulphonylureas) and insulin sensitizers (e.g. metformin or thiazolidinediones). However, there is a lack of randomised

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[13] damage to small blood vessels; retinopathy, neuropathy and nephropathy
[14] damage to large blood vessels; cardiovascular disease, myocardial infarction, stroke, carotid, coronal or peripheral arteries

control trials (RCTs) to determine their efficacy and limited research has shown that there is potential for them to cause damage to β cells, or be ineffective due to the primary defect in people with CFRD of insulin deficiency. Consequently, oral agents are not recommended for people with CF to treat the effects of diabetes (Hameed, Jaffé, & Verge, 2011).

1.5.3.2.1 Insulin

Insulin therapy is prescribed to people with CFRD with the aim of alleviating the decline in lung function and promoting weight gain caused by a catabolic state. Insulin has been the advocated treatment for these individuals since 1999 following the publication of the CF Foundation Consensus guidelines (Moran et al., 1999). It is important however, to acknowledge that hypoglycaemia is relatively common in CF (Battezzati et al., 2007) and hence insulin therapy poses an extra risk.

In CF centres which differentiated between with and without FH, there was a conflicting consensus about prescribing insulin in those without FH. More recently, it has been advocated that all people with CFRD are prescribed insulin (Hameed et al., 2011; Moran et al., 2009). This is because pre-prandial insulin has been shown to be beneficial for nutritional status i.e. weight gain and improving BMI. Multiple daily insulin injections have been found to significantly reverse weight loss compared to a placebo, and to be more effective than Repagalinide (Moran, Brunzell, et al., 2010). This has led some CF centres to advocate therapy prescribed before a confirmed CFRD diagnosis with the attempt to alleviate the development of the negative consequences of the pre-diabetic period. However, the effect of recurrent episodes of hypoglycaemia on cognitive function in people with CF is not known (see Section 3.3.3.2 for the effects of hypoglycaemia on cognitive function in people with T1DM and T2DM).

1.5.4 Impact of cystic fibrosis related diabetes

CFRD has a negative impact not only on the health of the individual, and also increases their risk of mortality.

1.5.4.1 **Mortality**

Research has shown that those with CFRD exhibit a 6-fold increase in mortality compared to people with CF without CFRD (Alves, Aguiar, Alves, & Santana, 2007).

1.5.4.1.1 Fasting hyperglycaemia (FH)

Although UK CF centres do not differentiate between those with and without FH, research has shown CFRD with FH increases the risk of mortality compared to CFRD without FH. In a study by Milla, Billings, and Moran (2005), the mean age of CFRD onset in their sample was 23 (+/-9) years. There was a 40% risk of progression from CFRD without FH to CFRD with FH, with the average time for development being 1.5 (+/- 2) years since the first diabetic OGTT. The median age of survival was 35.6 years for those with CFRD compared to 47.0 years for those without. This highlights the significant increased risk of mortality in those who develop CFRD.

1.5.4.1.2 Gender

Females have worse pulmonary function at the time of diabetes diagnosis compared to males which affects mortality (Milla et al., 2005). Based on a predictive model which compared FEV_1

at the time of CFRD diagnosis, females who had moderate to severe FEV$_1$ (<50% predicted) were 5 times more likely to die than females who had mild FEV$_1$ (>85% predicted). Using these same FEV$_1$ boundaries in males, risk of death was only twice a high in those with severe pulmonary function (Milla et al., 2005).

Given that females have been shown to have worse pulmonary function at the time of diabetes diagnosis, it is not surprising that this may lead to differences in the survival rates between males and females who have CFRD. The median age of survival has been found to be nearly 15 years more for males than females (Milla et al., 2005); for males, the median age was 47.4 years, whereas for females, it was 30.7 years. This supports research demonstrating a high mortality rate for females with CF during the ages of 30-39 years (Moran et al., 2009). Between males with CF who had and hadn't developed diabetes, there was only a small median survival difference of 2.4 years (Milla et al., 2005). Conversely, females who hadn't developed diabetes lived 16.3 years longer (based on median survival) compared to those who had diabetes. This effect of gender on CFRD survival accounted for a 54% increase in the risk of death. It is not known whether the earlier age of mortality in females in general is due to developing diabetes at an earlier age. Nevertheless, even with early identification of CFRD and aggressive treatment, females still have poorer prognosis compared to males.

1.5.4.2 Decline in pulmonary status

CFRD is associated with clinical deterioration in nutritional status and lung function (Lombardo et al., 2003; Marshall et al., 2005; Waugh et al., 2012). In the 'pre-diabetic' period (i.e. before the confirmed CFRD diagnosis), there is evidence that pulmonary and nutritional status have already started to decline due to the presence of acute hyperglycaemia. Decline can be evident up to 4 years before the confirmed diagnosis (Lanng, Thorsteinsson, Nerup, & Koch, 1992; Milla, Warwick, & Moran, 2000), with the degree of insulin deficiency affecting the rate of pulmonary decline. In some cases, this decline can be evident up to 6 years before diagnosis. Lanng et al., (1992) found that FEV$_1$ had declined by 20% and FVC by 10% in people with CFRD 6 years prior to a confirmed diagnosis, compared to those without diabetes. This emphasises the need for annual OGTT's from the age of 10 years in people with CF to identify those who may be a risk of developing diabetes.

Findings from the ERCF show that for those without diabetes, FEV$_1$% predicted was 72% compared to 52% for those with CFRD (Koch et al., 2001). This higher FEV$_1$% predicted value was consistently found for all age categories (i.e. below 10 years, 10-15, 15-20, 20-25, 25-30, and >30 years). Similar findings were found for FVC% predicted and weight-for-age percentiles for all age groups; these respective values were lower for those with CFRD compared to without CFRD.

Pulmonary function is correlated to glucose tolerance in a linear relationship. This is because lung function is negatively affected by insulin deficiency and hyperglycaemia (Moran, Becker, et al., 2010). Hyperglycaemia can cause a decline in lung function in people with CFRD directly or indirectly (Brennan et al., 2004). Directly, it can cause structural changes in lung tissue, and indirectly by reducing pulmonary defence against infection.

1.5.4.2.1   Direct effects of hyperglycaemia on lung function

There is evidence of direct damage to the lungs as a result of hyperglycaemia in T1DM and T2DM. In the Framingham Heart Study (Walter, Beiser, Givelber, O'Connor, & Gottlieb, 2003) and the Copenhagen City Heart Study (Lange, Parner, Schnohr, & Jensen, 2002) respectively, there was a decline in predicted FEV_1 and FVC in individuals who were diabetic compared to healthy individuals. However, Lange et al., (2002) found that there was no significant difference in the decline in lung function between diabetics and healthy controls longitudinally. So even though diabetics had worse lung function performance, the decline was similar across time between both groups. Nevertheless, both these studies highlight that even individuals who do not have a respiratory disorder can suffer from decline in lung function, and this is a consequence of developing diabetes and the resulting hyperglycaemia.

A number of mechanisms have been proposed to explain how hyperglycaemia directly causes chronic pulmonary abnormalities in CF (Brennan et al., 2004). These include an overproduction of superoxide molecules, an increased production of advanced glycation end (AGE) products or changes in inflammatory mediators. These processes all result in cellular stress and damage, which could lead to the decline in lung function exhibited in diabetics.

1.5.4.2.2   Indirect effects of hyperglycaemia on lung function

Hyperglycaemia can also cause lung function decline indirectly by making individuals more susceptible to pulmonary infection. People with CF are very susceptible to infection and during PEs even normoglycaemic individuals can experience acute hyperglycaemia, which supports that hyperglycaemia is caused by insulin resistance, rather than insulin deficiency (Holl et al., 1997). Hyperglycaemia can have both local and systemic effects (Brennan et al., 2004). It causes systemic neutrophil phagocytic activity, non-enzymatic glycosylation of proteins and chemokinesis to be impaired. Glycosylation also causes the function of collectins (immune proteins) to be reduced which heightens an individual's susceptibility to infection.

In healthy individuals, airway glucose levels are between 5 and 10% of that found in blood and this gradient is maintained in individuals with T1DM and T2DM (Stecenko & Moran, 2010). However, people with CF without diabetes have airway glucose systemic levels which are higher than normal, and these levels are even greater in those with CFRD; 29% and 54% respectively. Hyperglycaemia in people with CF causes a further increase in airway glucose concentrations which allows the growth of respiratory pathogens which can further affect lung function (Brennan et al., 2007). Research has also shown that people with either T1DM or T2DM are more prone to infection and have worse pulmonary outcomes than those without diabetes (Casqueiro, Casqueiro, & Alves, 2012; Joshi, Caputo, Weitekamp, & Karchmer, 1999).

1.5.4.3   **Catabolic state**

Healthy adults have a balance between protein synthesis and breakdown (Rafii et al., 2005). However, a catabolic state can be promoted in people with CF due to a lack of insulin (Zirbes & Milla, 2009). People with CF have some degree of increased protein catabolism which can be explained by all individuals experiencing some degree of insulin deficiency; even by those who are normoglycaemic and clinically stable. When people with CF are in a fasting state, protein

catabolism is suppressed as there is sufficient basal insulin. However, in the postprandial period, people with CF fail to inhibit protein breakdown in response to the defective secretion of insulin (Moran, Milla, Ducret, & Nair, 2001) resulting in protein catabolism. Furthermore, protein catabolism is enhanced in those who are not clinically stable. The degree of catabolism is linearly related to a person's insulin deficiency (Milla et al., 2000) and insulin therapy has been shown to decrease catabolism (Laguna et al., 2010). Increased protein catabolism negatively affects FEV_1, and as FEV_1 correlates with lean body mass, this can affect morbidity and mortality. This supports the CFRD consensus that insulin therapy should be given to all individuals with CFRD.

It has been suggested that males have better prognosis (in terms of survival) after CFRD diagnosis as androgens protect them against catabolic effects. Androgens, due to their anabolic effect, help males sustain muscle mass even though they may be experiencing insulin deficiency. An alternative explanation is that, because there is no gender difference in survival until after puberty, there may be an interaction between diabetes and female hormones which causes a pro-inflammatory state (Milla et al., 2005). In support of this explanation, C-reactive protein (CRP) levels are significantly elevated in diabetic females with CF compared to non-diabetic females, and males who are either diabetic or non-diabetic (Milla et al., 2005).

1.5.5 Diabetic complications of Cystic Fibrosis related diabetes (CFRD)

1.5.5.1 Diabetic ketoacidosis

Although diabetic ketoacidosis is rare in individuals with CF (Moran et al., 2014) case studies have been reported (Eenkhoorn, Van den Driessche, Van Gaal, Desager, & De Block, 2011). It is thought that as endogenous insulin secretion is still present and defective glucagon secretion occurs, this prevents people with CF from developing ketoacidosis (see section 1.5.1).

1.5.5.2 Microvascular complications

Diabetic treatment partly aims to alleviate microvascular complications and therefore those with undiagnosed CFRD have a greater risk of diabetic complications developing. Individuals with T1DM and T2DM have been shown to experience microvascular complications. It was previously thought that people with CFRD were at low risk of developing severe diabetic complications (Andersen, Lanng, Pressler, Laugesen, & Mathiesen, 2006). Even though there was not a great deal of emphasis on maintaining tight glycaemic control, life expectancy was shorter. Hence, it was thought likely that people with CFRD would have died before complications manifested. As people with CF are living longer and the incidence of developing CFRD increases with age, there is the potential for individuals to experience a longer duration of diabetes and thus for microvascular complications to develop.

Recent research has shown that people with CFRD do experience microvascular complications, but these tend to be relatively mild in comparison to those experienced by individuals with T1DM and T2DM (Moran et al., 2014). Developing complications are also of lesser importance than individuals with CF exhibiting decline in weight and nutritional status (Moran, Brunzell, et al.,

2010). Nevertheless, there have been a small number of documented cases of people with CFRD who exhibit severe complications.

1.5.5.2.1 Risk factors for developing microvascular complications

Research has shown there are several risk factors for people with CFRD developing microvascular complications.

1.5.5.2.1.1 CFRD duration and metabolic control

In people with CF, the development of microvascular complications has been found to correlate with CFRD duration (Moran, Brunzell, et al., 2010). This correlation is found regardless of whether duration was measured from an individual's first positive OGTT or when they first experienced persistent hyperglycaemia during a PE. Although HbA1c levels are spuriously low in people with CF and do not accurately reflect glycaemic control, elevated levels have been shown to be associated with an increased risk of microvascular complications. This association supports the T1DM and T2DM literature in that elevated HbA1c levels (i.e. >53 mmol/mol) increase the risk of developing microvascular complications (Zoungas et al., 2012).

The CF Foundation have advocated that people with CFRD should have the HbA1c goal of 53mmol/mol to reduce the risk of complications; although this goal can vary due to individual treatment (Moran, Brunzell, et al., 2010). Annual monitoring for complications is recommended, and should begin 5 years after an individual's diabetes diagnosis.

In support of microvascular complications developing as a consequence of diabetes duration, in a Danish study of 38 insulin treated people with CFRD (mean age= 30 years, CFRD duration= 0-31 years), retinopathy was not present in individuals who had had diabetes for less than 10 years (Andersen et al., 2006). This suggests that poor metabolic control and diabetes duration plays a role in the development of retinopathy in individuals with CF.

Schwarzenberg et al. (2007) completed detailed microvascular screening on 59 people with CFRD; there were slightly more individuals with FH than without. 42% had at least one neurologic abnormality and of those, 52% had had diabetes for more than 10 years. Thirty four percent (n=20) were found to have autonomic neuropathy, with a trend for those with FH to have an increased prevalence compared to those without FH (40% vs 18% respectively).Ten percent (n=6) had undergone lung transplantation and thus were expected to have an abnormal heart rate and deep breathing. Somatic neuropathy abnormalities were found in 17% (n=10) of individuals. Gastrointestinal complications were found in 51% (n=30). Both these respective complications were found to be more likely in those with longer diabetes duration and higher HbA1c levels (i.e. poor control of diabetes) which is expected. Of those found to have microvascular complications, 83% had a HbA1c ≥53mmol/mol. These findings highlight that although HbA1c may not be the best measure of glycaemic control in individuals with CF, it is important to adhere to the CF guidelines regarding <53mmol/mol HbA1c to avoid the potential development of microvascular complications. At present, it is unknown as to how such tight glycaemic control, in terms of HbA1c, impacts upon long-term lung function, nutritional status (Bridges, 2013) or indeed cognitive function (see Chapter 5).

1.5.5.2.1.2   Fasting hyperglycaemia in CFRD

Research has shown that those with CFRD and FH are more at risk of microvascular complications than those without FH (Schwarzenberg et al., 2007). This might be because people with CF are likely to progress to FH over time, and complications arise as a result of diabetes duration.

Schwarzenberg et al. (2007) found no prevalence of retinopathy or nephropathy in people without FH either overall (n=93), or with a diabetes duration of either <5 years, 5-10 years or >10years. In those with CFRD with FH (n=99), of the 37 people with FH and a diabetes duration >10 years, retinopathy had developed in 6 people; 5 cases were mild and 1 had proliferative retinopathy. However, the individual found to have proliferative retinopathy was thought to have T1DM. Microalbuminuria was found in 6 people; 5 cases were mild and one individual had gross proteinuria, but all these individuals had mild hypertension. Despite HbA1c levels being spuriously low, individuals who had CFRD with FH had higher HbA1c levels and longer diabetes duration compared to those without FH which may help to explain the prevalence of retinopathy and microalbuminuria found.

1.5.5.2.1.3   Nephrotoxic medication and microvascular complications

The chances of microvascular complications developing are increased in some people with CF because of nephrotoxic medication (e.g. aminoglycosides and cyclosporine). These medications are known to affect metabolic and renal function causing renal disease.

Andersen et al. (2006) compared the prevalence of diabetic nephropathy between non-transplanted (n=29) and post-transplanted (n=9) people with CF. In those who had not received a transplant, 9 individuals had hypertension, 1 had elevated creatinine, 3 had microalbuminuria and none had macroalbuminuria. In the 9 people who had received a transplant, 8 individuals had hypertension, 7 had elevated plasma creatinine, 2 had microalbuminuria, and like the non-post transplanted people, it may be that kidney dysfunction was caused by their nephrotoxic medication rather than as a result of diabetic nephropathy.

1.5.5.2.1.4   Other CF related factors

van den Berg et al. (2008) found no difference in the prevalence of microvascular complications (retinopathy, peripheral neuropathy, nephropathy and microalbuminuria) in a study of 79 adult insulin-treated non-transplanted CFRD and matched individuals with T1DM (paired and matched across groups on gender, age and duration of insulin therapy). Although both groups had the same number of complications, the prevalence of the respective complications differed between groups. The prevalence of microalbuminuria was more common in those with CFRD than T1DM (70 matched pairs; 21% vs 3.2%), and this prevalence was higher than that found by Andersen et al. (2006). However, people with CF regardless of diabetic status have been found to have higher levels of microalbuminuria compared to healthy controls (Dobson et al., 2005), so it may be other CF-related factors rather than diabetic nephropathy which explains the prevalence of microalbuminuria in CFRD. There was a lower prevalence of retinopathy in those with CFRD compared to T1DM (62 matched pairs; 10% vs 24.3%), which may reflect the greater prevalence of risk factors associated with retinopathy (i.e. smoking, high cholesterol levels and high BMI) and the strong trend for higher HbA1c present in those with T1DM, as you

would expect. There was no significant difference between both groups for peripheral neuropathy (70 matched pairs; 2 CFRD, 3 T1DM) and nephropathy (62 matched pairs; 1 CFRD, 1 T1DM) prevalence.

1.5.5.3 Macrovascular complications

Macrovascular complications have not been reported in individuals with CFRD (Perano, Rayner, Couper, Martin, & Horowitz, 2014). This may be explained by individuals with CF having generally low cholesterol levels as a result of gene mutation abnormalities and malabsorption of fat. As 90% of individuals with CF die from respiratory failure, it is less likely that those with CFRD will die from micro- or macro-vascular complications than those with T1DM or T2DM (Moran et al., 2014).

1.6 Psychosocial Issues in CF

It is widely acknowledged that those who suffer from a chronic illness are at an increased risk of developing psychological problems issues such as depression (Simmonds, 2013). People with CF are living longer and as their disease progresses, more aggressive and invasive treatment regimens are prescribed. Such individuals often experience a deterioration in physical functioning, which may impact on health status and/or schooling and employment.

1.6.1 Prevalence of anxiety and depression

1.6.1.1 Anxiety

Anxiety often precedes the development of depression (Brady & Kendall, 1992). Research has shown that the prevalence of anxiety in CF can range from 9 - 35% in children and adolescents and from 0-31% in adults (Cruz, Marciel, Quittner, & Schechter, 2009). The higher estimates reported by some research is due to the screening method employed; higher rates have been found in studies which used diagnostic interviews compared to self-report measures.

1.6.1.1.1 Factors influencing levels of anxiety and depression

1.6.1.1.1.1 Diagnosis of CFRD

In a large sample of 670 German adolescents and adults (aged 12-64 years) with CF, over a fifth (20.6%) reported moderate levels of anxiety on the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983), with a small percentage (6.6%) reaching clinical caseness (Goldbeck, Besier, Hinz, Singer, & Quittner, 2010). Interestingly, this study looked at the effect of CFRD and found that of the 14.3% who had developed CFRD, those newly diagnosed were more likely to have higher anxiety scores.

1.6.1.1.2 Gender

In a sample of 26 UK adults with CF (aged 18-48 years) in stable health, Chapman and Bilton (2004) reported that whilst 27% scored in the clinical range for anxiety symptoms using the HADS, females were more likely to score in the clinical range than men. This gender difference was not apparent for depressive symptomology; none of the sample reached clinical levels. This

gender difference in anxiety reporting has also been found by Cruz et al., (2009) who showed that males in the UK and Germany reported having lower clinical anxiety scores compared to females, which is in contradiction to research conducted in the US which found males to report higher levels.

1.6.1.1.3 Disease severity and anxiety

The health of an individual with CF may impact on the degree to which they report anxiety. In a cross-sectional study of 43 adults with CF, aged 18-49 years, Anderson, Flume, and Hardy, (2001) found those with lower pulmonary function reported higher anxiety levels on the State-Trait Anxiety Inventory (STAI; Spielberger, 1983), whereas, those with worse nutritional status (reflected by lower levels of ideal body weight) reported less anxiety. The former finding has also been reported in a more recent study (Yohannes, Willgoss, Fatoye, Dip, & Webb, 2012).

1.6.1.2 **Depression**

Depression has been shown to have a significant effect on the management of CF (Quittner et al., 2008) and the health of individuals with CF (Riekert, Bartlett, Boyle, Krishnan, & Rand, 2007). The multisystem effect of CF results in a daily treatment regimen which is complex and time-consuming (Sawicki, Sellers, & Robinson, 2009). It has been consistently found that individuals with chronic illnesses who are suffering from depressive symptoms are less likely to adhere to treatment and guidelines for these treatments, which includes medication, exercise and dietary recommendations, and are more likely to cancel or not attend hospital appointments (DiMatteo, Lepper, & Croghan, 2000). Riekert et al. (2007) found that individuals with CF who had moderate or severe pulmonary function (FEV_1 <70% predicted) were 3 times more likely to exhibit depressive symptoms on the Beck Depression Inventory (BDI; score≥10). Any alleviation of depressive symptoms could have a positive impact on daily functioning and improve adherence to treatment which highlights the importance of screening for depression in people with CF.

1.6.1.3 **The International Depression Epidemiological Study (TIDES)**

The International Depression Epidemiological Study (TIDES) is the largest psychological screening study of anxiety and depression to date in a chronic respiratory disease (Quittner et al., 2014). Two screening measures were used; the HADS and the Center for Epidemiologic studies (CES) -Depression Scale, partly because the HADS is not used in the USA. TIDES found that between countries, levels of reported depression on the HADS ranged from 8-15% and on the CES ranged from 20-31%, with an overall prevalence of 11% and 27% on the respective measures. Overall, there was a prevalence of 17% for people with CF, which is twice the rate of that observed in community populations (9.2%). Adults reported significantly more depressive symptoms than adolescents on both the CES (29% vs 19%) and HADS (13% and 5%) respectively. Interestingly, there were significant differences between the two measures in the prevalence of depressive symptoms; the odds ratio for adolescents was 4.45 and 2.90 in adults. The results from the 5 countries which used both depression measures highlight that the depression aspect of the HADS underestimates the prevalence of symptoms. The findings also indicated that people with CF also report high levels of anxiety using the HADS, with moderate

variability across countries (14-35%), and an overall prevalence of 30%. Significantly more adults than adolescents with CF (32% vs 22%) reported clinical levels of anxiety.

TIDES concurs with the common finding of comorbidity between anxiety and depression. The odds of adolescents with CF reporting depression were 14.97 times higher if they also reported elevated anxiety compared to those who had not. Furthermore, the odds of adults with CF reporting elevated depression were 13.64 times higher if they had reported elevated anxiety compared to those who hadn't. Elevations in both anxiety and depression were found in 6% of adolescents and 14% of adults.

TIDES-UK reports the results from 39 (25 adult/14 paediatric) UK CF centres (Duff et al., 2014). In these, the estimated prevalence of depression and anxiety in adults with CF was similar to that of the general population. Compared to their peers, adolescents with CF were less depressed and anxious, with adolescent males reporting minimally elevated depression scores. This may reflect the high importance placed on having access to psychological support (i.e. Clinical Psychologists) in the UK CF management guidelines. Nevertheless, 3.1% of males, and 4.6% of females, reported moderate (scores of 11-15) or severe (scores of 16 +) depression, and 11.5% of males and 17.2% of females reported moderate or severe anxiety. Elevated depression scores were associated with poor respiratory function, and both elevated anxiety and depression scores were associated with older age and unemployment due to health reasons.

1.6.2 Quality of life (QoL)

QoL is a multidimensional construct. It includes physical, psychological, social and functional areas of life. General and respiratory measures of QoL and health related QoL (HRQoL) have been shown to lack sensitivity in the CF population. The CFQoL questionnaire (Gee et al., 2000) is a patient derived measure assessing 9 domains relating to various aspects of life and the items are meaningful to people with CF; physical, social and emotional functioning, treatment issues, chest symptoms, concerns for the future, interpersonal relationships, body image and career concerns.

The first longitudinal effects of lung function in CF upon HRQoL have recently been reported by Abbott, Hurley, Morton, and Conway (2013). Over a 12 year period (1998-2010), a total of 234 people entered the study. The median age of death was 28 years and the majority of people (37/50) died within the first 2 years of the study. After adjusting for confounding variables, HRQoL scores followed the trend of $FEV_1\%$ predicted scores longitudinally; those who had better lung function reported a higher HRQoL. Interestingly, as lung function declined, scores on treatment issues, career concerns and future concerns (i.e. psychosocial issues) decreased most rather than physical issues as might be expected. However, both physical functioning and chest symptoms did decrease over the decade, at a similar rate to that of $FEV_1\%$ predicted at the population level.

1.6.3 Coping with CF

Coping is important in CF (Abbott, 2003). How people with CF deal with the emotional and physical demands of their condition can have an impact upon their health (Abbott, Dodd, Gee, & Webb, 2001) and QoL (Pfeffer, Pfeffer, & Hodson, 2003).

Coping styles are on a continuum ranging from avoidance-passive-repressive to active-monitoring-optimistic (Lazarus, 1966). Individuals will use a mixture of these coping styles depending on the situation. People with CF have to deal with both chronic and short term difficulties, and may adapt their coping style depending on the complexity of the problem and controllability of the situation (Abbott, 2003). Generally, people with CF adopt an optimistic coping style (Abbott et al., 2001), with one strategy of this coping style, social comparison, associated with a better QoL (Staab et al., 1998).

There is a poor relationship between the severity of CF disease and an individual's QoL (Pfeffer et al., 2003). This is partly explained by individuals with CF showing resilience and learning to cope as their disease progresses over time. The change in disease severity is generally gradual, which may allow the individual to adapt once they have reappraised the situation (Abbott, 2003). However, those who have severe disease may be more likely to use denial due to their inability to change their situation. Although denial is generally seen as a negative coping style, it may actually be a beneficial strategy in those with severe disease to maintain psychological wellbeing.

1.6.4 Adherence to treatment

People with CF have to adhere to onerous treatment in order to remain well (Peckham & Whitaker, 2013). Treatment is daily and involves multiple therapies prescribed for both preventative and treatment purposes. For most adults with CF, this involves "at a minimum, the daily intake of pancreatic replacement enzymes, nutritional monitoring, airway clearance, inhaled and nebulized medications and oral anti-inflammatory medications" (Sawicki et al., 2009, p91). As people with CF get older and their disease progresses, the treatment burden increases and becomes more complex.

A high treatment burden has been shown to have a negative impact on adherence. Despite the higher treatment demands of people with CF compared to other chronic illnesses, the levels of adherence are similar; although in CF, certain treatments have been shown to have higher adherence rates than others (Kettler, 2002). This suggests that given the time-consuming and demanding nature of daily treatment regimens, people with CF make decisions as to which treatment is most beneficial for them, and what can they realistically complete alongside work and home life (Kettler, 2002). Antibiotic treatment has the highest rates of adherence (80-95%), nebulised medications and pancreatic enzyme therapy have moderate rates (65-80%), and the lowest rates of adherence (40-55%) are seen for vitamin therapy, dietary changes, exercise and physiotherapy. Poor adherence can increase during adolescence as people with CF are given more responsibility for their own health and encouraged to be less reliant on their caregivers (Sawicki et al., 2009). In adulthood, the pressures of work, education, family and other responsibilities of managing a chronic illness have been shown to decrease adherence.

Adherence in CF is further complicated by two factors (Peckham & Whitaker, 2013). Firstly, people can appear relatively healthy and be asymptomatic despite organ function declining significantly. This causes the individual to lack motivation and perceive that they don't need to adhere to all aspects of prescribed daily treatment. Even if an individual is symptomatic, this is usually a poor marker of disease severity. The second issue is that as CF disease progression is inexorable, even if an individual adhered to 100% of their treatment, their health will still eventually decline. Treatment in CF includes preventative therapy; however the effects of these treatments are not seen immediately. This results in people with CF often regarding preventative therapy as a less important treatment to adhere to compared to that which has immediate tangible beneficial effects. People who have severe CF disease are at high risk of non-adherence because the benefits of adhering to treatment are often not apparent due to the lack of positive reinforcement. Hence, despite adhering to medication, their lung function does not improve drastically as previously experienced.

With the added complexity of having to treat a second chronic illness in those who have developed diabetes (i.e. CFRD), it becomes even more difficult for people with CF to achieve age-related developmental tasks (Besier & Goldbeck, 2012). In addition to trying to adhere to their CF medication and therapy, a diabetes diagnosis also introduces daily monitoring and controlling of blood glucose with insulin injections (Brennan et al., 2004) which often leads to poor adherence to insulin treatment (de Noronha, Calliari, Damaceno, Muramatu, & Monte, 2011). Furthermore, as mentioned in previous sections, insulin resistance can fluctuate during periods of illness and hence trying to control blood glucose concentrations adds to the daily hassle of treatment.

Higher levels of depression and anxiety are common in people with CF and unsurprisingly, depression has been shown to have an effect on adherence rates (see Section 1.6.1.2; Quittner et al., 2008). The treatment regimen in CF can potentially take up to 4 hours per day and therefore the decreased motivation and energy experienced severely impacts on their ability to complete all prescribed treatment. Furthermore, the cognitive distortions which accompany depression impact on self-efficacy and thus people with CF have a perception that they cannot accomplish all their treatment. Finally, depression has an effect on concentration levels, which are important in organising or remembering medication or therapy. As treatment is time-consuming, this may impinge on how treatment fits effectively into daily life. This further highlights the importance of screening for depression in people with CF. Whereas depression has been found to be a significant predictor of non-compliance to treatment in those with chronic illnesses, there is variable evidence for anxiety (DiMatteo et al., 2000). It has been argued that anxiety may have an adaptive role in CF management as optimal adherence is promoted by a reasonable level of anxiety (Modi, Driscoll, Montag-Leifling, & Acton, 2011; White, Miller, Smith, & McMahon, 2009).

With respect to coping, an optimistic coping style does not only have a beneficial effect on quality of life. Treatment adherence is better in individuals who used optimistic acceptance and hopefulness coping styles to a larger degree, and worse in individuals who used avoidance

coping style (Abbott et al., 2001). This is supported by research which shows, unsurprisingly, that adherence is poor in those who adopted an avoidant coping style (Pfeffer et al., 2003).

1.6.5 Educational attainment

Because aggressive treatment is advocated from an early age, this has enabled people with CF to maintain a better health status for longer. The high treatment burden endured during infancy enables a child with CF to start primary school relatively well (Conway et al., 2014). Although, additional treatment may be prescribed, this does not cause too much inconvenience. However, as people get older, this high treatment burden may be at the expense of time spent in education (Ernst, Johnson, & Stark, 2010).

Despite episodes of illness, complex and time-consuming treatment regimens and coping with the progression of the disease, the educational attainments of individuals with CF today have been shown to be similar to their peers (Ratjen & Döring, 2003). However, this has not always been the case. Table 1.4 summarises the research investigating educational attainment of people with CF in the UK to date. Given the current improved predicted survival rates, individuals with CF will have the same educational aspirations as their peers (Claxton, Latchford, Duff, & Peckham, 2013).

Table 1.4 Studies which have investigated educational attainment in people with CF in the UK

Authors (year)	Sample	Study design	Results	Notes
Walter et al. (1993)	866 adults (>16 years old)	Cross-sectional (survey conducted in 1990)	46% had completed some form of further qualification since leaving school. A larger percentage of people with CF had completed A Levels or equivalent qualifications compared to the general population (26% vs 19%), and women with CF were more likely to have a degree (12% vs 6%) than males	A large majority had left school without any basic qualifications and this was related to the severity of the disease i.e. those with more severe disease had not achieved any qualifications. The higher percentages may have been an effect of responder bias and social class; of those who had achieved higher education qualifications, 53% were from non-manual social classes compared to 32% in manual social classes.
Walters (2001)	1246 adults (mean age 25.5 years)	Cross-sectional	78% obtained GCSE or equivalent qualifications, 28% A Level or equivalent, 24% a degree, and 4% a post-degree qualification (Masters or Doctorate).	Disease severity was self-reported; 29% mild, 64% moderate, 7% severe. A large percentage had achieved basic school leaving qualifications despite rating their disease as moderate.
Huq et al., (2011)	92 adults (48% female, mean age 28 years, 18-66 years)	Cross-sectional	15% had not received any formal qualifications. A large percentage had achieved at least basic school qualifications; 28 people obtaining GCSE's, 14 people achieved A Level qualifications, 20 had attended college, and 16 had received a University degree.	Liverpool CF Centre study

Authors (year)	Sample	Study design	Results	Notes
Claxton et al., (2012)	162 adults (17- 69 yrs, mean age 29.2 yrs; 57% Male; 88% diagnosed ≤2 years). 10 were post-transplant; age of transplant unknown	Cross-sectional	151 reported their attainments; 5 adults had not achieved any qualification, and over half (n=93) had left school before they were 18 years old. 28% had achieved an undergraduate degree.14 responders had achieved post graduate qualifications (Masters n=12, Doctorate n= 2). 12 adults perceived CF to have a large impact on educational attainment whereas 29 reported CF having no impact at all. There was no relationship between the perceptions of CF impacting on education and school leaving age, or achieving an undergraduate degree level.	Leeds CF Centre study. People had moderate disease severity (mean FEV_1= 55.6 +/-21.8), but current FEV_1 was not a significant predictor of either leaving school after the age of 18 years or achieving a degree. Socioeconomic status was found to be the strongest predictor of school leaving age, attaining an undergraduate degree, and perceiving CF to have a greater impact on education.
Claxton et al. (2013)	6 adults (3 male), mean age 22.8 yrs, 21-24 yrs, diagnosed ≤ 2 years of age, not currently in education or employment.	Qualitative	Experience of attending high school and college was reported by all; however educational achievement differed. Based on the 6 interviews, four themes were reported: 1.CF had caused disruption to education either due to illness or treatment duration. Participants compared themselves to their peers and reported that they were behind both academically and socially due to CF having an impact on education as they got older. 2.Potential impact CF had on their lives was either alleviated or aggravated by influential people. 3.Achieving life goals were sometimes ambivalent due to personal concerns about health and life expectancy 4. Learned helplessness caused by repeated experiences of failure and hindrance from others, led to the educational aspirations and potential resulting careers to be abandoned.	Leeds CF Centre study. All had attempted to achieve the education and career aspirations they had during childhood. Only 50% received GCSE qualifications. Only 2 of these participants completed AS Levels (with varying degrees of success) and neither progressed onto A Level qualifications. People with CF can experience practical, physical and emotional barriers to educational attainment.

In 2001, the educational attainment of people with CF had improved since 1990 (Walters, 2001; Walters et al., 1993). This may be reflective of the increasing life expectancy, more modern disease and the desire to achieve the same development-related tasks as their peers, as well as to gain employment and independence. A more recent survey of people registered to the Liverpool CF Unit in 2011 found that there is still a small percentage of people with CF who do not achieve any formal educational qualifications (Huq et al., 2011). In 2012, a survey regarding the educational experiences of adults registered to the Leeds CF Unit (Claxton et al., 2012) reported findings which were in line with those registered to the Liverpool CF Unit and highlighted that educational achievement is still below that of the general population. Socioeconomic status (SES) was found to be the strongest predictor of school leaving age, attaining an undergraduate degree, and perceiving CF to have a greater impact on education. A qualitative study involving 6 adults (3 males) registered to the Leeds CF Unit supported the findings that some people with CF still face barriers in achieving the same educational attainment as their healthy peers (Claxton et al., 2013).

1.6.6 Employment

The rising life expectancy of those with CF has resulted in more individuals being able to work (Abbott, 2009). However, the level of education attained by people with CF has been shown to affect employment (Burker, Sedway, & Carone, 2004; Claxton et al., 2012; Laborde-Castérot et al., 2012; Targett et al., 2014; Walters et al., 1993). Table 1.5 summarises the research which has investigated employment in people with CF.

Table 1.5 Studies investigating the employment and occupation of people with CF in the UK

Authors (year)	Sample	Study design	Results	Notes
Walters et al. (1993)	866 adults (>16 years of age)	Cross-sectional	Just over 50% (n=468) reported being in paid employment. This rose with increasing age, up until 40 years when the proportion decreased. Regardless of disease severity, employment was more likely in those who had achieved qualifications. Significantly more men than women were employed (60% vs 51%). Those in employment may have been due to a survivor effect, i.e. they had better health than those who were unemployed 70% of those who were unemployed reported it was due to poor health. 30% were students. Significantly more women were unemployed due to poor health or 'homemaking' whereas men reported it was a consequence of being unable to find work. Compared to the general population, people with CF were significantly more likely to be in non-manual occupations.	The choice of occupation may have been reflective of the job trend at the time, or because they were unable to cope with more manual, labour intensive occupations. Those who were in employment reported that they were less likely to reveal having CF in their job interviews whereas those who were unemployed reported that they sometimes or always reveal that they have CF. Employment was also more likely in those with moderate disease if they had not revealed about CF.
Walters, (2001)	1246 adults (mean age 25.5 years)	Cross-sectional	47% of respondents were in paid employment. Compared to the general population, employment rates were lower across all age ranges, except for those 50 years and over.	Employment rates were particularly low for young people with CF.
Huq et al. (2011)	92 adults (18-65 years old, mean age 28 years, 55% male)	Cross-sectional	37 were in employment (18FT; 19PT), 12 were students (either FT or PT), 5% were FT home-makers, 34 reported that they were unemployed and 3% classified themselves as disabled.	Liverpool CF Centre study Despite 85% attaining at least basic school qualifications and 40% being in some form of employment, people with CF were not living as independently compared to the general population.

Authors (year)	Sample	Study design	Results	Notes
Taylor-Robinson et al. (2014)	People enrolled to the UK CF Registry.	Longitudinal (1996-2010)	Approximately 50% of the UK CF population were reported to be in FT or PT employment at any one time, across all ages. Being male, having better lung function and BMI and less hospitalisation were associated with increased rates of employment, whereas social deprivation was associated with lower rates. The chances of employment were reduced even further if an individual was in an area of high deprivation and had poor lung function i.e. people living in the most deprived areas were least likely to be employed if their lung function was poor.	Deprivation is a moderator in the relationship between lung function and chances of employment.
Targett et al. (2014)	254 adults (46% female, median age=26 yrs, mean $FEV_1\%$ predicted= 60%; CFRD=34%) from 3 UK centres Aberdeen= 41, Birmingham= 63, Newcastle= 150	Cross-sectional	65% of responders were either in employment or education. The number of hours worked ranged between 22 and 40 hours (median = 37.3 hours). Presenteeism (i.e. reduced productivity and/or below normal work quality) scores were high (range= 24.3- 26; mean= 25.1), and 84% reported that their employer was aware of them having CF. Employment was associated with higher educational attainment, HRQoL scores on role and health perceptions, and the centre participants were registered to. 69% of those reporting that they had worked had stopped due to CF. Nearly half the sample (47%) felt that their choice of career had been affected by CF and a quarter (24%) had changed their duties because of CF.	Although respondents felt that CF had impacted on their career choice, it did not stop them from working, and for those who were working, CF seemed to be having little impact on their daily working life which may be a result of the change in duties to accommodate the decline in clinical status.

Key: FT, full time; PT, part time;

In 1990, the number of people with CF in paid employment was found to be lower than the general population for those who were over 16 years of age (Walters et al., 1993). Although the survey reported that revealing CF status may be detrimental to their employment prospects, the study was conducted before the Disability Discrimination Act 1995. The 2001 survey (Walters, 2001) of those living in the UK with CF revealed that 47% of respondents were in paid employment. However, compared to the general population, employment rates were lower across all age ranges, except for those in the 50 years and over age group. Employment rates were particularly low for young people with CF. In 2011, of the 92 adults with CF registered to the Liverpool Heart and Chest Hospital, 85% of the sample had attained at least basic school qualifications and 40% were in some form of employment. However, people with CF were not living as independently compared to the general population.

As well as socioeconomic status having a negative effect on people with CF attaining educational qualifications, the level of social deprivation has been shown to have a negative effect on the chances of employment (Taylor-Robinson et al., 2014) and to moderate the relationship between lung function and chances of employment.

Although people with CF may be capable and skilled to work, their presenteeism may have an effect on employment. Hence, people with CF may have reduced productivity and/or below normal work quality. Nevertheless, Targett et al. (2014) reported that 65% of responders were either in employment or education which mirrors the findings from the other UK surveys of people with CF. Although respondents felt that CF had impacted on their career choice, it did not stop them from working; SPS-6 presenteeism scores were high. For those who were working, CF seemed to have little impact on their daily working life which may be a result of a change in duties to accommodate the decline in clinical status.

1.7 **Summary**

- CF is a complex multisystem disease caused by a gene mutation resulting in defective production and function of CFTR.
- In the lung, defective CFTR leads to dehydration of airway surface liquid, abnormally thick sticky mucus and a predisposition to pulmonary infections and inflammation.
- Mutations can be categorised into 7 classes depending on the type of CFTR protein dysfunction.
- The most common mutation is called F508del (class II mutation).
- Phenotypic expression and severity can differ even if individuals have the same genotypes.
- There is poor correlation between genotype and degree of lung function
- 90% of people with CF suffer from pancreatic insufficiency (PI).
- There is a strong correlation between genotype and PI; individuals with mutations from class I-III are more likely to be diagnosed at an earlier age and have PI.
- In the pancreas, CFTR is expressed in β cells and has an essential role in insulin regulation.

- CFRD is caused primarily by severe insulin deficiency, and variable insulin resistance, and the only recommended therapy is insulin.
- CFRD is associated with clinical deterioration (nutritional status and lung function).
- As lung function and weight decline up to 4 years prior to CFRD diagnosis, some CF centres advocate the use of insulin prior to diabetes diagnosis.
- Increasing age, being female, and severe genotypes are important risk factors for developing CFRD.
- People with CFRD can develop microvascular complications, but these tend to be mild in relation to individuals with type 1 and 2 diabetes respectively.
- People with CF are susceptible to higher levels of depression and anxiety, report a decline in health-related quality of life scores mirroring FEV1 % predicted, and generally, use an optimistic coping style.
- People with CF, despite episodes of illness, time consuming treatment and coping with disease progression, still have the same educational and career aspirations and attainment as their peers.
- The high treatment burden has been shown to have a negative impact on adherence in CF; a CFRD diagnosis further complicates this.

1.8 **Conclusion**

CF is a complex multisystem disease caused by a gene mutation resulting in defective production and function of CFTR. CFTR is present throughout the body including the brain and the pancreas. Glucose tolerance abnormalities are common in CF and the prevalence of CFRD, which shares clinical characteristics with type 1 (T1DM) and type 2 diabetes (T2DM), increases with age. Type 1 and type 2 diabetes mellitus are associated with a negative impact on cognitive functioning (see Chapter 3). Therefore, it is plausible people with CFRD may also have some degree of impairment. Previous literature which has investigated intellectual functioning and cognitive function in CF is presented in Chapter 2 of the thesis. However, research to date has not investigated the effect of CFRD on cognitive function.

Chapter 2

Cognitive function in people with cystic fibrosis (CF) who have not undergone transplantation

2.1 Introduction

It was originally thought that CF did not to have any effect on the brain. This led to the conclusion that children with CF do not exhibit intelligence quotient (IQ) and cognitive function deficits (National Institutes of Health Consensus Development Conference Statement on Genetic Testing for Cystic Fibrosis, 1999). However, given that CFTR is present in the brain (Guo, Su, McNutt, & Gu, 2009; Mulberg et al., 1994), it is plausible that people with CF may have some degree of cognitive impairment.

A number of studies have examined IQ and cognitive function in people with CF although a comprehensive review of these studies and their findings has not been published. Not all of these studies have used objective measures, and for some of these studies, cognitive function was a secondary or exploratory outcome measure. Therefore, these studies were unlikely to be powered to detect effects on cognitive function.

2.2 Intelligence quotient (IQ) and cognitive function

IQ is a numerical score derived from standardised tests of intelligence appropriate for a person's age, i.e. child and adult test versions are available. Scores are assigned on a scale, with the average score typically between 90 and 110. A score of 130 or higher indicates the person is of above average intelligence whereas a score of 70 or below indicates the person is of below average intelligence.

IQ tests are made up of subtests which correspond to verbal or performance IQ. Verbal IQ (VIQ) refers to the ability to understand information and solve problems using language based reasoning. Performance IQ (PIQ) refers to the visuo-spatial intellectual abilities, i.e. non verbal skills. Full scale IQ (FSIQ) is calculated from the subtest scores of both VIQ and PIQ. Intelligence can also be referred to as crystallised or fluid. Crystallised intelligence refers to the ability to utilise learned knowledge, experience and skills and is measured using VIQ subcomponents. In contrast, fluid intelligence refers to the ability to solve new problems, use logic in new situations, and identify patterns and relationships without prior knowledge and is measured using PIQ subcomponents.

IQ and cognitive function are not the same construct. Cognitive function refers to 'abstract thinking, reasoning, judgement, language, memory, attention and concentration, motor performance, constructional ability, speed of processing and perception' (Inkster & Frier, 2012, p221). The terms of cognitive function and cognitive performance are used

interchangeably in the literature (Lamport, Saunders, Butler, & Spencer, 2014). Cognitive tasks usually involve single components that help assess how people respond to more complex every-day tasks such as driving a car (Dye, Lluch, & Blundell, 2000). Table 2.1 below describes the cognitive domains frequently assessed in the literature, and the corresponding tests used.

Table 2.1 The cognitive domains frequently assessed in the literature, including subcomponents of these larger domains, typical task requirements and examples of tests (Adapted from Lezak, Howieson, Bigler, and Tranel, 2012)

Cognitive Domains and Subcomponents	Task Requirements	Examples of Tests
Attention, Processing Speed		
Attentional Capacity	Accuracy of attention span (e.g., repeating digit sequence)	Digit Span (forward & backwards), Digit Symbol Substitution (DSST)
Vigilance/Focus	Sustaining attention over a period of time whilst detecting target stimuli, often with a demand to ignore distractors	Bakan/Rapid Visual Information Processing (RVIP), Digit/Letter Cancellation
Processing Speed	Ability to process information and execute relevant operations within the allotted time	Trail Making Test (TMT; Part A & B), Simple Reaction Time (SRT), Choice Reaction time (CRT), RVIP
Executive Functions		
Reasoning/Planning	Thinking with conscious intent to reach a conclusion (planning involves induction, reasoning is more deductive)	Tower of Hanoi (TOH)
Cognitive flexibility	Switching between tasks or rules within a period of time.	Attention Switching Task (AST)
Inhibition	Interruption of an automatic response	Go/No-Go; Stroop Color and Word Test
Working Memory (short term memory)	Allows information maintained in temporary storage to be manipulated for complex cognitive operations	Serial 3s, Serial 7s, Corsi Block Tapping Test, Serial addition and subtraction
Memory		
Immediate Recall: Verbal or Visual	Learning/encoding of new information (contextual e.g. story) or non contextual (unrelated word list)	List Learning tasks (e.g., California Verbal Learning, (CVLT), Selective Reminding Test), Paired Associate Learning Test (PAL), Pattern Recall, Paragraph memory, Picture memory
Delayed Recall: Verbal or Visual	Recall of previously learned information(contextual or non contextual)	List Learning tasks (e.g., CVLT, Selective Reminding Test), PAL, Pattern Recall, Paragraph memory, Picture memory

Cognitive Domains and Subcomponents	Task Requirements	Examples of Tests
Recognition: Verbal or Visual	Ability to accurately recognize rather than recall learned information. Source monitoring requires identifying the context in which the information was learned.	List Learning tasks (e.g., CVLT, Selective Reminding Test), PAL, Pattern Recall, Paragraph memory, Picture memory
Language		
Semantic Processing	Language comprehension and speed of retrieval of information from general knowledge	Experimental semantic processing tasks (e.g., true or false questions)
Verbal Fluency	Oral production of words fitting a specified category or beginning with a specified letter	Category Fluency, Phonemic fluency
Motor Speed		
Gross	Speeded gross manual dexterity	Simple tapping task
Fine	Speeded fine manual dexterity	Purdue Pegboard Test

2.2.1 Early studies examining IQ in people with CF

Early research examined the intellectual functioning of people with CF and focused on academic achievement rather than cognitive functioning per se. These studies were largely descriptive; IQ was not the primary study outcome, and were performed using small sample sizes, which reflected the median age of survival at the time. Early studies examining IQ scores found that people with CF tended to be in the average, above average or higher ranges when the mean score of the group was examined (Boyle, di Sant'Agnese, Sack, Millican, & Kulczycki, 1976; Goldberg, Isralsky, & Shwachman, 1979; Kulczycki, Robinson, & Berg, 1969; Lawler, Nakielny, & Wright, 1966; Spock & Stedman, 1966) whereas Falkman (1977) found IQ scores to be normally distributed in CF. These differences may reflect the higher SES in samples. Four of these studies examined academic achievement, but none used standardised measures.

Thompson et al. (1992), using standardised measures of academic achievement in a sample of 76 children and adolescents (aged 7-17 years) with CF, examined how SES and health status may contribute to IQ and academic functioning. IQ and academic functioning were found to be normally distributed within the sample. Scores of IQ were inversely related to age (adolescents with CF had on average lower scores on VIQ, PIQ and FSIQ than children with CF, but their scores still fell within the normal range). However, this study used both the WISC-R (in children aged 7-12 years) and WAIS-R (in adolescents aged 13-17 years). The lower scores in adolescents may reflect the incorrect use of the WAIS-R which is intended for use in adults aged 16 years and over. Nevertheless, both IQ and academic functioning were significantly associated and correlated with SES level (lower scores were found in those with lower SES levels than in those with medium and high SES). Although those with poor health status (based on their Shwachman score) had lower scores of IQ and academic functioning than those with good health, this association was not significant. However, 90% of the sample had good or very good health status. This study suggests that in relatively healthy people with CF, a low SES is associated with poor intellectual and academic functioning, and that adolescents may be particularly vulnerable to performance decrements.

Table 2.2 below summarises the early studies which reported the IQ scores of people with CF.

Table 2.2 Summary of the early studies which reported IQ scores of people with CF (IQ not necessarily the primary study outcome)

Author(s)	Sample (People with CF)	IQ assessment	Results
Olmsted et al. (1976)	N=27, aged 13 to 30 yrs. All adults (n=22) were from middle or upper class families.	WISC (<16yrs age), WAIS (>16yrs age).	IQ ranged from 82 to 150. Mean IQ for the group was 113.
Goldberg et al. (1979)	N=52, adolescents and young adults (mean age 15.4 yrs)	AGCT	People with CF scored higher than their same age and grade level peers, indicating above-average intelligence.
Kulczycki et al. (1969)	N=26, young children	(not reported)	IQ ranged from 90 - 132. For those older than 3 yrs of age, mean IQ was 110. For those less than 3 yrs, mean IQ score was 97
Strauss and Wellisch (1980)	N=21 (12M, 9F), aged 18 to 33 yrs. Majority of women were below 23 yrs, and majority of men were over 23 yrs. All high school graduates ranged from none to PhD.	Shipley Hartford Institute for Living Test	Mean IQ score of the group was 111 (above average intelligence. Male IQ was higher (112) than female IQ (109). Mean VIQ was 117 and mean abstraction IQ score was 118; males slightly higher scores than females, but not significant. IQ may reflect SES of patients in the study.
Lawler et al. (1966)	N=11 (6F, 5M), aged 4 to 19 yrs of age. Females = 5 to 17 yrs of age Males = 4.5 to 19 yrs of age	Preschool group: CAT and Stanford Binet Intelligence Scale. School age children: WISC, Schonell Reading and Rorschach Ink-Blot Test. School leavers: WAIS and Rorschach Ink-Blot Test. Both groups: Draw-A-Person and Bender Gestalt tests.	Nine were in the superior and bright normal ranges of intellectual functioning and 2 were in the average range.

Author(s)	Sample (People with CF)	IQ assessment	Results
Spock and Stedman (1966)	N=21 (13F, 8M), 3 to 16 yrs of age	PPVT, the Goodenough Draw-A-Person test, Bender Gestalt test	IQ ranged from 81 to 150. Mean IQ score of the group was 104. Mean male IQ was 103 and female IQ was 105
Falkman (1977)	N=39, school-age children	(not reported)	IQ ranged from 70 to 127 with a mean of 95.6. The distribution was essentially normal, with 8 children in the above average range, 22 in the average range, 5 in the low average range (85-90), and 4 below 85.
Thompson et al. (1992)	N=76: Children aged 7-12 yrs (N=52, 17F, 35M). Adolescents aged 13-17 yrs (N=24, 13F, 11M). 90% good or very good health status	WISC-R and WAIS-R Standardised reading and maths scores: WJ ACH	IQ and academic functioning were found to be normally distributed. Scores of IQ were inversely related to age (adolescents had on average lower scores on VIQ, PIQ, FSIQ than children, but their scores still fell within the normal range). Both IQ and academic functioning were significantly associated and correlated with SES level (lower scores were found in those with lower SES levels than in those with medium and high SES).

Key: Average IQ, typically between 90 and 110; Above average IQ, score of 130 or higher; Below average IQ, a score of 70 or below; AGCT, Army General Classification Test; CAT, Children's Apperception Test; F, female; IQ, intelligence quotient; M, male; PIQ, performance IQ; PPVT, Peabody Picture Vocabulary Test; SES, socioeconomic status; VIQ, verbal IQ; WAIS (-R), Wechsler Adult Intelligence Test (-Revised); WISC (-R), Wechsler Intelligence Scale for Children (-Revised); WJ ACH, Woodcock-Johnson Tests of Achievement.

2.2.2 People with CF used as control or comparison groups to assess IQ and cognitive functioning in other chronic diseases

The majority of early research into cognitive functioning was published using people with CF as control or comparison groups, comparing their performance to people with other diseases (Beers, Yaworski, Stilley, Ewing, & Barksdale, 2000; Kent, Murphy, & Milla, 1990; Kerr, Ellis, Dupuis, Rommens, & Durie, 2010; Krull, Fuchs, Yurk, Boone, & Alonso, 2003; Stewart, Campbell, McCallon, Waller, & Andrews, 1992; Stewart, Hiltebeitel, et al., 1991; Stewart, Silver, et al., 1991). This allowed the effects of chronic illness and early hospitalisations to be controlled for.

2.2.3 Shwachman-Diamond syndrome, IQ and cognitive functioning

Like CF, Shwachman-Diamond syndrome (SDS) is the result of a gene mutation. It is an autosomal recessive disease characterised by PI, bone marrow dysfunction and skeletal abnormalities. Kent et al., (1990) found that in a sample of 11 people with CF (aged 4-20 years; mean 12.6 years) with a mean IQ of 102 (80-132), performance was worse on tests of dexterity, similar on tests of immediate and delayed visual memory and better on tests of motor function, word reading and visuomotor development compared to those with Shwachman Syndrome but none of these differences were significant. Similar findings have also been observed in a larger sample of children with SDS (N=32, 6-17 years) compared to children with CF (N=20; Kerr et al., 2010). The authors postulate that the deficits in those with SDS are the consequence of the associated gene mutation and resulting CNS dysfunction, and not because of chronic illness or poor nutritional status due to pancreatic dysfunction.

2.2.4 End stage liver disease, liver transplantation, IQ and cognitive functioning

Stewart and colleagues published several studies comparing children who either were recipients of liver transplants or had end-stage liver disease to a CF control group. Children with CF were proposed to be an appropriate comparison group matching on life-threating chronic illness, growth retardation, and varying ages of diagnosis.

The first study examined intellectual and cognitive functioning in 28 children aged 4-13 years who were 1-4 years (mean duration 26 months) post liver transplantation, compared to 18, age and SES matched, children with CF who were in good health (Stewart, Hiltebeitel, et al., 1991). Liver transplant recipients performed significantly worse on domains of intellectual and academic functioning, learning and memory, abstraction and concept formation, visuo-spatial abilities and motor function and had a tendency for worse alertness and concentration. However, when liver transplant children were compared with normal age-peers, the deficits became even larger which suggested that children with CF were not performing as well as healthy age-matched peers; this was confirmed for the domain of mental flexibility. A limitation of this study was the use of multiple IQ and cognitive batteries to control for the wide age range of children studied.

Stewart and colleagues subsequently published a second study focusing on liver transplant children (N=20) with a smaller age range (4-8 years old). Children with CF had VIQ and PIQ in the normal range, and scored significantly higher than those children who were, on average 26 (12-42) months post liver transplantation (Stewart, Silver, et al., 1991). Children with CF also performed significantly better on domains of abstraction, reasoning, logical analysis and integration, and visuo-spatial abilities than children who had undergone liver transplantation. Both these studies show that children who have undergone liver transplantation appear to have intellectual and cognitive deficits, particularly visuo-spatial deficits compared to a control group of children with CF.

In 1992, Stewart and colleagues examined the intellectual and cognitive functioning of 43 children (aged 6-16 years) with end-stage liver disease compared to a control group of 15 children with CF (aged 6-14 years). Children with CF had VIQ, PIQ and FSIQ within the normal range, whereas those with liver disease generally performed below average on all measures (Stewart et al., 1992). Those with biliary atresia[15] performed significantly worse on PIQ, visuo-spatial and short-term memory storage. In contrast, performance in those with alpha-1 antitrypsin deficiency[16] was not significantly different to those with CF, but deficits were apparent when compared to normative data. Thus, type of liver disease, age of onset of symptoms (appearing during the first year of life) and duration of disease appear to influence the pattern of cognitive function in those with end-stage liver disease. Early onset may be particularly detrimental to cognitive function due to brain development being more vulnerable during the early years of life.

The effect of liver transplantation was assessed in a more recent study which compared 15 children (mean age 6.8 years old) who were at least 2 years post liver transplantation to 15 children with CF (mean age 7.4 years) who had not received a transplant (Krull et al., 2003). Although IQ scores were within the normal range for both groups, children with CF were found to have slightly higher VIQ scores. Children with CF also performed significantly better on language, non-contextual verbal and visual memory, but not on contextual verbal or visual tasks. There was no difference between groups for tasks of visual perceptual and visual motor skills. These results suggest that liver disease has an effect on cognitive function independent of chronic disease.

2.2.4.1 **Short bowel syndrome, IQ and cognitive functioning**

A more recent study published in 2000, assessed cognitive function in 8 children (mean age 9.7 years) with severe short bowel syndrome, compared to 8 age, gender, SES and education matched children with CF (Beers et al., 2000). Performance was similar for domains of language, learning and memory and problem solving between the groups, but children with CF performed better on tests of visual-spatial abilities and psychomotor function.

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[15] A disorder in which inflammation develops within the bile ducts around the time of birth leading to scarring of the liver
[16] A genetic disorder in which a person is deficient of the enzyme alpha-antitrypsin leading to healthy tissue being damaged

The authors propose the difference in performance between groups is due to children with severe short bowel syndrome experiencing right hemisphere CNS changes.

Table 2.3 summaries the studies which have used people with CF as a control group to examine IQ and cognitive function in individuals with other chronic diseases.

Table 2.3 Summary of studies which have used people with CF as a control or comparison group to examine IQ and cognitive function in individuals with other chronic diseases

Author(s)	People with CF	Chronic disease group	Study design	Cognitive assessment	Results	Comments
Kent et al. (1990)	N=11 (3M, 9F), aged 4-20 yrs old, mean age 12.6 yrs.	Shwachman syndrome. N=12 (3M, 9F), aged 3.9 -20 yrs, mean age 12.5 yrs.	Cross-sectional	Annett and Kilshaw Pegboard, BOT, BAS, Bender-Gestalt test	Mean IQ of people with CF was 102 (80-132) compared to 82 (61-105) in people with Shwachman syndrome. People with CF were worse on dexterity, similar on immediate & delayed visual memory, but better on motor development, word reading & visuo-motor development.	Groups were matched on gender & social class. Included an unaffected sibling control group.
Kerr et al. (2010)	N=20 (10F,10M), mean age 11.5 yrs.	SDS. N=32 (14F, 18M), aged 6-17 yrs, mean age 12.5 yrs.	Cross-sectional	WISC-III, PPVT-III, TEA-Ch, EVT, WIAT-II, WCST, Test of Language Comprehension, CMS, Beery-VMI, CTOPP.	People with CF had significantly better FSIQ and were better than SDS on domains of language, perceptual skills, attention, memory and academic achievement than those with SDS.	Groups were matched on gender & age. Included an unaffected sibling control group.
Stewart, Hiltebeitel, et al. (1991)	N=18 (11M, 7F), aged 4-14 yrs, in good health.	Paediatric liver transplant recipients (1-4 yrs post, mean 26 months). N=28 (14M, 14F), aged 4-13 yrs.	Cross-sectional	WISC-R, HRINTB, RINTB	Transplant recipients were significantly worse on domains of IQ and academic functioning, learning and memory, abstraction and concept formation, visuo-spatial abilities and motor function, and a trend for worse attention. Deficits became larger when compared with normal age-peers. This suggests children with CF were not performing as well as healthy age-matched peers; this was confirmed for the domain of mental flexibility.	Groups were matched on age and SES. Limitation- use of multiple IQ and cognitive batteries to control for the wide age range of children studied

Author(s)	People with CF	Chronic disease group	Study design	Cognitive assessment	Results	Comments
Stewart, Silver, et al. (1991)	N=20 (11M, 9F), aged 4-8 yrs (mean 7.1 yrs).	Paediatric liver transplant recipients (12-42 mths post, mean 26 mths). N=20 (10M, 10F), aged 4-8 yrs.	Cross-sectional	WPPSI or the WISC-R, RINTB	Children with CF had VIQ and PIQ in the normal range, and scored significantly higher than transplant recipients. Children with CF also performed significantly better on domains of abstraction, reasoning, logical analysis and integration, and visuo-spatial abilities.	Children who have had liver transplantation due to end-stage liver disease appear to have IQ and cognitive deficits, particularly visuo-spatial.
Stewart et al. (1992)	Children, N=15 (7M, 8F), mean age 9.3 yrs.	End stage liver disease. N=43 (17M, 26F), mean age 10.9 yrs.	Retrospective analysis of clinical data	WISC-R	People with CF had the normal range VIQ, PIQ and FSIQ. Those with liver disease generally performed below average. Type of liver disease (biliary atresia), age of symptom onset (during first year of life) and duration of disease appear to influence the pattern of cognitive function in those with end-stage liver disease.	
Krull et al. (2003)	Children, N=15 (4F, 11M), mean age 7.4 yrs, non-transplanted.	Post liver transplantation (mean 5.7 yrs, range 2.9–8.9 yrs). N=15 (11F, 4M), mean age 6.8 yrs (range 5-10 yrs).	Cross-sectional	WISC-III, WPPSI-R, WJ-R ACH, CELF-R/ preschool, DTVP-2, TOMAL.	IQ scores were within the normal range for both groups. Children with CF had slightly higher VIQ and performed significantly better on language, non-contextual verbal and visual memory, but not on contextual verbal or visual tasks. No difference for visual perceptual and visual motor skills.	Liver disease has an effect on cognitive function independent of chronic disease.
Beers et al. (2000)	Children, N=8, mean age 9.8 yrs.	Short bowel syndrome. N=8, mean age 9.7 yrs.	Cross-sectional	CELF, WISC-III, WRAML, RINTB	Similar performance for language, learning and memory and problem solving between groups. Children with CF were better on tests of visual-spatial abilities and psychomotor function.	Groups were age, gender, SES and education matched.

KEY: BAS, British Ability Scales; Beery VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; BOT, Brunininks-Osertesky Test of Motor Development; CELF (-R), Clinical Evaluation of Language Fundamentals (-Revised); CMS, Children's Memory Scale; CTOPP, Comprehensive Test of Phonological Processing; DTVP-2, Developmental Test of Visual Perception (2nd ed); EVT, Expressive Vocabulary Test; F, Female; (H)RINTB, (Halstead) Reitan-Indiana Neuropsychological Test Batteries for Children; M, Male; PIQ, performance IQ; PPVT-III, Peabody Picture Vocabulary Test-III; TEA-Ch, Test of Every Day Attention For Children; TOMAL, Test of Memory and Learning; VIQ, verbal IQ; WCST, Wisconsin Card Sorting Test; WIAT-II, Wechsler Individual Achievement Test-II; WISC (-III or -R), Wechsler Intelligence Scale for Children (-III or –Revised); WJ-R ACH, Woodcock-Johnson-Revised Tests of Achievement; WPPSI (-III or -R), Wechsler Preschool and Primary Scale of Intelligence (-III or –Revised); WRAML, Wide Range Assessment of Memory and Learning.

2.2.5 Summary: IQ in CF, and IQ and cognitive function in comparison to other diseases groups (CF used as control group)

- CF was originally thought not to have an effect on the brain.
- The majority of early research into cognitive functioning was published using people with CF as control or comparison groups, comparing their performance to people with other diseases. This allowed the effects of chronic illness and early hospitalisations to be controlled for.
- People with CF perform better on measures of IQ and cognitive function than those with other chronic diseases (SDS, end-stage liver disease, post transplantation liver disease and short bowel syndrome).
- Although people with CF generally perform better on tests of IQ than individuals with other chronic diseases, the lack of a non-CF control group does not allow investigation into whether any differences would be present between people with chronic diseases and healthy matched peers.

2.3 Cognitive functioning in people with CF and factors which may influence performance

Children with CF have been shown to exhibit delays in intellectual development before the age of 5 years, but these subsequently disappear (Lloyd-Still, Hurwitz, Wolff, & Shwachman, 1974). This finding may reflect the delay in a CF diagnosis and screening at the time of the study. However, it is possible that delays may still persist as subclinical brain defects that could be missed with global IQ measures. Section 1.1.1 shows that CFTR is expressed in the brain. Therefore, it is plausible that people with CF may have some degree of cognitive impairment. Several studies have investigated whether some aspect of CF disease or treatment may influence cognitive function in people with CF who have not undergone transplantation.

2.3.1 Disease severity in CF, IQ and cognitive function

In 1995, Stewart and colleagues were the first to investigate cognitive function in children (N=20, aged 5-8 years) with CF compared to a physically healthy control group (N=20, matched on gender, age and SES) in a cross-sectional study (Stewart et al., 1995). Although scores for VIQ, PIQ and FSIQ were in the normal range and not significantly different to healthy control children, the scores for controls were slightly higher extending into above 'average' scores. However, children who had greater severe disease severity were more likely to show pronounced deficits on tests of VIQ and FSIQ, sensory-perceptual abilities and incidental learning. Sensory-perceptual abilities moderately to largely correlated with all Shwachman scores.

Early negative effects of CF (growth and nutrition) are important factors in intellectual and cognitive functioning in young children with CF. Growth during infancy in particular (rather than during childhood) is an important predictor for intellectual function as, based on all the Shwachman variables, it is the most sensitive to disease severity (Stewart et al., 1995). It

may be that disease severity diminishes tactile perceptual skills and thus children with CF are particularly vulnerable to decrements on simple perceptual and problem solving tasks. The study by Stewart et al. (1995) highlights that disease severity is related to aspects of cognitive dysfunction in a young, albeit small, sample of 'fairly' well children with CF. Therefore, older patients with CF who are more likely to show disease progression, and thus more severe disease, may be more likely to have cognitive deficits, particularly if they had significant growth and nutrition deficits during infancy. A subsequent study by Bacon, Matt Maddrey, and Stavionha, (1999) reported that, based on their preliminary findings, verbal and nonverbal memory functioning was within the normal range in 29 children with CF aged 10-16 years, which supports the findings by Thompson et al., (1992).

A recent prospective Dutch study, which assessed IQ (VIQ and PIQ), social cognition (emotional recognition, theory of mind[17]) and executive functioning (planning, working memory, mental flexibility) in a small sample of 20 people with CF, aged 5–13 years, found that scores were not significantly different to normative data (Kok et al., 2013). The results of people with CF were also compared to a healthy control group (N=30). There was no difference between patient and control groups on emotion recognition or working memory, worse patient performance on theory of mind, and better patient performance on cognitive flexibility and working memory; although these differences were small (<1 SD; e-poster, unpublished data). Unlike previous research, disease severity (age at diagnosis, FEV_1%predicted, BMI, number of PEs per year) did not predict any aspect of intellectual or cognitive functioning.

2.3.2 Neonatal screening, vitamin E deficiency and cognitive function in CF

Neonatal screening for CF is becoming routine practice (Castellani et al., 2009). It has been hypothesised that people with CF diagnosed by traditional screening methods may have worse cognition function (due to delayed diagnosis and greater nutritional deprivation) compared to those diagnosed by neonatal screening. This was investigated by Koscik and colleagues who describe an association between early malnutrition, vitamin E deficiency and later cognitive dysfunction in people with CF (Koscik et al., 2004; Koscik et al., 2005). In 2004, cognitive function was assessed in 89 children and adolescents (aged 7-17 years) with CF diagnosed either by traditional screening (N=47) or neonatal screening methods (N=42). Overall, performance by people with CF was similar to normative data. However, factors such as being from a lower SES background, a single parent family and less parental education were associated with lower cognitive scores. When comparing screening methods, those with traditional diagnosis and vitamin E deficiency (α-tocopherol(T) <300 ug/dL) had significantly worse cognitive function compared to those with adequate vitamin E levels and those diagnosed by neonatal screening (including those who had short-term vitamin E deficiency). This study supported the benefit of early screening for CF and the associated improvements in nutritional status.

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[17] ability to attribute and understand mental states of oneself and others

A subsequent study examined the effect of screening method (traditional vs neonatal) in 71 children (7-16 years) who did not have meconium ileus at birth (Koscik et al., 2005). Cognitive function scores were significantly lower in those who were traditionally screened who were vitamin E deficient, compared to those traditionally screened who were not vitamin E deficient, and those who were neonatally screened (with and without vitamin E deficiency). The difference in scores is of clinical as well as statistical significance, and is likely to translate into functional differences e.g. lower academic functioning and occupational achievement. The poor nutritional status in those screened using traditional methods was still apparent after 3 years despite treatment to rectify the deficit which highlights the importance of early diagnosis in CF. The two studies by Koscik and colleagues show that although CF performance on the whole is comparable to normative data, a prolonged period of vitamin E deficiency has deleterious effects for cognitive function later in life.

2.3.3 Hypoxaemia, hypoxia, IQ and cognitive function in CF

As CF disease progresses, people are very susceptible to hypoxaemia[18]. Hypoxaemia is associated with morbidity and mortality and is postulated to be a possible mechanism for cognitive dysfunction in people with CF. In a double-blind, randomised 3 year trial of 28 people with advanced CF, there was no difference in cognitive function (processing speed, memory or achievement) between those receiving oxygen compared to room air over the first year of the study (Zinman et al., 1989). However, those receiving oxygen were able to maintain school or work attendance in contrast to those receiving room air whose attendance deteriorated.

The first known studies to investigate cognitive function as the primary outcome in adults with CF were conducted by Matt Maddrey and colleagues in 1997. They proposed people with CF may suffer from cognitive impairment due to hypoxia[19]. In a sample of 31 adults with CF, 68% showed cognitive impairment on at least one domain compared to matched age and education healthy controls, in particular working memory and visuo-spatial skills (Matt Maddrey, Cullum, & Prestidge, 1997). In a subsequent study, again with 31 adults with CF, impairments were observed for domains of attention (23%), memory (32%), working memory (61%) and abstraction/reasoning (19%) compared to (age, gender and education appropriate) normative data (Matt Maddrey, Cullum, & Prestidge, 1998). Nonverbal incidental memory has also been found to be significantly impaired in 22 adults with CF (mean age 25.1 years), compared to normative data (Cooper, Matt Maddrey, & Cullum, 1997). Interestingly, a study which examined the degree of impairment based on self-report symptoms in people with CF (N=33) found that 27% reported poor attention and concentration and 61% (N=20) reported symptoms which are consistent with mild impairment in one domain or more, with 12 of these people impaired on 2 or more domains (Epker & Matt Maddrey, 1999). Thus, people with CF experience some cognitive dysfunction, particularly in terms of attention, and seem to be aware of this deficit to some extent.

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[18] Arterial oxygen tension or partial pressure of oxygen (PaO2) is below normal. Normal: 80-100mmHg
[19] Reduction in oxygen supply at the tissue level, which is not measured directly by laboratory value

Following the hypothesis that people with CF are at high risk of chronic hypoxia and poor nutritional status, Netson and colleagues performed a pilot study in 5 adolescents (13-17 years) with CF investigating cognitive function and white matter integrity (Netson, Carey, Moffett, Baer, & Haut, 2008). Compared to age-based norms, adolescents with CF performed below peers on tests of IQ, processing speed and executive function. The integrity of the genu of the corpus callosum correlated significantly with mental flexibility, and moderately to largely correlated with processing speed, working memory, visual problem-solving. There was a large, positive correlation between BMI and FEV_1 with working memory, and a negative correlation between BMI and FEV_1 with IQ and academic functioning. These results suggest adolescents with CF may be vulnerable to mild executive function and processing speed impairments.

It has been hypothesised that the increased incidence of hypoxemia and hypercapnia[20] are mechanisms for cognitive impairment in people with CF. In 2011, Fukushima and colleagues did not find evidence for cognitive dysfunction based on the Mini Mental State Examination (MMSE) in 18 adults with CF (mean age 28.6 years) who were normoxic[21] (Fukushima, Evangelista, Rao, & Afshar, 2011). Subsequently, they examined whether there was any difference in sensitivity in detecting cognitive impairment between the Montreal objective cognitive assessment (MoCA) and the MMSE in 23 adults (mean age 31 years) with CF (Fukushima, Evangelista, Afshar, & Rao, 2012). According to the MoCA, there was evidence of mild cognitive impairment in the sample but this was not detected using the MMSE. Although, measures of FEV_1% predicted, FEV, FEF_{25-75}[22], oxygen saturation, BMI and education level, were collected, it is not stated how these factors interact with cognitive function scores for either testing tool.

2.3.4 Sleep disturbances, sleep quality and cognitive function in CF

People with CF are very susceptible to disrupted sleep or loss of sleep efficiency. Sleep disturbances have been shown to affect cognitive function in both healthy children and those with CF (Holley, 2011). In 26 children aged 6-12 years with CF, longer duration of sleep and better sleep quality were associated with better executive function performance, but not faster processing speed.

Dancey, Tullis, Heslegrave, Thornley, and Hanly, (2002) compared sleep quality and daytime function (sleepiness and cognition) in 19 adults with CF (mean age 30 years) relative to 10 healthy controls (mean age 27 years). Adults with CF with severe disease (FEV_1 <40% predicted) experienced increased daytime sleepiness and showed significant cognitive impairment on tasks of simple addition/subtraction, serial reaction and colour-word conflict compared to healthy controls. Those with CF performed at a level of 60% of the controls. There was no difference in performance on tasks of grammatical reasoning or spatial-orientation. Across the day, controls also significantly improved performance on the simple

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[20] abnormally elevated carbon dioxide (CO_2) levels in the blood)
[21] normal levels of oxygen in tissue or blood
[22] the average forced expiratory flow during the mid 25-75% portion of the FVC

addition/subtraction task whereas people with CF maintained performance, only showing slight improvement. The findings suggest this is due to people with CF compensating for chronic sleep loss by slowing their responding rate in order to maintain accuracy. The authors suggest the deficits in cognitive function may be the result of chronic sleep deprivation (significantly reduced total sleep time, increased wakefulness after sleep onset, higher frequency of awakenings and reduced sleep efficiency) and nocturnal hypoxaemia. In a similar study, Milross et al., (2002) found that in 37 clinically stable people with CF who had moderate to severe lung disease, FEV_1%predicted correlated with subjective sleep quality and daytime dysfunction (as measured by the PSQI) respectively. Thus, both objective and subjective measures of cognitive function are impaired in clinically stable people with CF who have moderate to severe lung disease.

2.3.5   Pulmonary exacerbations (PEs) and cognitive function in CF

As CF disease progresses, people are very susceptible to PEs. It is hypothesised that when people are not clinically stable, their cognitive function may worsen. Research by Dobbin, Bartlett, Melehan, Grunstein, and Bye, (2005) examined the effect of PE on cognitive function. PEs are associated with increased sleep disruption and hypoxaemia, and alleviation of symptoms could potentially result in improved task performance. 22 adults with moderate CF disease (mean age 26 years, mean FEV_1 59% predicted) suffering from a PE were studied at the beginning and end of treatment, and compared to people with CF who were clinically stable with moderate lung disease (mean age 30 years, FEV_1 61% predicted), who acted as controls.

During a PE, people with CF experienced feelings of mental exhaustion, fatigue and sleepiness, which significantly improved following treatment. People with CF at the start of a PE performed significantly slower on the serial addition and subtraction and digit symbol substitution task (DSST) compared to CF controls. Following treatment of a PE, people with CF significantly improved on both speed and accuracy on the serial addition and subtraction test and a psychomotor vigilance task. Although they improved in terms of accuracy, they were still significantly slower on the DSST. There was no significant improvement in word pair recall following treatment of a PE.

Interestingly, both groups showed similar improvements on the addition/subtraction task. On the DSST and addition/subtraction tasks, gender modified the effect of a PE. Analysing those with PEs, women had better accuracy on the addition/subtraction test, whereas men had faster reaction times (i.e. fewer lapses) on the psychomotor vigilance task. Even though the sample consisted of people with varying degrees of lung disease, there was no association between lung function and cognitive function, after adjusting for age and IQ. Driving performance was also assessed using a simulator with 17 people with PEs, and 19 CF controls. Although there was no significant difference between those with and without PEs at the start of the study, following treatment of a PE, mean brake response time significantly improved when a truck appeared on the road. Thus, although there was no apparent cognitive impairment between groups, those with PEs may be vulnerable to making errors in everyday complex tasks. This study shows that PEs have a negative effect on cognitive

function and driving ability in young people with CF, regardless of underlying disease severity and performance improves following treatment.

Dobbin and colleagues presented their preliminary results of the above study at the NACFC conference in 2003 but also included the results of 16 healthy controls (Dobbin, Bartlett, Grunstein, & Bye, 2003). On the psychomotor task and addition/subtraction test, as reported above, speed and accuracy were improved on the respective tests after a PE but there were no significant improvements in the group of people without PEs and healthy controls. However, when assessing speed on the addition/subtraction test, all three groups significantly improved which suggests this result is due to practice effects. However, after adjusting for education levels, age-matched healthy controls had significantly better word recall, and faster reaction time on the addition/substitution and DSST than clinically stable people with CF. These findings support Dancey et al., (2002), in that clinically stable people with CF, but who have moderate lung disease, show impairment in memory and processing speed compared to healthy controls.

2.3.6 Psychosocial factors and IQ in CF

The potential effects of CF on psychosocial, IQ and academic development were examined in a correlational study of 40 people with CF, aged 16-21 years (Grieve et al., 2011). IQ and academic functioning were within the normal range. There was a positive, moderate correlation between self-efficacy and with FSIQ, arithmetic scores and school achievement respectively. However, this study failed to measure lung disease severity in people with CF. Nevertheless, it highlights that psychosocial factors may also have an effect on IQ, cognitive abilities and school achievement.

2.3.7 End-stage CF lung disease, IQ and cognitive function in CF

The prevalence of individuals with CF who have FEV_1 ≤40% predicted has increased because of improved survival rates. Transplantation is now a viable option for people with CF. When an individual experiences significant deterioration in their health status, lung function, nutritional status, and quality of life, they are often considered for lung transplantation.

Crews and colleagues examined intellectual and cognitive functioning in 18 people (mean age 26 years) with end-stage CF who were being evaluated as potential lung transplant candidates, compared to normative data for age, gender and education level (Crews, Jefferson, Broshek, Barth, & Robbins, 2000). Of the 18 participants, there was no overall IQ deficit, 3 exhibited no signs of cognitive impairment (although one individual did not have complete data), and 8 showed impairment on only one of the tests. The outcome measure of non-contextual verbal memory on the Selective Reminding Test was commonly found to be impaired. Immediate and delayed (30 minutes) free recall as well as long term retrieval strategies were impaired in 7 out of 17 people and 8 of the 17 showed consistent long-term retrieval impairment. Five people also had long-term storage deficits. Therefore, although encoding and storage strategies may be impaired, there is greater impairment for retrieval abilities in people with CF.

Impairments in contextual verbal memory were seen in 22% of people for immediate and 11% of people for delayed recall. This is much less than the 40% observed for immediate and delayed recall on non-contextual verbal memory respectively. As a large proportion of people (12/15) did not exhibit impairment on the non-verbal/figure test, this suggests that people with CF have greater impairment in executive function (i.e. organising verbal information). Impairments were also seen on simple and complex tasks of processing speed, mental flexibility and visuo-motor scanning abilities (trail making tests); 4 people showed impairment on part A (simple task), and 3 of these individuals also showed impairment on part B (complex task). This further supports that people with CF show some impairment in executive function. The authors postulate that these deficits in cognitive function are due to progressive decline in lung function, resulting hypoxaemia and poor nutritional status.

Since Crews and colleagues published the study about cognitive function in people with end-stage CF, subsequent studies have examined end-stage disease in various pulmonary disease populations (Crews et al., 2003; Parekh et al., 2005; Rodrigue, Kanasky Jr., Marhefka, Perri, & Baz, 2001; Ruchinskas et al., 2000). Crews et al., (2003) assessed cognitive function in 134 people with end-stage lung disease who were lung transplant candidates; prevalence of CF is unknown. Like the authors' previous study (Crews et al., 2000), the greatest impairment was seen in non-contextual verbal memory. It is presumed the abstract published in 1999 corresponds to this 2003 study, and shows that males are more impaired on cognitive flexibility and non-verbal contextual memory compared to females (Crews et al., 1999). Ruchinskas et al. (2000) present normative data for measures of cognitive function in 100 potential lung transplant candidates; 10 had CF. Unfortunately, the results are not segregated for lung disease. However, the authors do report that 50% of people exhibit greater risk for non-contextual verbal memory impairments, which supports the above literature.

Like Ruchunskas et al. (2000), Rodrigue et al. (2001) reported normative data for measures of cognitive function for a larger group of lung transplant candidates (N=201, 19 had CF), but also compared the results to norms for liver and heart transplant candidates, and examined the relationship between psychosocial functioning and disease severity (FEV_1, FVC) and exercise tolerance (6 minute walk test). Scores on the IQ measure (WAIS-R; Vocabulary, Block design, arithmetic, and digit span) were within the normal range and within 1 SD of the population mean. Compared to lung-transplant candidates, liver candidate scores were significantly lower on the subtests, whereas heart candidates did not differ significantly. Lung function and exercise tolerance were not significantly correlated with cognitive and affective functioning, psychosocial adjustment, coping or life satisfaction.

Finally, Parekh et al., (2005) examined how gas exchange and exercise capacity affects cognitive function in a sample of 94 people; 13 (14%) had CF. There was no significant difference between the different lung disease categories for executive function and verbal memory when age and education were adjusted for. However, the study found that 37% of people had moderate to severe cognitive impairment on at least two measures. After adjusting for age and education level, pulmonary carbon dioxide (PCO_2) was negatively

associated with executive function, and attention and verbal memory, whereas pulmonary oxygen (PO_2) was only marginally associated with better executive function and attention performance. Exercise tolerance was also positively associated with verbal memory. This study also supports previous literature showing that people with end-stage lung disease have executive function and verbal deficits.

A recent study examining cognitive function in end-stage lung disease in children (N=6) found average IQ ability, intact memory function, but subtle deficits on tasks involving processing speed and fine-motor coordination (J. Wong et al., 2011). As part of the study rationale, the authors note that diabetes in CF is associated with subtle deficits in motor speed and memory. Despite an extensive literature search, no published research has been found investigating the effects of CFRD on cognitive function to support this statement. It is unclear whether this statement is based on objectively measured cognitive function, clinical judgement, or the results of a case study as part of the transplant assessment protocol. Contacting the authors did not prove successful. It is proposed that the testing may have been in children with CF and as part of the transplantation process given the topic of the abstract. Therefore, a large scale study is needed to objectively examine the effects of CFRD on cognitive function in adults with CF.

Table 2.4 below summaries the studies which have investigated cognitive function in people with CF who have not undergone transplantation.

Table 2.4 Summary of studies investigating cognitive function in people with CF who have not undergone transplantation

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Zinman et al., (1989).	N=28, advanced CF, receiving nocturnal oxygen treatment.	People with CF breathing room air.	Hypoxaemia	Double-blind, randomised 3 year trial	Standardised measures of cognitive function.	No difference in processing speed, memory or achievement between those receiving oxygen compared to room air over the first year of the study.	Those receiving oxygen were able to maintain school or work attendance. In those receiving room air, attendance deteriorated
Stewart et al. (1995)	N=20, aged 5-8 yrs.	Physically healthy children, N=20. Matched on gender, age and SES.	Disease severity	Cross-sectional	WPPSI, WISC-R, RINTB	IQ scores (VIQ, PIQ, FSIQ) were in the normal range and not significantly different to controls. Greater severe disease severity was associated with pronounced deficits on tests of VIQ and FSIQ, sensory-perceptual abilities and incidental learning. Growth during infancy in particular is an important predictor for intellectual function as it's the most sensitive to disease severity (Shwachman score). Its proposed disease severity diminishes tactile perceptual skills and thus children with CF are particularly vulnerable to decrements on simple perceptual and problem solving tasks.	First study to investigate cognitive function in children with CF. Disease severity was related to aspects of cognitive dysfunction.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Koscik et al. (2004)	Children and adolescents (N=89, age range 7-17 yrs). Diagnosed by neonatal screening (N=42, mean age 10.1 yrs).	Diagnosed by traditional screening (N=47, mean age 10.5 yrs).	Neonatal screening and vitamin E deficiency.	Wisconsin CF Neonatal Screening Project: RCT of early diagnosis through neonatal screening during 1985-1994	TCS/2	Overall, CF performance was similar to normative data. Being from a lower SES background, a single parent family and less parental education were associated with lower cognitive scores. Those with traditional diagnosis and vitamin E deficiency had significantly worse scores compared to those with adequate vitamin E levels and those diagnosed by neonatal screening (including those who had short-term vitamin E deficiency).	This study supported the benefit of early screening for CF, and the associated benefits of better nutritional status.
Koscik et al. (2005)	N=71 (7-17 yrs) who did not have meconium ileus at birth. Neonatal screened (N=37), with or without vitamin E deficiency (a-T level <300 mg/dL).	Traditional screening diagnosis (N=34), with or without vitamin E deficiency (a-T level <300 mg/dL).	Neonatal screening and vitamin E deficiency.	RCT of early diagnosis through neonatal screening during 1985-1994	TCS/2	Cognitive function was worse in those who were traditionally screened and vitamin E deficient compared to not deficient, and compared to those who were neonatally screened (with/out vitamin E deficiency). The poor nutritional status in those screened using traditional methods is still apparent after 3 yrs despite treatment to rectify the deficit.	A prolonged period of vitamin E deficiency has deleterious effects for cognitive function later in life. The difference in scores is of clinical as well as statistical significance, and is likely to translate into functional differences.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Netson et al. (2008)	Adolescents, N=5, 13-17 yrs.	N/A	White matter integrity	Pilot study	Not reported	Below age-based norms for IQ, processing speed and executive function. Integrity of the genu of the corpus callosum significantly correlated with mental flexibility and moderately to largely correlated with processing speed, working memory, visual problem solving. A large, positive correlation between BMI and FEV_1 with working memory. A negative correlation between BMI and FEV_1 with IQ and academic functioning.	Adolescents with CF may be vulnerable to mild executive function and processing speed impairments.
Holley (2011)	Children, N=25 (13M, 12F), aged 6-12 yrs, mean age 9.25 yrs.	Healthy control data from previous study. Children, N=59 (27M, 32F) aged 6.2 -12 yrs. Mean age 9.3 yrs	Sleep disturbances	Cross-sectional	TEA-Ch, WISC, NEPSY, AWMA	In people with CF, longer duration of sleep and better sleep quality were associated with better executive function performance, but not faster processing speed.	In healthy children, sleep disturbances affect cognitive function.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Kok et al. (2013)	Children and adolescents, N=20 (14F, 16M), aged 5-13 yrs, mean age 8.4 yrs.	Normative data. Healthy control group (N=30, 18F, 12M, mean age 8.9 yrs).	None proposed	Prospective	NEPSY II, BADS-c, TMT A, TMT B, WPPSI-III & WISC-III	Similar scores to normative data for VIQ and PIQ, social cognition (emotional recognition, theory of mind) and executive functioning (planning, working memory, mental flexibility). No difference between groups on emotion recognition or working memory, worse patient performance on theory of mind, and better patient performance on mental flexibility; differences were <1SD.	Disease severity (age at diagnosis, FEV_1%predicted, BMI, number of PEs per year) did not predict IQ or cognitive function.
Matt Maddrey et al. (1997)	Adults, N=31, aged >17 yrs.	Healthy controls matched on age, education.	Hypoxia	Cross-sectional	MicroCog	68% of people with CF showed cognitive impairment on at least one domain in particular working memory and visuo-spatial skills.	First known CF study investigating cognitive function as the primary outcome in adults.
Matt Maddrey et al. (1998)	Adults, N=31, aged >17 yrs.	Age, gender, and education-referenced test norms.	Systemic illness and associated risk factors (nutritional status, liver disease, hypoxia, diabetes)	Cross-sectional	Digit Vigilance Test, CVLT, MicroCog (Tic Tac subtest), WCST	Impairments were observed for domains of attention (23%), memory (32%), working memory (61%) and abstraction/reasoning (19%) compared to normative data.	Significant portion of adults with CF show evidence of impairment in one or more cognitive domains.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Cooper et al. (1997)	Adults, N=22 (mean age 25.1 yrs).	Data from similar age controls.	Subclinical hypoxic states	Cross-sectional	ROCF	Nonverbal incidental memory is significantly impaired in people with CF compared to normative data.	
Epker and Matt Maddrey (1999)	Adults, N=33.	N/A	Episodic or low-level chronic hypoxia.	Cross-sectional	NIS	27% reported poor attention and concentration and 61% (N=20) reported symptoms which are consistent with mild impairment in one domain or more, with 12 of these patients impaired on 2 or more domains.	People with CF seem be aware of some degree of cognitive dysfunction
Grieve et al. (2011)	Adults, N=40 (22M, 18F), mean age 18.6 yrs (range 16-21 yrs).	N/A	Psychosocial factors	Cross-sectional	WASI	IQ and academic functioning were within the normal range. A positive, moderate correlation between self-efficacy and with FSIQ, arithmetic scores and school achievement.	No measurement of lung disease severity.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Dancey et al. (2002)	Adults, N=19, mean age 30 yrs.	Healthy controls, N=10, mean age 27 yrs.	Chronic sleep deprivation (significantly reduced total sleep time, increased wakefulness after	Cross-sectional	Sleep onset, higher frequency of awakenings and reduced sleep efficiency) and nocturnal hypoxaemia.	Those with severe disease (FEV_1 <40 % predicted) experienced increased daytime sleepiness and significant impairment on tasks of simple addition/subtraction, serial reaction and colour-word conflict compared to healthy controls. Those with CF performed at a level of 60% of the controls. No difference on tasks of grammatical reasoning or spatial-orientation. Across the day, controls significantly improved on the simple addition/subtraction task whereas CF maintained performance, only showing slight improvement.	People with CF compensate for chronic sleep loss by slowing their responding rate in order to maintain accuracy.
Milross et al. (2002)	N=37 (20M, 17F), mean age 27 yrs, clinically stable, FEV_1 36% predicted. 'Poor sleepers' N=23.	'Good sleepers' N=14	Sleep quality	Cross-sectional	PSQI questionnaire	FEV_1%predicted correlated with subjective sleep quality and daytime dysfunction.	Subjective cognitive function is impaired in clinically stable people with moderate to severe disease.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Dobbin et al. (2005)	Adults, moderate CF disease (N=22, 36%M, mean age 26 yrs, mean FEV_1 59% predicted) suffering from a PE.	People with CF, clinically stable, moderate lung disease (N=22, 64%M, mean age 30 yrs, FEV_1 61% predicted).	PEs (increased sleep disruption, hypoxaemia).	Repeated measures; beginning and end of IV antibiotic treatment.	Neuro-behavioral Assessment Battery and AusEd Driving simulator (PE N=17, controls N=19).	Feelings of mental exhaustion, fatigue and sleepiness significantly improved following PE treatment. At the start of a PE, performance was significantly slower on serial addition/subtraction and DSST compared to controls. Following treatment, both speed and accuracy on the serial addition/subtraction and psychomotor vigilance significantly improved. Despite improved accuracy on the DSST, speed did not improve. No significant improvement in word pair recall following treatment. Gender modified the effect of PE; women had better accuracy on the addition/subtraction test, men had faster reaction times (i.e. fewer lapses) on the psychomotor vigilance task. No association between lung function and cognition, after adjusting for age and IQ. No significant difference between those with and without PE at the start of the study. Following treatment of a PE, mean brake response time significantly improved when a truck appeared on the road.	Although there was no apparent cognitive impairment between groups, those with PEs may be vulnerable to making errors in everyday complex tasks. PEs have a negative effect on cognitive function and driving ability in young people with CF, regardless of underlying disease severity and performance improves following treatment.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Dobbin et al. (2003)	Adults, moderate CF disease (N=20, mean age 26.1 yrs, mean FEV_1 59% predicted) suffering from a PE.	Healthy controls (N=16, mean age 29 yrs). People with CF, clinically stable, moderate lung disease (N=20, mean age 29 yrs, FEV_1 60% predicted).	PEs (increased sleep disruption, hypoxaemia).	Repeated measures; beginning and end of IV antibiotic treatment	Neuro-behavioral Assessment Battery	On the addition/subtraction test and psychomotor task, speed and accuracy improved after a PE but there were no significant improvements in the control groups. All three groups significantly improved speed on the addition/subtraction test which suggests practice effects. After adjusting for education levels, healthy controls had significantly better word recall, and faster reaction time on the addition/ substitution and DSST than clinically stable people with CF.	Clinically stable people with CF, who have moderate lung disease, show impairment in memory and processing speed compared to healthy controls
Fukushima et al. (2011)	Adults, N=18 (9M, 9F), mean age 28.6 yrs range 22-47 yrs, normoxic.	N/A	Increased incidence of hypoxemia and hypercapnia. CFTR dysfunction.	Cross-sectional	MMSE	No evidence for cognitive dysfunction.	

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Fukushima et al. (2012)	Adults, N=23 (13M,10F), mean age 31 yrs.	N/A	Malnutrition, education, decreased lung function, hypoxemia and hypercapnia.	Cross-sectional	MMSE and MoCA	Evidence of mild cognitive impairment in the sample using the MoCA which was not detected using the MMSE.	Clinical parameters (lung function, oxygen saturation, BMI and education level) were collected; It is not stated how these factors interact with scores for either testing tool.
Crews et al. (2000) .	N=18, mean age 26 yrs with end-stage CF who were being evaluated as potential lung transplant candidates.	Normative data for age, gender and education level.	End stage CF disease: progressive decline in lung function resulting in hypoxaemia and poor nutritional status.	Cross-sectional	WISC-III, WAIS-R, TMT (A, B) WCST, WMS, WMS-R, Selective Reminding Test	No overall IQ deficit. Non-contextual verbal memory was commonly found to be impaired. Deficits include Immediate and delayed (30 minutes) free recall, long term retrieval strategies, consistent long term retrieval, long-term storage. Minimal impairment on the non-verbal/figure test suggests that people with CF have greater impairment in executive function (i.e. organising verbal information). Impairments were also seen on simple and complex tasks of processing speed, mental flexibility and visuo-motor scanning abilities.	Although encoding and storage strategies may be impaired, there is greater impairment for retrieval abilities. People with CF show some impairment in executive function.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Crews et al. (2003)	Lung transplant candidates with end-stage disease, N=134 (59M). Prevalence of CF is unknown.	N/A	End-stage lung disease	Cross-sectional	WISC-III, WAIS-R,TMT (A, B),WCST, WMS-R, Selective Reminding Test, RAVLT	The greatest impairment was seen in non-contextual verbal memory. >40% of both genders displayed impairments on the Selective Reminding Test for measures of Total Recall, Long Term Retrieval, and Consistent Long Term Retrieval tasks. Males are more impaired on cognitive flexibility and non-verbal contextual memory compared to females.	Crews et al. (1999) is the published conference abstract of this study. 1SD below the mean was the criterion for impaired cognitive performance.
Ruchinskas et al. (2000)	Lung transplant candidates N=100 (54F), mean age 47.1 yrs (range 18-68); 10 had CF	Normative data for age, gender and education level.	End stage lung disease	Cross-sectional	WAIS-R; TMT (A,B) WMS-R Selective Reminding Test, WCST	Majority exhibited normal functioning on most tests. 25% exhibited impaired attentional set shifting and short-term visual memory. 50% exhibited greater risk for non-contextual verbal memory impairments.	A preliminary normative study of lung transplant candidates. Results not segregated by lung disease.
Rodrigue et al. (2001)	Potential lung transplant candidates N=201; 19 had CF.	Norms for liver and heart transplant candidate.	Type of end stage organ disease, lung function, exercise tolerance, psychosocial functioning.	Cross-sectional	WAIS-R	IQ scores were within the normal range and within 1 SD of the population mean. Lung function and exercise tolerance were not significantly correlated with cognitive and affective functioning, psychosocial adjustment, coping or life satisfaction.	Compared to lung-transplant candidates, liver candidate IQ scores were significantly lower, whereas heart candidates did not differ significantly.

Authors (year)	People with CF (experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Parekh et al. (2005)	N=94. End-stage lung disease. 13 (14%) had CF.	N/A	Gas exchange and exercise capacity.	Cross-sectional	TMT (A, B), COWA, Animal Naming, Stroop Color–Word Test, DSST Digit Span (forward, backwards), WMS-R	No significant difference between the different lung disease categories for executive function and verbal memory when age and education were adjusted for. However, 37% had moderate to severe cognitive impairment on at least two measures. After adjusting for age and education level, PCO_2 was negatively associated with executive function, attention and verbal memory whereas PO_2 was only marginally associated with better executive function and attention performance. Exercise tolerance was also positively associated with verbal memory.	People with end-stage lung disease have executive function and verbal deficits.

KEY: AWMA, Automated Working Memory Assessment; BADS-c, Behavioural Assessment of the Dysexecutive Syndrome in Children; BMI, body mass index; COWA, Controlled Oral Word Association Test; CVLT, California Verbal Learning Test; DSST, digit symbol substitution test; F, Female; FEV_1, forced expiratory volume in 1 second; FSIQ, full scale IQ; IQ, intelligence quotient; IV, intravenous; M, Male; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NEPSY II, A Developmental NEuroPSYchological Assessment; NIS, Neuropsychological Impairment Scale; PEs, Pulmonary Exacerbations; PIQ, performance IQ; PCO2, Pulmonary carbon dioxide; PO2, pulmonary oxygen; PSIQ, Pittsburgh Sleep Quality Index; RAVLT, Rey Auditory Verbal Learning Test; RCT, randomised control trial; RINTB, Reitan-Indiana Neuropsychological Test Batteries For Children; ROCF, Rey-Osterrieth Complex Figure; SD standard deviation; SES, socioeconomic status; TCS/2, Test of Cognitive Skills/Second Edition; TMT (A,B), Trail Making Test (Part A, Part B); TEA-Ch, Test of Every Day Attention For Children; α-tocopherol(T)<300 ug/dL, vitamin E deficiency; VIQ, verbal IQ; WASI, Wechsler Abbreviated Scale of Intelligence; WCST, Wisconsin Card Sorting Test; WISC-III, Wechsler Intelligence Scale for Children; WMS (-R), Wechsler Memory Scale (-Revised); WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence-III

2.3.8 Summary: cognitive function in CF and factors which may affect performance

- Up until 1995, no research had examined cognitive function as a primary outcome measure in people with CF in comparison to a healthy control group.
- Intellectual functioning in CF follows a similar pattern to that seen in healthy controls and thus is not impaired. In contrast, cognitive function has been shown to be impaired on a range of tests assessing different domains, with some studies suggesting that the cause of impairment is related to some aspect of CF disease or treatment e.g. traditional screening, chronic sleep deprivation, PEs, end-stage CF.
- Treatment of PEs may improve cognitive function.
- Although studies are limited, impairments on tests of memory, processing speed and executive function are commonly observed.

2.4 **Conclusion**

Chapter 1 reviewed the pathophysiology of CF and the comorbidities associated with the disease. Survival rates of people with CF have increased, but this has come at the cost of developing additional complications. CFRD is an important and common complication that emerges with increasing age. Chapter 2 showed that people with CF (who have not undergone transplantation) commonly exhibit impaired performance in domains of memory, processing speed and executive function. Various factors of CF disease have been investigated as mechanisms for cognitive dysfunction such as disease severity, nutritional status, hypoxaemia, sleep disturbances and quality, PEs and end-stage lung disease. People who have impaired glucose regulation (IGT, T1DM, and T2DM) have been shown to exhibit some degree of cognitive impairment relative to healthy controls (see Chapter 3). Research to date has not objectively examined the effect of CFRD on cognitive function in a large scale study. Given that people with CF are susceptible to glucose dysregulation because of the underlying gene defect, and since CFRD shares clinical characteristics with T1DM and T2DM, it is postulated that people with CF may exhibit cognitive dysfunction, with those who have developed CFRD having a greater degree of impairment compared to those with NGT.

Chapter 3

Cognitive function in people with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM): implications for cognitive function in CF and CFRD

3.1 Introduction

Research has shown people who have impaired glucose regulation (IGT, T1DM, and T2DM) exhibit some degree of cognitive impairment relative to healthy controls. This has implications for cognitive function in CF and CFRD given people with CF are susceptible to glucose dysregulation because of the underlying gene defect, and CFRD shares clinical characteristics with T1DM and T2DM.

3.2 Homeostatic control of blood glucose levels

In healthy individuals, the homeostatic control of blood glucose ensures there is tight regulation of the concentration of glucose in blood plasma so that it stays within the normal range of 4-6mmol/L (Sünram-Lea, Owen & Robertson, 2015). Glucose levels rise in response to food ingestion which stimulates β cells in the pancreas to release insulin. The secretion of insulin results in lower levels of circulating glucose, and the subsequent negative feedback of glucose causes insulin to stop being released. This results in the body's metabolism returning to basal state. In contrast, if blood glucose levels are low, glucagon is secreted from the pancreas. Glucagon breaks down liver glycogen to glucose and increases gluconeogenesis[23] in the liver.

3.2.1 Glucose utilisation in the CNS

Glucose is the main metabolic fuel for the brain (Amiel, 1994). The oxidative metabolism of glucose utilises nearly all the oxygen which enters the brain via the bloodstream (McIlwain, 1959) as there is no storage capacity for oxygen in the brain (Owen & Sünram-Lea, 2011). Contrary to previous research (Boyle et al., 1994), the brain can store a minimal amount of glucose in the short term (Sünram-Lea et al., 2015). Glycogen stores are diminished within 10 minutes if not replenished. Therefore, the brain requires a continuous exogenous supply of blood glucose and oxygen to meet its requirements to function adequately.

The blood brain barrier (BBB) consists of the luminal (inner surface) and abluminal (outer surface) membranes of brain capillary endothelial cells (Pardridge, 1993). Oxygen is a small molecule which can readily pass through the BBB (Iversen, 1979). In contrast, due to the close proximity of the endothelial cells (Drewes, 1998), larger molecules such as glucose

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[23] the biosynthesis of glucose from certain non-carbohydrate carbon substrates

require special transport mechanisms to enter into cells through the periphery to the brain. Glucose is transported from the periphery to the central nervous system (CNS) via facilitative glucose transporter proteins (GLUT; McEwen & Reagan, 2004). In the brain, GLUT- 1 and GLUT-3 are the two main transporters (Duelli & Kuschinsky, 2001). Within the brain, glucose is broken down in two ways (Owen and Sünram-Lea, 2011). Glucose largely undergoes glycolysis (via glycolytic and tricarboxylic acid pathways) within neurons and generates a large amount of energy in the form of adenosine triphosphate (ATP; cellular energy carrying module) and pyruvate through oxidation (Rao, Oz & Seaquist, 1996; Mergenthaler, Lindauer, Dienel & Meisel, 2013; Owen & Sünram-Lea. 2011). Alternatively, glycogenesis occurs and glucose is synthesised and stored as glycogen within astrocytes. During euglycaemia, glucose is transported at a rate which is sufficient for brain metabolism. Neuroglycopenia ensues if transport into the brain is not sufficient for demand.

3.1.1 The Selfish Brain Theory and cognitive function

The brain uses a disproportionate amount of glucose relative to its size (Rooijackers, Wiegers, Tack, van der Graaf & de Galan, 2016). The brain accounts for approximately 2% of total human body weight but uses nearly 20% of the body's oxygen use and 25% of the body's glucose use (Love & Webb, 1992). This has led to the development of the Selfish Brain Theory (Peters et al., 2004). The theory's principle is based on the energy supply chain. Energy fluxes from the remote environment to the near environment (i.e. suppliers), through the body, towards the brain; the final consumer. According to the theory, the brain is able to maintain the ATP concentration through high affinity and low affinity ATP-sensitive potassium (K_{ATP}) channels. When the concentration decreases, a K_{ATP} channel is opened allowing the flux of potassium to the extracellular space, which hyperpolarises the neuron (i.e. promoting a change in the cell's membrane potential resulting in it becoming more negatively charged) and makes it refractory (unable to generate subsequent action potentials for a limited period of time). Bound high affinity K_{ATP} channels permit glutamatergic neuronal activity, with glutamatergic (excitatory) neurons raising brain ATP. In contrast, bound low affinity K_{ATP} channels permit γ (gamma)-Aminobutyric acid (GABA)-ergic activity, with GABA-ergic (inhibitory) neurons lowering brain ATP. Systemic homeostasis is maintained by a "competent brain-pull".

3.2.2 Role of insulin in the brain

Despite previous research suggesting that the brain was 'insulin insensitive' (Bachelard, 1981), it is now well known that insulin exerts potent effects in the brain (Cholerton, Baker, & Craft, 2013; Ketterer et al., 2011). Within the brain, the two main factors which insulin affects are appetite regulation and cognition (Banks, Owen & Erickson, 2012). Circulating insulin (derived from pancreatic β cells) is transported into the CNS by cerebral spinal fluid (CSF) across the BBB via an active, saturable, receptor-mediated process (Duarte, Moreira & Oliveira, 2012). Insulin receptors and insulin sensitive transporters (GLUT-4 and partially GLUT-1) are present on the endothelial cells to facilitate receptor-mediated active transport (McEwen & Regan, 2004; Pardridge, Eisenberg & Yang, 1985). Within the human brain, insulin receptors and insulin-like growth factor-1 (IGF-1) receptors are highly abundant but

selectively distributed (Kleinridders, Ferris, Cai, &Kahn, 2014; Duarte, Moreira, & Oliveira, 2012). They are expressed in the synapses of astrocytes and neurons and high concentrations are found in the hypothalamus, cerebral cortex and hippocampus (Ketterer et al., 2011). GLUT-4 has been found within cells in the cerebellum, hypothalamus, and hippocampus (Grillo et al., 2009). Although most of the insulin within the brain is derived from pancreatic β cells, it is also partially formed in pyramidal neurons which are found in areas such as the hippocampus, prefrontal and entorhinal cortex and olfactory bulb (Hoyer, 2003).

A slight increase in peripheral insulin levels leads to higher levels of insulin in the CSF (Moreira, Duarte, Santos, Rego, & Oliveira, 2009). Uptake of insulin into the brain is specific to physiological state. In murine models, hypoinsulinemia[24] increases the uptake of insulin in pharmacologically induced diabetes. In contrast, insulin transport into the brain is hindered during chronic peripheral hyperinsulinemia[25] due to the downregulation of insulin receptors at the BBB.

In contrast to the periphery, insulin does not largely affect transport or metabolism of glucose in the CNS (Ketterer et al., 2011). Some exceptions have however been noted as insulin has been shown to promote glucose utilisation within some areas of the brain (Park, 2001). Hence, in the hypothalamus, the neural uptake of glucose analogue gold-thio-glucose is increased by insulin (Debons, Krimsky & From, 1970). Additionally, in the hippocampus, glucose metabolism is sensitive to exogenous insulin via the insulin receptor (Hoyer, Henneberg, Knapp, Lannert, & Martin, 2003). Energy homeostasis[26] is sensitive to insulin levels in the CNS (Schwartz, Figlewicz, Baskin, Woods & Porte, 1992; Woods, Figlewicz-Lattemann, Schwartz, & Porte, 1990). Finally, the firing rates of hypothalamic, suprachiasmatic nucleus and hippocampal neurons are insulin sensitive (Oomura, 1976; Shibata, Liou, Ueki & Oomura, 1986; Palovcik, Phillips, Kappy, & Raizada, 1984). This suggests that insulin may play an independent role from glucose utilisation in the CNS.

3.2.3 The effects of glucose and insulin on cognitive functioning

The regulation of both glucose and insulin is instrumental for cognitive functioning (Wrighten, Piroli, Grillo, & Reagan, 2009). Certain brain areas are extremely sensitive and responsive to changes in glucose homeostasis, such as the hippocampus (Gray, Meijer, & Barrett, 2014; Wrighten, Piroli, Grillo, & Reagan, 2009). The ways in which glucose and insulin affect cognitive functioning are described below.

3.2.3.1 Glucose administration

Glucose administration has been shown to have beneficial cognitive effects using different experimental paradigms (Messier, 2004). The domain of memory has been shown to benefit the most from glucose i.e. the glucose facilitation effect (Riby, 2004). Older adults (65 years and older) show the greatest benefit from glucose consumption compared to younger adults

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[24] abnormally low concentration of insulin in the blood
[25] Higher blood insulin levels than what is considered normal in people without diabetes; i.e. as a result of insulin resistance
[26] the control of food intake and energy expenditure

(e.g. university students). This is because younger adults are nearer to their 'cognitive peak' (Foster et al., 1998). Alternatively, older adults benefit more because they are more likely to suffer from poor glucose regulation (Awad et al., 2002). In healthy young adults, glucose facilitation enhances performance on divided attention tasks, and is most beneficial when the cognitive demand of the task is high (Smith et al., 2011).

3.2.3.2 **Hypoglycaemia**

In healthy individuals, impaired cognition becomes apparent when blood glucose levels fall to between 2.6 and 3.0 mmol/L (Warren & Frier, 2005). The hyperinsulinaemic glucose clamp technique (DeFronzo, Tobin, & Andres, 1979) is the gold standard for assessing insulin sensitivity and has been employed to examine the effect of hypoglycaemia on cognitive function. During experimentally induced hypoglycaemia, aspects of memory, particularly working memory and delayed memory (Deary, Sommerfield, McAulay, & Frier, 2003; Sommerfield, Deary, McAulay, & Frier, 2003) as well as visual selective attention and mental flexibility (McAulay, Deary, Ferguson, & Frier, 2001), are susceptible to impaired functioning. This is because during neuroglycopenia, tasks which involve higher cognitive processing (i.e. those that are more cognitively complex or demanding on attention processes) are more affected by glucose depletion than simple motor or cognitive tasks on which performance is relatively well preserved (Cox, Gonder-Frederick, Schroeder, Cryer, & Clarke, 1993; Deary et al., 1993; McAulay et al., 2001). On simple tasks, hypoglycaemia does not affect accuracy but instead the speed at which the individual completes the task (Warren & Frier, 2005). After an acute episode of severe hypoglycaemia, individuals may experience transient cognitive dysfunction, but this usually subsides and normal functioning resumes after 1.5 days (Strachan, Deary, Ewing, & Frier, 2000). Prolonged severe hypoglycaemia (i.e. <1.0 mmol/L) however can result in irreversible cognitive dysfunction (Auer, 2004). When blood glucose levels reach and are sustained at such low levels, cerebral energy failure can be induced resulting in neuronal necrosis.

3.2.3.3 **Hyperglycaemia**

There is also evidence that hyperglycaemia may have damaging physiological effects with cellular dehydration occurring because of the osmotic pressure high levels of glucose exert in the extracellular fluid (Sünram-Lea et al., 2011). The effect of hyperglycaemia on cognitive function will be discussed in more detail later (Section 3.3) in relation to T1DM and T2DM.

3.2.3.4 **Brain areas involved in cognitive function**

Disruption to the supply of exogenous glucose causes functional disturbances in the brain (Wessels, Scheltens, Barkhof, & Heine, 2008). The medial temporal region is the area of the brain which is affected the most from both the administration of glucose and impaired glucoregulatory mechanisms (Sünram-Lea et al., 2015). This region includes the hippocampus which is fundamental to memory function (Squire, Stark, & Clark, 2004). Within the hippocampus, cellular glucose uptake is promoted by the high density of insulin receptors and GLUT-4 transporters (McEwen & Reagan, 2004; Messier, 2004; Watson & Craft, 2008).

Insulin has been found to be involved in the regulation of memory and learning (Zhao & Alkon, 2001), and intranasal insulin over an 8 week period improves memory in healthy individuals (Benedict, Hallschmid, Hatke, Schultes, Fehm, Born, & Kern, 2004). Therefore, any impairment in glucose regulation will likely result in impaired cognitive functioning, especially memory, as areas such as the hippocampus are more susceptible to energy decrements.

3.3 Diabetes and cognitive function

Both T1DM and T2DM are associated with long term cognitive dysfunction and brain abnormalities (Biessels, Deary, & Ryan, 2008) and are discussed below. Over the course of the life span, two key periods have been proposed in which diabetes has a significant impact (Biessels et al., 2008). Firstly, when the brain system is in development, specifically during the first 5-7 years of life, and secondly, when the brain experiences neurodegenerative changes due to ageing, specifically in individuals older than 65 years. Outside of these periods, the development of diabetes-related comorbidities are the primary mechanism for cognitive impairment.

3.3.1 Type 1 diabetes mellitus, treatment and cognitive function

The peak onset of T1DM is during childhood or adolescence, with 50-60% of individuals diagnosed before 16-18 years of age (Daneman, 2006). However, a small percentage of people can present with T1DM during adulthood. T1DM is characterised by absolute insulin deficiency. Insulin replacement therapy does not always result in tight glucose regulation, such that either the negative effects of hyperglycaemia are not avoided, or hypoglycaemia can be produced. In such individuals, insulin analogues may also be prescribed, or stricter control achieved through diet, use of insulin pumps or monitoring using CGM (Hirsch, 2009).

Individuals with T1DM are reported to have a wide range of deficits in cognitive function compared to non-diabetic controls. A meta-analysis of 33 studies found that individuals with T1DM have a significant reduction in overall cognition, lower fluid and crystallised IQ, slower speed of information processing and psychomotor efficiency, poorer visual and sustained attention, diminished mental flexibility and visual perception compared to matched healthy controls (Brands, Biessels, de Haan, Kappelle, & Kessels, 2005). The majority of these deficits are modest. The most commonly found decrements are in the domains of crystallised IQ, psychomotor efficiency and cognitive flexibility. Contrary to some findings (Hershey, Craft, Bhargava, White, 1997; Hershey, Lillie, Sadler, & White, 2003), memory and learning are not consistently affected in those with T1DM. Impairments on tests of crystallised IQ, a cognitive domain not usually considered to show deterioration, may be explained by the slowing of psychomotor efficiency and diminished cognitive flexibility as these domains are important in tasks assessing crystallised IQ. An recent meta-analysis on 32 adult studies found that there were small to modest performance decrements on tests of IQ (VIQ, PIQ and FSIQ), mental flexibility, spatial memory and motor speed in adults (>18years old) with T1DM (Tonoli et al., 2014).

3.3.2   Type 2 diabetes mellitus, treatment and cognitive function

Historically, the peak onset of T2DM was typically during late adulthood, but the incidence of T2DM during young adulthood and even childhood is increasing (Koekkoek, Kappelle, van den Berg, Rutten, & Biessels, 2015). In contrast to people with T1DM, those with T2DM can be prescribed a combination of diet, exercise, oral medications and insulin to help alleviate the negative effects of hyperglycaemia. Diet and exercise are prescribed because T2DM is considered to be predominantly due to excess body weight and lack of physical activity. Improvement in these lifestyle factors causes an increase in muscle mass, a decrease in fat tissue and improvement in insulin resistance (Awad, Gagnon, & Messier, 2004).

Unlike T1DM, people with treated T2DM are less likely to suffer from severe hypoglycaemic episodes (Reijmer, Van Den Berg, Ruis, Kappelle, & Biessels, 2010). This is because the treatment options are largely dependent on the degree of insulin secretion dysfunction. Thus the main cause of hypoglycaemia in those with T2DM is iatrogenic (caused by treatment; Amiel, Dixon, Mann, & Jameson, 2008). However, as people with T2DM get older, there is a loss of endogenous insulin secretion, and therefore insulin therapy is advocated in order to maintain tighter glycaemic control. Insulin therapy in turn lowers the threshold for counterregulatory responses, and thus the risk of hypoglycaemia is increased.

In people with T2DM, deficits have been found in psychomotor speed, executive function, verbal memory and fluency, processing speed, complex motor functioning, working memory, immediate and delayed recall, visual retention and attention (Kodl & Seaquist, 2008). Previous systematic reviews report that the most commonly found decrements in people with treated T2DM are verbal memory and processing speed, with less consistent results for executive function, compared to matched controls (Awad et al., 2004; Koekkoek et al., 2015; Palta, Schneider, Biessels, Touradji, & Hill-Briggs, 2014). Effect sizes range from small to large, and partly reflect the age of the sample being studied (Awad et al., 2004; Biessels et al., 2008; van den Berg, Kloppenborg, Kessels, Kappelle, & Biessels, 2009). Cross-sectional studies show that relatively younger adults (<60 years old) with T2DM tend to have small to moderate magnitude of change, whereas older adults (>65 years old) are more likely to demonstrate moderate to large changes, particularly in the presence of poor glycaemic control (i.e. higher HbA1c; Awad et al., 2004; van den Berg et al., 2009). The most recent meta-analysis in middle aged to older adults (50-85 years) with T2DM revealed impairments with small to moderate effect sizes in 5 of 6 cognitive domains assessed compared to non-diabetic controls (Palta et al., 2014). Impairments in motor function had the largest effect size followed by executive function, processing speed, verbal and visual memory, with the smallest for attention/concentration. Although mean age was matched as closely as possible across diabetics and controls, it is important to note that 50% of the reviewed studies included T2DM samples with a mean age over 65 years, and the authors did not report the results stratified by age. Thus, these results cannot be generalised to samples of younger adults with T2DM.

The commonly found decrements in people with T2DM may reflect a decrease in the ability to effectively process unstructured information (Koekkoek et al., 2015). Cognitive ageing

reflects a decline in effective processing of resources, and T2DM appears to parallel accelerated cognitive decline (Ruis et al., 2009). The speed of decline is thought to be in the same range (E van den Berg et al., 2010), or up to twice as fast as that of normal ageing (Koekkoek et al., 2015). However, not all studies have demonstrated that those with T2DM perform significantly worse than controls (Cosway et al., 2001). Hence, as in T1DM, risk factors may contribute to the development of cognitive dysfunction in people with T2DM.

3.3.3 Mechanisms underlying cognitive dysfunction in individuals with T1DM and T2DM

A number of mechanisms have been proposed which contribute to cognitive dysfunction in people with T1DM and T2DM. These include the metabolic syndrome (exclusively associated with T2DM), glucose control and duration of diabetes, hypoglycaemia, hyperglycaemia (including micro- and macrovascular complications) and age of onset, which are discussed below.

3.3.3.1 Metabolic syndrome factors

T2DM has a slow onset. It is characterised by a period, known as pre-diabetes, where blood glucose levels are elevated in conjunction with hyperinsulinemia, which results in the individual developing IGT (Awad et al., 2004; Reijmer, van den Berg, Ruis, Kappelle, & Biessels, 2010). Deficits in cognitive function have been observed in those with IGT (Lamport, Lawton, Mansfield, & Dye, 2009). However, IGT and T2DM often occur in conjunction with vascular risk factors and features of the metabolic syndrome such as hypertension, obesity, dyslipidaemia, and inflammation, which have all been found to be independently associated with cognitive dysfunction (Yates, Sweat, Yau, Turchianoa, & Convit 2012). Table 3.1 summaries the studies investigating cognitive function and the mechanism of dysfunction in the metabolic syndrome.

3.3.3.1.1 Hypertension

People with raised blood pressure (hypertension) are commonly found to have worse cognitive function than people without high blood pressure (normotension; Waldstein, 2003); this is true of young and middle-aged adults, but there is greater variability in older adults (Hassing et al., 2004). In a cohort of community dwelling middle to older aged individuals, a linear negative correlation was observed between systolic blood pressure (SBP) and cognitive function even within the normotensive range (Knecht et al., 2008). The association was particularly apparent in individuals who were middle-aged. This suggests that individuals who have high-normal SBP are at risk of cognitive impairment. Knecht, Wersching, Lohmann, Berger, and Ringelstein, (2009) support this finding in that SBP may account for up to one tenth of the impairment in cognitive function found in middle-aged community dwelling individuals. In a more recent cross-sectional study, hypertension was associated with worse

memory and executive function performance and a decline in cognitive reserve[27] (Giordano et al., 2012).

Hypertension has also been associated with a decline in cognitive performance in people with T2DM. The results from the Framingham study of people aged 68.8 (+/-7.05) years, showed that both T2DM and hypertension are significant risk factors for cognitive dysfunction (Elias et al., 1997). The diagnosis and duration of T2DM was associated with an increased risk of worse visual memory and composite score for those with hypertension, while hypertension alone was associated with poor verbal memory. Those who were treated with oral diabetic agents and diet performed better than those treated with insulin, which may reflect less severe disease. It was concluded that people with T2DM who are hypertensive are at greatest risk for worse cognitive performance. Similar results were observed by Pavlik, Hyman, and Doody, (2005) in the third National Health and Nutrition Examination Survey (NHANES III). In this study, hypertensive people with T2DM aged 30-59 years exhibited worse cognitive performance on tests of SRT and DSST, but there was no independent association between worse cognition and diabetes or hypertension. In a longitudinal study assessing the comorbid impact of hypertension and diabetes on cognitive decline, Hassing et al., (2004) found that although those with T2DM demonstrated a decline in cognition compared to those without diabetes, the presence of hypertension exacerbated the diabetes-related decline over a 6 year period. There was no significant decline in those with hypertension alone, which, in this study, might reflect the high rate of attrition due to old age of this sample. A recent systematic review found that hypertension in T2DM is associated with executive function and processing speed impairments while memory and language seem to be spared (Meusel et al., 2014). In conclusion, these studies show that the presence of T2DM and hypertension results in more severe cognitive impairment.

3.3.3.1.2 Obesity

Obesity is associated with a significant decrease in insulin sensitivity which is a risk factor for T2DM and subsequent cognitive dysfunction (S. Roriz-Filho et al., 2009). van den Berg et al., (2009) report that there is a more consistent relationship between obesity and a decline in cognitive functioning during mid-life than later life (> 65 years). Gunstad et al. (2007) found that overweight and obese younger and older adults had worse executive function performance than normal weight younger and older adults. Additionally, Lamport, Chadwick, Dye, Mansfield, and Lawton, (2014) found that, independent of IGT, increased central adiposity in females, aged 30-50 years, was associated with impaired verbal memory and executive function performance compared to females with low central adiposity. In contrast, the Framingham Heart study showed that obesity had a negative impact on cognitive performance, but only in men (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2005). Although this may have been due to the higher prevalence of central obesity in males in this cohort.

Kim et al. (2008) investigated central obesity in people with T2DM and found that those without hypertension and without central obesity performed better on delayed cued recall,

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[27] the resilience of the brain to adequately function despite clinical damage

digit span forward total and digit span forward span compared to those with central obesity. For the forward digit span test, there was no difference in performance for those with hypertension, with or without central obesity. However, for delayed cued recall those with central obesity and hypertension performed better than those without central obesity with and without hypertension. These results show that there are differential effects of hypertension in those with and without central obesity.

3.3.3.1.3 Dyslipidaemia

Dyslipidaemia in T2DM is characterised by the elevation of triglycerides (hypertriglyceridemia) and/or low high density lipoprotein (HDL) cholesterol. High HDL is an independent protective factor against the development of cardiovascular disease, whereas high low density lipoprotein (LDL) confers greater risk (Krauss, 2004). Although the concentration of LDL cholesterol is not usually different from individuals without diabetes, people with T2DM often have an increase in smaller, denser LDLs in blood concentrations. This can lead to atherogenic dyslipidaemia (a triad of increased blood concentrations of small, dense LDL particles, decreased HDL particles, and increased triglycerides; American Diabetes Association, 2003). The changes to plasma lipoproteins can be caused by defective insulin action and hyperglycaemia, as well as the two main mechanisms for the development of T2DM, obesity and insulin resistance (Goldberg, 2001)

Dyslipidaemia has been shown to be a risk factor for cognitive dysfunction in people with and without diabetes In middle-aged adults, Muldoon, Ryan, Matthews, and Manuck, (1997) found lower levels of total and LDL-cholesterol and triglycerides were associated with better information and vocabulary subtests, whereas higher total and LDL-cholesterol were associated with better block design performance. In middle-aged women, there was an association between LDL-cholesterol and memory. Here, improvements in memory were seen as a result of improved levels of total and LDL-cholesterol over a 3 year period (Henderson, Guthrie, & Dennerstein, 2003).

In middle aged adults with T2DM, dyslipidaemia has been associated with worse performance on tasks of declarative memory (Bruehl et al., 2009), attention switching and inhibition (Yogi-Morren et al., 2014). In a group of mid to older aged adults with T2DM (aged 55-74 years), significant performance decrements were observed in digit symbol substitution, backward digit span and on reaction times in those with elevated triglyceride levels which suggests a decline in short-term memory ability in those with dyslipidaemia (Perlmuter et al., 1988). In older adults with T2DM, high triglyceride levels (total and LDL) were associated with slower reaction times and verbal fluency decrements (Helkala, Niskanen, Viinamaki, Partanen, & Uusitupa, 1995).

Research has also suggested that improvements in dyslipidaemia may have a positive impact on cognitive function. Hence, treatment with Atorvastatin in hyperlipidaemia individuals with T2DM can improve verbal memory by increasing HDL-cholesterol and reducing LDL-cholesterol and triglycerides (Berk-Planken, de Konig, Stolk, Jansen, & Hoogerbrugge, 2002).

3.3.3.1.4   Inflammation

T2DM is regarded as an inflammatory condition with elevated levels of circulating inflammatory markers (Dandona, Aljada, & Bandyopadhyay, 2004). Previous research has shown that increased levels of acute phase proteins, such as CRP, precede insulin resistance and T2DM development (Strachan, Reynolds, Marioni, & Price, 2011). It is hypothesised that cerebral or systemic inflammation may contribute to the risk of cognitive dysfunction in people with T2DM.

Previous research has shown associations between CRP and cognitive function in non-diabetic individuals. In older adults (>65years), high CRP levels were associated with memory and visual spatial impairment, but not executive function or language (Noble et al., 2010). In older adults with metabolic syndrome (65-88years), performance was worse on tasks of information-processing speed, immediate and delayed recall, fluid IQ and the MMSE in those who had elevated CRP levels (Dik et al., 2007). Risk of cognitive impairment was also increased in those who had higher levels of inflammation (Yaffe et al., 2004). Sweat et al. (2008) found that CRP was associated with impaired performance on a cognitive task requiring frontal lobe capacity but only in females who were overweight or obese, suggesting an interaction between metabolic syndrome factors.

Inflammation in people with T2DM has also been associated with cognitive dysfunction. In a cross-sectional study of people with T2DM, aged 60-75years, higher CRP levels were associated with worse visual spatial performance (Marioni et al., 2010). Higher IL-6 levels were associated with worse visual spatial, working memory, verbal fluency and processing speed. TNF-α levels were associated with worse visual spatial, processing speed, and visual memory. After the adjustment for baseline cognitive ability (estimated by vocabulary performance), the association with poor cognitive ability and IL-6 was still apparent.

Table 3.1 Summary of studies investigating cognitive function in the metabolic syndrome, organised by proposed mechanism of cognitive dysfunction

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Knecht et al. (2008, 2009)	N=377 (171 male), community dwelling adults, aged 44-82 yrs, mean age 64 yrs, mean SBP 144 mmHg (95-250 mmHg).	N/A	Hypertension	SEARCH-Health study: Cross-sectional	AVLT, Digit span, ROCF, Stroop, DSST, TMT (A,B), category and letter fluency, BNT	*2008:* linear negative correlation between SBP and cognitive performance even within the normotensive range. *2009:* SBP may account for one tenth of cognitive impairment. In midlife age groups, SBP explained up to 11% of the variance in cognition.	People with high-normal SBP, particularly middle aged adults, are at risk of cognitive impairment.
Giordano et al. (2012)	N=288 (164M; 124F), aged ≥50 yrs, mean SBP 154.7 mmHg.	N/A	Hypertension	Cross-sectional, general population.	MMSE, Digit span, CLOX, TMT (A,B), overlapping figures, working memory, phonemic verbal fluency test, immediate and delayed prose memory	Hypertension was associated with worse memory, executive function and global cognition and a decline in cognitive reserve.	
Meusel et al. (2014)	People with Mild Cognitive Impairment/ Alzheimer disease/ dementia	Healthy/ normal adults	Hypertension/ T2DM	Systematic review	Various	Hypertension in T2DM is associated with executive function and processing speed impairments while memory and language seem to be spared. Impairment is more likely in middle-aged and older adults with T2DM and hypertension.	There are signs of widespread structural atrophy, vascular damage, and functional changes in older T2DM adults, compared to healthy controls.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Elias et al. (1997)	T2DM, N=187, mean age 68.8 yrs.	Non-diabetic N=1624.	Hypertension	Framingham Heart Study; Large, Prospective, community based sample. Followed for 28-30 yrs.	WAIS, WMS, Multilingual Aphasia Examination	Greatest risk for worse cognition was having both T2DM and hypertension. Diagnosis and duration of T2DM was associated with an increased risk of worse visual memory and composite score for those with hypertension, while hypertension alone was associated with poor verbal memory.	Those who were treated with oral diabetic agents and diet performed better than those treated with insulin, which may reflect less severe disease.
Pavlik et al. (2005)	N=3,385, adults, 30-59 yrs of age, no history of stroke.	N/A	Hypertension	NHANES III	SRT, DSST, SDLT	Hypertensive people with T2DM exhibited worse cognitive performance on SRT and DSST. There was no independent association between worse cognition and T2DM or hypertension.	The combination of hypertension and T2DM is associated with detectable cognitive impairment in people under 60 yrs of age.
Hassing et al. (2004)	T2DM without hypertension N=16, comorbid diabetes and hypertension N=22.	Free from diabetes and hypertension N=128, diagnosis of hypertension N=92.	Hypertension	The OCTO-Twin Study: population-based, longitudinal; 4 time points, 2 yrs apart N=258 (mean age 83 yrs)	MMSE	T2DM had decline in cognition compared to those without diabetes. Presence of hypertension exacerbated decline over 6 yr period. No significant decline in those with hypertension alone.	No significant decline in hypertension alone group may be due to high attrition rate due to old age of sample.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Gunstad et al (2007)	Overweight/ obese. Young adults: N=140, mean age 32.4 yrs. Older adults: N=58, mean age 60.4 yrs.	Normal weight. Young adults: N=178, mean age=31.6 yrs. Older adults: N=58, mean age=60.4 yrs	Obesity	Cross-sectional. N=408, 20-82 yrs.	Spot the Real Word test, Digit span forward, CRT, TMT(A,B) modified Spatial Span, Stroop, Austin Maze	Overweight and obese younger and older adults had worse executive function performance than normal weight younger and older adults.	Association between high BMI and impaired cognitive function does not vary with age.
Lamport et al. (2014)	IGT/ low WC (WC; N= 9), IGT/high WC (N=9).	NGT/low WC (N=25), NGT/high WC (N=22).	Obesity; increased central adiposity/ WC	Randomised, crossover, counter-balanced. N=65F, 30-50 yrs	VSLT, VVLT, Corsi, TOH, Pegboard, Psychomotor Test, Word Recognition test.	Independent of IGT, high WC was associated with impaired verbal memory and executive function performance compared to low WC.	
Elias et al. (2005)	Males (N=551, mean age 65.7 yrs, T2DM N=44). Females (N=872, mean age 67.2 yrs, T2DM N=52).	N/A	Obesity	Framingham Heart Study; Prospective, community based sample. N=872	WAIS and WMS. Logical memory- immediate recall, visual reproductions, paired associates learning, COWA, Digit span forward and backward, similarities, and logical memory- delayed recall.	Obesity was related to cognitive performance in men but not women. Duration of T2DM was related to poorer cognitive performance, but only when men and women were combined for analyses.	Gender-specific results for obesity, but not for T2DM, suggests that the underlying mechanisms linking them to cognition may be different.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Kim et al. (2008)	N= 60 older adults with T2DM. With central obesity N=42, mean age 66.3 yrs.	Without central obesity N=18, mean age 64.8 yrs.	Central obesity, Hypertension	Cross-sectional	Elderly Memory Disorder Scale: verbal learning test, simplified ROCF, Digit span (forward and backward), K-BNT (short form), SRT, CRT	Central obesity without hypertension performed better on delayed cue recall, digit span, relative to those with hypertension. No difference for digit span (forward) between those with central obesity, with and without hypertension. For delayed cue recall, those with obesity and hypertension performed better than those without central obesity, with and without hypertension.	Differential effects of hypertension in those with and without central obesity.
Muldoon et al. (1997)	N=177, healthy adults, aged 25-60 yrs, mean age 43.7 yrs, widely varying total cholesterol concentrations.	N/A	Dyslipidaemia	Cross-sectional	WAIS-R: Information and Vocabulary, Block Design. Computerized version of the Letter Rotation test	Lower levels of total-, LDL-cholesterol and triglycerides were associated with better crystallised IQ. Higher total and LDL cholesterol were associated with better fluid IQ.	Opposite relationships between serum cholesterol and crystallised and fluid IQ.
Henderson et al. (2003)	N=326 middle-aged women, mean age 56.7 yrs (52–63 yrs).	N/A	Dyslipidaemia	Melbourne Women's Midlife Health Project. Longitudinal.	10 item supraspan word list recall task.	Association between LDL-cholesterol and memory, a trend between current total cholesterol and total memory score, but no association for HDL-cholesterol or triglyceride levels.	Improvements in memory were seen as a result of improved levels of total and LDL-cholesterol over a 3 yr period.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Bruehl et al. (2009)	N=41, middle-aged adults withT2DM (mean 7 yrs since diagnosis), mean age 59.05 yrs, mean BMI 32.63 kg/m^2, hypertension in 68%, dyslipidaemia in 85%.	N=47 age-, education-, and gender-matched healthy controls. Mean age 60.02 yrs, mean BMI 25.5 kg/m^2, hypertension in 23%, dyslipidaemia in 51%.	Dyslipidaemia, Obesity	Cross-sectional	WAIS-R FSIQ, SILS, MMSE, CWAT, GDS, CVLT, Guild paragraphs, WMS-R (tapping backwards, paragraph recall, verbal paired associates, DSST), Digit span (backward), Stroop, TOL, Perceptual Speed	T2DM had verbal declarative memory impairments, reduced hippocampal and prefrontal volumes, and impaired HPA axis feedback control. Dyslipidaemia was associated with worse performance, whereas obesity was negatively related to hippocampal volume. Prefrontal volume was influenced by worse glycaemic control.	Obesity and altered cortisol levels may contribute to the impact of T2DM on the hippocampal formation, resulting in decreased verbal declarative memory.
Yogi-Morren et al. (2014)	N=47, mean age 57.97 yrs (18-75 yrs), T2DM and metabolic syndrome. Mean T2DM duration 11.2 yrs, hyper-lipidaemia in 83%, Hypertension in 76.6%.	Existing normative data from the Brain Resource International Database	Dyslipidaemia	Cross-sectional	Webneuro battery: Spot-the-Real-Word test, Digit span, CPT, computerised adaptation of TMT (B), Austin Maze, Memory Recognition	T2DM had impaired memory, attention and executive function. Longer T2DM duration was associated with poorer basic attention, working memory and executive function. Strong associations between very LDL and poor inhibition and attention switching.	People with T2DM and metabolic syndrome are at high risk for cognitive impairment.
Perlmuter et al. (1988)	N=246 T2DM, aged 55-74 yrs.	N/A	Dyslipidaemia	Cross-sectional	DSST, Digit span (backward), reaction time test	Elevated levels of triglycerides were associated with significant impairment on all 3 cognitive measures.	High triglycerides levels appear to contribute to worse ability on short term memory tasks independent of glucose control.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Helkala et al. (1995)	N=20 elderly adults with T2DM.	N=22 controls with NGT.	Dyslipidaemia	Cross-sectional	Digit span, word-list learning, TMT (A,B), Heaton Visual Memory Test, Moss Visual Span Test, Verbal and Category Fluency, WAIS (block design)	T2DM had preserved memory span, but poor learning. Elevated serum total, very-LDL and triglyceride levels were associated with slower reaction times and verbal fluency decrements	Elevated serum triglyceride levels may be related to control of mental processing in T2DM.
Berk-Planken et al. (2002)	N=30, T2DM, aged 45–75 yrs. Fasting triglycerides 1.5-6.0 mmol/l and total cholesterol levels between 4.0-8.0mmol/l.	N/A	Dyslipidaemia	DALI longitudinal study.	Orientation and auditory-verbal memory, attention, psychomotor speed, executive functioning DART	Treatment with Atorvastatin improved verbal memory by increasing HDL- and reducing LDL-cholesterol and triglycerides. Atorvastatin did not affect psychomotor speed, attention, and executive functioning.	Placebo (N=8), 10mg atorvastatin (N=7), or 80mg atorvastatin (N=11) during 30 weeks. Improvements in dyslipidaemia may have a positive impact on cognitive function.
Noble et al. (2010)	N=1331, older adults (>65yrs).	Normative sample	Inflammation	Longitudinal, prospective, cross-sectional	BNT, Selective Reminding Test, Benton Visual Retention Test, Rosen Drawing & Matching Tests, COWA, Category Fluency, Colour Trails Test, WAIS-R (Similarities)	High CRP levels were associated with memory and visual spatial impairment, but not executive function or language	The association between high CRP and memory seemed to occur in the presence of APOE-ε4.

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Dik et al. (2007)	N=429, metabolic syndrome, mean age 75.3 yrs.	N=754, no metabolic syndrome, mean age 74.9 yrs.	Inflammation	Longitudinal Ageing Study Amsterdam. N=1183 (65-88 yrs)	MMSE, Verbal learning test, RPM, coding task	Those with elevated CRP had worse fluid IQ, processing speed, immediate and delayed recall and MMSE	
Yaffe et al. (2004)	High inflammation. With metabolic syndrome: N=348, mean age 73.5 yrs. Without metabolic syndrome: N=317, mean age 73.4 yrs.	Low inflammation. With metabolic syndrome: N=668, mean age 73.4 yrs. Without metabolic syndrome: N=1299, mean age 73.7 yrs.	Inflammation	5 yr prospective observational study. N=2632	MMSE	Those with metabolic syndrome were more likely to exhibit cognitive dysfunction. Risk of cognitive impairment was increased in those who had higher levels of inflammation	Metabolic syndrome contributes to cognitive impairment but mainly in those with high level of inflammation.
Sweat et al. (2008)	Overweight. Females: N=42 (T2DM=17), mean age 62.3 yrs. Males: N=49 (T2DM=19), mean age 61.3 yrs.	Normal BMI. Females: N=20, mean age 61.75 yrs. Males: N=14, mean age 62.06yrs.	Inflammation	Cross-sectional	MMSE, CVLT, WMS-R (Digit span, Visual memory span backwards), TOL, SILS	No differences between normal BMI and overweight/obese. CRP is linked to lower cognitive performance (FSIQ, executive function, visual memory) in overweight and obese women.	

Authors (year)	Experimental group	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Marioni et al. (2010)	N=1,066 (547M), with T2DM mean age 67.9 yrs (60–75 yrs).	N/A	Inflammation	Edinburgh Type 2 Diabetes (ET2DS) Study	WMS-III (Faces & Family Pictures Subtest, Logical Memory) WAIS-III (Letter Number Sequencing, Matrix Reasoning, DSST), Verbal Fluency, TMT (A,B), Junior and Senior MHVS, synonyms.	Higher CRP levels were associated with worse visual spatial performance (adjusted for age & gender). Higher IL-6 levels were associated with worse visual spatial, working memory, verbal fluency and processing speed. TNF-α levels were associated with worse visual spatial, processing speed, and visual memory.	After the adjustment for baseline cognitive ability, the association with poor cognitive ability and IL-6 was still apparent.

KEY: APOE-ε4, Apolipoprotein E- -ε4; AVLT, Auditory Verbal Learning Test; BMI, body mass index; CLOX, Clock drawing test; COWA, Controlled Oral Word Association Test; CPT, Continuous Performance Test; CRP, c-reactive protein; CRT, choice reaction time; CVLT, California Verbal Learning Test; CWAT, Controlled Word Association Test; DALI, Diabetes Atorvastatin Lipid Intervention; DART, Dutch Adult Reading Test; DSST, digit symbol substitution test; F, Female; FSIQ, full scale IQ; GDS, Global Deterioration Scale; HDL, high density lipoprotein; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; IGT, Impaired Glucose Intolerance; IQ, intelligence quotient; IV, intravenous; (K-) BNT, (Korean-) Boston Naming Test; LDL, low density lipoprotein; M, Males; MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; NHANES, National Health and Nutrition Examination Survey; ROCF, Rey-Osterrieth Complex Figure; RPM, Raven's Progressive Matrices; SBP, systolic blood pressure; SD standard deviation; SDLT, Serial Digit Learning Test; SES, socioeconomic status; SILS, Shipley Institute of Living Scale; SRT, Simple reaction time; T2DM, Type 2 Diabetes Mellitus; TMT (A,B), Trail Making Test (Part A, Part B); TNF-α, tumor necrosis factor-α; TOH, Tower of Hanoi; TOL, Tower of London; VSLT, Visual Spatial Learning Test; VVLT, Visual Verbal Learning Test; WAIS, Wechsler Adult Intelligence Scale; WASI, Wechsler Abbreviated Scale of Intelligence; WC, Waist Circumference; WMS –R/III, Wechsler Memory Scale- Revised/3rd edition

3.3.3.2 **Hypoglycaemia**

Both transient and recurrent episodes of hypoglycaemia have been investigated as mechanisms underlying cognitive impairment in T1DM and T2DM.

3.3.3.2.1 T1DM

Although tight blood glucose control is advocated in people with T1DM to avoid the negative effects of prolonged postprandial hyperglycaemia, this also heightens the risk of inducing hypoglycaemia (Fullerton et al., 2014). In those with T1DM, cognition is transiently impaired when blood glucose levels are between 2.8 and 3.6 mmol/L (Jacobson et al., 2007). This threshold is slightly higher than in healthy individuals. Transient cognitive impairment can be sufficient enough to interfere with the ability to perform everyday tasks, (Warren & Frier, 2005) and hypoglycaemia-related driving incidents have been reported in those with T1DM (Cox et al., 2009).

Even though the brain is resilient to insulin-induced hypoglycaemia in the short term (Chabriat et al., 1994), it is postulated that recurrent episodes of moderately severe hypoglycaemia might over time have a cumulative effect and induce cognitive dysfunction (Ryan, 2006). This is based on case studies of patients exhibiting worse cognitive performance following either a prolonged episode of extremely severe hypoglycaemia (Chalmers et al., 1991), or several moderately severe hypoglycaemic episodes (Ryan, 2006). Furthermore, there is also anecdotal evidence that recurrent episodes of hypoglycaemia in many diabetics result in cognitive impairment over time (Kodl & Seaquist, 2008). However, the meta-analysis by Brands et al. (2005) concluded that people who had experienced recurrent severe hypoglycaemic episodes were not significantly more impaired relative to those without hypoglycaemic episodes.

There is the possibility that those individuals who experienced recurrent hypoglycaemic episodes had lower HbA1c levels (i.e. better glycaemic control). However, when those with and without hypoglycaemic episodes but similar HbA1c levels were compared, there was no difference in cognitive performance. The conclusion drawn by Brands et al., (2005) is also supported by the Diabetes Control and Complications Trial /Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) research group (Jacobson et al., 2007, 2011). After an approximate 18 year follow-up, there was no association between the occurrence of one or more episodes of hypoglycaemia-associated seizure or coma (i.e. severe hypoglycaemic episode) and a decline in cognition function. It should be noted that those registered to the DCCT/EDIC study were relatively young and had good glucose control, thus the effect of repeated episodes of severe hypoglycaemia may not have resulted in cognitive dysfunction. In contrast, the recent meta-analysis of 11 studies by Tonoli et al. (2014) found that severe transient hypoglycaemia in adults, causes significant impairment on domains of executive function and memory. None of the adult studies included results about recurrent episodes of severe hypoglycaemia and therefore it cannot be concluded that recurrent episodes result in impairment.

In summary, although transient hypoglycaemia results in impaired cognition, recurrent episodes do not seem to have an effect. It has also been proposed that episodes of moderate

hypoglycaemia, despite not resulting in permanent cognitive impairment, may cause subclinical brain damage (Warren & Frier, 2005) or interact with chronic hyperglycaemia to influence the degree of dysfunction (Ryan, 2006).

3.3.3.2.2 T2DM

Since cognitive dysfunction is already apparent in people with IGT and in newly diagnosed individuals with T2DM, episodes of acute hypoglycaemia are unlikely to be the primary cause of cognitive dysfunction in people with treated T2DM (Biessels, van der Heide, Kamal, Bleys, & Gispen, 2002). However, recent research has suggested a bidirectional relationship between impaired cognition and severe episodes of hypoglycaemia in older adults (Biessels, 2014; de Galan et al., 2009; Feinkohl et al., 2014). Hence, the risk of cognitive dysfunction is increased as a result of the occurrence of severe episodes of hypoglycaemia, whilst having impaired cognition increases the risk of severe hypoglycaemia.

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (de Galan et al., 2009) found that in that individuals aged >55 years old with severe cognitive dysfunction (MMSE score ≤ 23), there was a twofold increased risk of severe hypoglycaemia compared to those with normal cognitive function. The increased risk was not a result of older age, low HbA1c, longer diabetes duration or cardiovascular risk. Thus, cognitive function was suggested to be an independent predictor of clinical outcomes.

The Edinburgh Type 2 Diabetes Study (ET2DS; Feinkohl et al., 2014) found that in individuals with T2DM, aged 60-75years old, having severe hypoglycaemia at 4 year follow-up was associated with worse cognitive function at baseline, and that a history of severe hypoglycaemia at both baseline and follow-up was associated with greater cognitive decline after 4 years.

The ACCORD-MIND Trial (Punthakee et al., 2012) found that after a 3.25 year median follow-up, the first severe hypoglycaemia episode requiring medical assistance was predicted by a lower score at baseline on the digit symbol substitution test (DSST) in individuals aged 55 years and older. Interestingly, whether individuals were on an intensive or standard glycaemic control intervention had no effect on the relationship between cognitive function and severe hypoglycaemic risk, which is consistent with the ADVANCE trial. Taken together, the evidence suggests that cognitive dysfunction is associated with the risk of severe hypoglycaemia, and importantly the occurrence of episodes of severe hypoglycaemia may influence the rate of cognitive decline.

The research reviewed above suggests that decline in cognitive function is a risk factor for severe hypoglycaemia, and that the risk may be particularly heightened for those who already have poor cognitive function. Therefore, good diabetes management in people with T2DM requires a level of normal cognitive functioning. In contrast to individuals with T1DM, those with T2DM show an association between severe hypoglycaemic episodes and cognitive dysfunction. However, studies of individuals with T2DM tend to include older participants and do not exclude those with a history of microvascular, macrovascular, or cardiovascular complications which may have exacerbated the strength of the relationship found.

3.3.3.3   Glucose control and hyperglycaemia

Glucose control, hyperglycaemia and duration of diabetes have been investigated as a mechanism for cognitive impairment in T1DM and T2DM.

3.3.3.3.1   T1DM

Acute and transient cognitive impairment can occur during periods of hyperglycaemia. People with T1DM exhibit significantly slower psychomotor performance, mental subtraction speed and increased subtraction errors, and there is a trend for slowing of choice reaction time, when blood glucose levels are above 15 mmol/L (Cox et al., 2005). Data suggest that 15mmol/L may be the threshold at which individuals with T1DM start to exhibit cognitive dysfunction. However, cognitive function was not impaired in all individuals who had a blood glucose reading >15mmol/L, which demonstrates that high blood glucose can affect cognitive function differently. There was a small to moderate effect of the frequency of hyperglycaemia (higher HbA1c and greater percentage of self-monitored blood glucose readings >15mmol/L) and the number of tests in which performance was impaired. Furthermore, greater impairment was observed whilst hyperglycaemic if performance was also poor whilst blood glucose levels were within the normal range. Although acute hypoglycaemia is associated diminished speed rather than absolute ability, hyperglycaemia is associated with mental slowing and increased errors, particularly when blood glucose levels exceed 15mmol/L. The fact that performance is worse with increased frequency of hyperglycaemia suggests no cerebral adaptation to such high levels of blood glucose and that there is a homeostatic neuroglycaemia range within which cognitive functioning is optimal. However, this optimal range is yet to be decided (Kawamura, Umemura, & Hotta, 2012).

Chronic hyperglycaemia has also been shown to have a negative effect on cognitive function. In support of Cox et al., (2005), the DCCT/EDIC group (Jacobson et al., 2007) demonstrated that better glycaemic control is associated with better cognitive function. Higher HbA1c levels (>72.7mmol/mol) were associated with worse psychomotor efficiency and moderately slower motor speed compared to performance associated with lower HbA1c levels (<57.4 mmol/mol). Although in the original DCCT study, people with T1DM who had diabetic microvascular complications were excluded, there is no mention as to whether they were included in the follow-up study. This is important to note, as the presence of microvascular complications in people with T1DM is associated with an increased risk of cognitive impairment (Biessels et al., 2008).

3.3.3.3.2   T2DM

Like people with T1DM, those with T2DM also suffer from cognitive dysfunction when blood glucose levels are acutely hyperglycaemic (Greenwood, Kaplan, Hebblethwaite, & Jenkins, 2003; Sommerfield, Deary, & Frier, 2004). Sommerfield et al., (2004) found that in individuals with T2DM, aged 53-72 years, acute hyperglycaemia (16.5 mmol/L) significantly impaired their ability on tasks of speed of information processing, working memory, and some aspects of attention. These tasks require quick responding, which suggests there was a speed-accuracy trade off, with accuracy preserved at the expense of speed. The preference to preserve accuracy over speed during hyperglycaemia supports the findings of Cox et al.

(2005). Furthermore, decrements in performance were seen predominantly on tasks which have a degree of complexity. Acute hyperglycaemia was also found to negatively affect mood, with increased feelings of agitation, anxiety, tiredness and decreased feelings of happiness. However, mood was not a significant covariate for cognitive performance.

As well as acute hyperglycaemia, the effects of chronic hyperglycaemia (i.e. poor glucose control; HbA1c) have also been associated with cognitive dysfunction in those with T2DM (Bruehl et al., 2009; Kodl & Seaquist, 2008; Meusel et al., 2014). Although not consistently found, several studies have found an inverse relationship between HbA1c levels and working memory, executive function, new learning, overall cognition and complex psychomotor performance in those with T2DM (Cukierman-Yaffe et al., 2009; Munshi et al., 2006; Reaven, Thompson, Nahum, & Haskins, 1990; Ryan & Geckle, 2000). Cukierman-Yaffe et al. (2009) found that a 1% increase in HbA1c score was associated with a 1.75 point decrease on the DSST, a 0.2 point decease on the MMSE , a 0.11 score decrease in memory score, and a worse score (>0.75) on the Stroop task. However, HbA1c levels only explained a small amount of cognitive test score variability. This latter finding is also supported by a systematic review by Geijselaers, Sep, Stehouwer, and Biessels, (2015) who found that although high HbA1c (and glucose variability) was associated with worse cognitive function, HbA1c accounted for less than 10% of the variability. Nevertheless, the findings by Cukierman-Yaffe et al. (2009) show that there was a 0.7 point decrease in DSST score for every 1 year increase in HbA1c which equates to a 1-1.5 DSST score difference per 1% higher HbA1c and to 2 years of decline. In summary, these studies highlight an inverse relationship between HbA1c and cognitive function.

Prolonged poor glucose control in those with T2DM increases the risk of diabetic complications. Thus, the duration of diabetes can contribute to cognitive dysfunction. West et al., (2014) found an association between the duration of diabetes and cognitive function, which was modulated by glycaemic control. Performance on tasks of executive functioning, attention, working memory, semantic categorisation and overall cognition were worse in those with a longer diabetes duration, but only if they also had higher HbA1c levels. This suggests that diabetes duration per se does not result in cognitive dysfunction but interacts with poor glycaemic control and that intensive treatment might be beneficial to reduce decline. Improvement in HbA1c values has been shown to improve performance on tests of working memory (Ryan et al., 2006). Treatment with either rosiglitazone (thiazolidinedione insulin sensitizer) or glyburide (sulphonylurea insulin secretagogue) significantly improved fasting blood glucose levels within 24 weeks. This improved glycaemic control led to a significant reduction in errors (25-31%) on a CANTAB working memory task (Paired Associates Learning). Thus, in people with T2DM, working memory tasks appear particularly sensitive to improvements in fasting blood glucose levels possibly due to the task complexity and the wide range of brain structures activated. However, a recent meta-analysis has shown no benefit of conforming to intensive glycaemic control (compared to standard glycaemic control) to prevent the increased rate of cognitive decline in those with T2DM (Tuligenga, 2015). Instead, intensive control may actually increase hypoglycaemia risk, which is associated with cognitive dysfunction.

3.3.3.4 **Microvascular complications**

Microvascular complications have been investigated as a mechanism for cognitive impairment in T1DM and T2DM.

3.3.3.4.1 T1DM

Retinopathy has been associated with cognitive dysfunction in people with T1DM. Ferguson et al., (2003) found that people who had developed T1DM in childhood or adolescence and developed retinopathy (n=25) had worse scores on tasks of spatial ability, mental flexibility, psychomotor speed, information processing ability and sustained attention compared to those without retinopathy (n=46). The magnitude of these differences was moderate (0.4 - 0.7 SD) and could not be explained by years of education, estimated premorbid cognition or the effects of developing retinopathy (i.e. decline in visual function) as the visual aspect of information processing (P100 latency) was not affected. In this study, it was proposed that retinopathy is a consequence of chronic hyperglycaemia and that suboptimal glucose control also leads of the development of microangiopathy which affects cognitive function. Wessels et al., (2007) found that relatively young people with T1DM perform worse on tests of information processing and visuoconstruction compared to controls matched on age, gender and education. However, while those without proliferative retinopathy performed worse on information processing, those with retinopathy performed worse on visuoconstruction. This suggests that the development of proliferative retinopathy is associated with cognitive dysfunction in people with T1DM.

Neuropathy has also been shown to be associated with T1DM cognitive dysfunction. A cross-sectional study by Ryan, Williams, Finegold, and Orchard, (1993) found that cognition was significantly worse in middle aged adults with T1DM (mean diabetes duration >26years) compared to age and education matched controls. However, the presence of cognitive dysfunction was predicted by having developed clinically significant diabetic complications (distal symmetrical polyneuropathy (DSP), advanced background or proliferative retinopathy, overt nephropathy, one or more episodes of severe hypoglycaemia), and not by having diabetes itself. Those who had one or more diabetic complications had significantly worse performance than both the group without complications (on tasks of visual scanning, rapid decision making and hand-eye coordination) and a control group (on tasks of sustained attention, visual scanning, rapid decision making and hand-eye coordination). The diagnosis of DSP was the best predictor of performance on sustained attention, visual scanning, rapid decision making, mental flexibility and hand-eye coordination tasks but not memory tasks. Hypoglycaemia was not associated with cognitive dysfunction but the findings suggest it may interact with neuropathy to increase the extent of cognitive impairment.

A longitudinal study by Ryan and colleagues found those with T1DM had significantly slower psychomotor performance at baseline compared to healthy non-diabetic controls, and the degree of decline was greater in those with diabetes 7 years later (Ryan, Geckle, & Orchard, 2003). Psychomotor slowing was predicted by the presence of microvascular complications at baseline, and microvascular complications, SBP and duration of diabetes at follow-up. Those who developed retinopathy between baseline and follow-up showed greater

psychomotor slowing compared to those without retinopathy, with performance similar to those who had retinopathy at baseline. This pattern of results was also observed in those who developed autonomic neuropathy during the study. Conversely, the development of either DSP or overt nephropathy predicted psychomotor slowing at baseline but not at follow-up. Thus, there is a greater decline in psychomotor slowing over a 7 year period in those with T1DM compared to controls. Proliferative retinopathy and autonomic neuropathy have a more pronounced effect of cognitive decline.

Contrary to these findings, Brismar et al., (2007) found that retinopathy did not predict cognitive dysfunction; rather retinopathy predicted a high score in tests of executive function. It may be that people with visual impairments compensate in non-visual tasks. Nephropathy was however found to be strongly correlated with and a significant predictor of psychomotor (excluding pegboard) dysfunction. Neuropathy was also found to be a significant predictor of slow psychomotor speed (including pegboard), poor visual perception-organisation and poor memory scores, which supports the finding by Ryan et al., (1993). Given that the Pegboard task requires tactile and visual information to perform rapidly, the presence of peripheral neuropathy probably contributed to the psychomotor dysfunction.

3.3.3.4.2 T2DM

Intensive glycaemic control in T2DM protects against the development of microvascular complications compared to standard glycaemic control but as mentioned previously (see Section 3.3.3.3.2), it does not confer beneficial effects in terms of slowing cognitive decline (Tuligenga, 2015; Zoungas et al., 2012). The development of microvascular complications in people with T2DM has also been implicated as a mechanism for cognitive dysfunction, however the findings are mixed.

The development of moderate to severe diabetic retinopathy in people with T2DM registered in the ET2DS was associated with worse general cognitive ability, particularly in men (Ding et al., 2010). In contrast, de Bresser et al., (2010) found the presence of retinopathy or neuropathy were not associated with cognitive performance at baseline or cognitive decline during a 4 year period, but albuminuria, a marker of nephropathy, was found to be a predictor of accelerated cognitive decline. Albuminuria as a mechanism for the development of cognitive dysfunction has also been found in a recent study. The results from the ACCORD-MIND study (Barzilay et al., 2013) show that the presence of persistent albuminuria (i.e. present at baseline, 20 and 40 months) and progressive albuminuria were associated with a greater than 5% decline in scores for information processing speed in relatively young individuals with T2DM, but not performance on tasks of verbal memory or executive function. In terms of information-processing speed decline relative to 1 year of ageing, having persistent albuminuria was equivalent to 7.2 years of ageing, while progressive albuminuria was equivalent to 3.2 years of ageing. Thus, persistent albuminuria is associated with greater information-processing speed decline.

3.3.3.5 **Macrovascular complications**

Macrovascular complications have been investigated as a mechanism for cognitive impairment in T1DM and T2DM.

3.3.3.5.1 T1DM

Macrovascular complications have also been shown to be associated with cognitive dysfunction in people with T1DM, although the evidence is not always consistent. This might be because macrovascular complications tend not to be common in people with T1DM below the age of 40-50 years (Biessels et al., 2008). Ryan, Geckle, and Orchard, (2003) found that the prevalence of macrovascular complications increased significantly over a 7 year period (mean age at baseline 40.4 +/-6.2 years), and an increase in psychomotor slowing was associated with the development of macrovascular complications (coronary heart disease and/or peripheral vascular disease) during this period. Ryan, (2005) found that in addition to peripheral vascular disease, proliferative retinopathy, duration of diabetes and peripheral neuropathy were significant predictors, accounting for 27% of the variance, in age related psychomotor slowing in people with T1DM. In contrast, the DCCT (Jacobson et al., 2011) found no evidence that macrovascular complications were associated with cognitive decline.

3.3.3.5.2 T2DM

Macrovascular disease is significantly more prevalent in people with T2DM (than T1DM) due to the presence of multiple cardiovascular risk factors (S. Roriz-Filho et al., 2009). Furthermore, the development of macrovascular disease has consistently been shown to influence the degree of cognitive decline in people with T2DM (Koekkoek et al., 2015), but the domains exhibiting impairment are not always consistent.

The ACCORD-MIND trial found that coronary heart disease (excluding stroke) was associated with worse performance on memory tasks, but not on tasks of executive function or information processing speed (Cukierman-Yaffe et al., 2009). Manschot et al., (2006, 2007) found that people with T2DM who had a history of vascular events had impaired information processing speed and memory. Furthermore, the association was attenuated by the exclusion of patients who had a history of stroke, but it was not reported whether the association was still significant. The findings from the Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) study found that a history of macrovascular disease (and current smoking) was associated with a decline in information-processing speed but not memory performance in people with T2DM (Ruis et al., 2009). In addition, the ET2DS found that stroke, subclinical markers of cardiac stress and generalised atherosclerosis (serum N-terminal probrain natriuretic peptide (NT-proBNP), ankle branchial index (ABI), and carotid intima-media thickness (cIMT)) were all significantly associated with a decline in cognition function over 4 years whereas non-stroke vascular events were not (Feinkohl et al., 2013).

3.3.3.6 **Age of onset of diabetes**

The age at which a person develops diabetes may influence the degree of cognitive dysfunction.

3.3.3.6.1 T1DM

Very early onset of T1DM is associated with more severe cognitive dysfunction. Schoenle et al., (2002) found that, although the IQ of children with T1DM and healthy controls is similar up to 7 years, there was a significant decline in VIQ and PIQ between the ages of 7 and 16

years in boys with T1DM who were diagnosed before 6 years of age. This decline was not prevalent in girls either diagnosed before or after the age of 6 years. The decline in VIQ was correlated with the degree of metabolic control (HbA1c and degree of ketoacidosis; severe lack of insulin results in the body's inability to use glucose for energy) at 7 years of age. As reported in previous studies (see section 3.3.3.2), the presence of severe hypoglycaemia was not found to affect cognitive development. These results suggest that boys who have early onset of T1DM and have high HbA1c levels and poor metabolic control may be vulnerable for cognitive dysfunction.

A meta-analysis conducted by Gaudieri, Chen, Greer, and Holmes, (2008) found that although learning and memory were similar between both diabetics and controls, children who had early onset T1DM (< 7 years) were more likely to exhibit lower verbal and visual learning and memory, crystallised IQ, attention, executive function skills and academic attainment than those who had late-onset T1DM. However, the magnitude of these differences was small. When children with early and late onset T1DM were compared to control participants, the impairment decrements between those with early T1DM onset and controls was larger, particularly for learning and memory domains.

3.3.3.6.2   T2DM

As mentioned in section 3.3.3.1, the metabolic syndrome precedes the development of T2DM, and the related factors are independently associated with cognitive dysfunction. As a result, there has been limited research investigating the age of onset as a mechanism for cognitive dysfunction in T2DM. Despite T2DM being associated with accelerated ageing, Awad et al. (2004) report that before the age of 70 years old, T2DM probably has little effect on cognitive function if good glycaemic control is achieved and maintained. However, the degree of cognitive impairment may increase with early T2DM onset, poor glycaemic control, and the presence of microvascular and macrovascular complications. After the age of 70 years old, cognitive decline is likely to accelerate due to diabetes interacting with processes of dementia.

3.3.3.7   **CNS dysfunction**

Diabetes has not only been shown to affect cognitive functioning, but also cause CNS dysfunction. Chronic hyperglycaemia plays a key role in cerebral dysfunction (Seaquist, 2010), partly as endothelial cells are particularly vulnerable to its effects (Meusel et al., 2014). Intracellular hyperglycaemia can cause an increase in the production of reactive oxygen species (ROS; in particular O_2^-), which results in oxidative stress within the cell. Tissue damage due to hyperglycaemia arises through the mechanisms of increased activation of the polyol pathway, intracellular formation of AGEs and activation of their receptors, diacylglycerol activation of protein kinase C and shunting in the hexosamine pathway (Kodl & Seaquist, 2008; Meusel et al., 2014). All these mechanisms are activated by ROS (Giacco & Brownlee, 2011). Although AGEs are produced as a consequence of normal metabolism, hyperglycaemia causes production to exceed normal levels, which leads to intracellular damage and induces apoptosis through 'cross-linking' (Meusel et al., 2014). Insulin resistance may also contribute to the increase in AGEs as insulin inhibits oxidative stress and apoptosis. AGEs also activate inflammatory signalling cascades, and induce the

production of pro-inflammatory cytokines and growth factors in endothelial cells. Thus, the increase and accumulation of AGEs and oxidative stress has been suggested as a potential mechanism for brain ageing in diabetics (Wrighten et al., 2009).

3.3.3.7.1 T1DM

The vulnerability, or diathesis hypothesis, proposed by Ryan (2006) suggests that chronic hyperglycaemia in children with early onset T1DM causes functional and structural changes within the CNS which causes normal brain development to be disrupted. These early changes make the individual more susceptible to additional insults on the brain, e.g. neuroglycopenia.

Brain imaging studies have shown that, compared to controls, people with T1DM have reductions in brain volume (Biessels & Reijmer, 2014). Hughes et al. (2014) report that grey matter volume is reduced overall, in particular in the frontal lobe by 7%, in middle aged adults with childhood T1DM onset compared to controls, independent of age and gender. However, other studies have only found specific brain regions of grey matter density to be reduced. Musen (2006) used voxel-based morphometry (VBM) in people with T1DM aged 25-40 years, of whom most had childhood or adolescent onset. Compared to an age, education and sex-matched non-diabetic control group, those with T1DM had reduced grey matter densities in frontal, posterior, temporal and cerebellar regions. Reductions in the densities of grey matter were most pronounced within the diabetic group in those with worse glycaemic control (assessed by HbA1c), who experienced recurrent, severe, hypoglycaemic episodes, and developed retinopathy.

Perantie et al., (2007) performed VBM in children and adolescents with T1DM aged 7-17 years and found no differences in white or grey matter density compared to healthy sibling controls. Nevertheless, poor glycaemic control was associated with brain volumes; those with history of severe hypoglycaemia had smaller grey matter volume at the left superior temporal–occipital cortex suggesting hypoglycaemia causes more damage to the left than right side of the brain. Those with greater hyperglycaemia exposure had smaller grey matter volumes in the right posterior cortical regions, but larger grey matter volumes in the right prefrontal region, in addition to smaller white matter volume in the right superior parietal region. The authors suggest that these differences are not a function of age of diabetes onset. A 2 year follow up of these participants revealed no difference between groups in whole brain or voxel-wise change (Perantie et al., 2011). However, there was a greater decrease in whole grey matter in those with T1DM who experienced more hyperglycaemia compared to those who experienced less. Also, there were greater decreases in occipital and parietal white matter volumes in those who experienced episodes of severe hypoglycaemia, compared to those experiencing no episodes and controls. Thus, although hypoglycaemia may not cause overt changes in cognitive function, it may cause subclinical brain damage. As evidenced by the follow-up study, even after 2 years, hyper- and hypo-glycaemia can cause subtle changes in normal brain development.

People with early onset T1DM have been shown to have more prevalent brain abnormalities than those with late onset. Although ventricular atrophy occurs as a function of age, the

greater prevalence of mild to moderate atrophy in those with early onset (compared to late onset) suggests either suboptimal brain development, or accelerated brain ageing (Ferguson et al., 2005). The brain abnormalities observed in those with early onset were not a result of microangiopathy, diabetes duration or previous severe hypoglycaemic episodes.

Research has suggested that differences in brain volumes may be associated with the aspects of cognitive functioning which are disrupted in T1DM. As rapid communication between brain regions via white matter tracts is needed for storage and manipulation of new information, damage to these connections may result in slower processing speed. Research has shown an association between decreases in the speed of information processing, a characteristic of T1DM cognitive dysfunction, and reduced white matter volume. Wessels et al. (2007) found that diminished performance on tasks of speed of information processing, attention and executive functioning was associated with smaller white matter volume. There was no correlation observed between grey matter volume and cognitive function.

3.3.3.7.2 T2DM

It has been suggested that CNS complications caused by diabetes occur more rapidly in people with T2DM than T1DM (Wrighten et al., 2009). This may be due to diabetes-specific factors (e.g. glycaemic control) interacting with co-morbid conditions (e.g. hypertension, obesity) associated with T2DM (Manschot et al., 2006). Research has shown that T2DM is associated with cerebral atrophy and lacunar infarcts (classic markers of small vessel disease revealed using MRI), and less consistently associated with cerebral white matter hyperintensities (C. Moran et al., 2013; van Harten, de Leeuw, Weinstein, Scheltens, & Biessels, 2006). Features of Alzheimer's disease, such as lower hippocampal and total brain volume, are also common in people with T2DM (C. Moran et al., 2013) which supports the view that T2DM is a risk factor for dementia (Chatterjee et al., 2016).

Manschot et al., (2006) found that, compared to controls, performance was significantly worse on tests of attention, executive function, processing speed, and memory in those with T2DM. Using MRI, cognitive function in people with T2DM was found to be inversely related to white matter lesions, brain atrophy and the presence of infarcts, such that deep and punctate white matter lesions, cortical and subcortical atrophy and silent infarcts were significantly associated with poorer information processing speed, whereas subcortical atrophy was associated with worse attention and executive function. There was also a modest association between cognitive dysfunction, glycaemic control (assessed by HbA1c) and diabetes duration. Age was related to atrophy and severity of white matter lesions, and was also significantly associated with memory and processing speed decrements in the group with T2DM.

In a recent study, Moran et al., (2013) investigated the regional distribution of brain atrophy in similarly aged people with T2DM, and whether atrophy mediates or moderates the effect of T2DM on cognition. In those with T2DM, in addition to hippocampal volume atrophy and more cerebral infarcts, grey matter atrophy was observed in temporal, frontal and limbic regions and white matter atrophy was found to a lesser degree in frontal and temporal regions. Although there was no difference between those with T2DM and controls for cerebral

microbleeds or white matter hyperintensities, T2DM was associated with worse executive function, visual memory and processing speed. This suggests that atrophy rather than cerebrovascular lesions plays an important role in cognitive dysfunction in those with T2DM. Reijmer et al. (2013) found that in slighter older people with T2DM (mean = 71 years), microstructural abnormalities were significantly increased in white matter tracts compared to age, gender, education matched controls and these abnormalities were associated with cognitive dysfunction in domains of processing speed and memory, independent of white matter hyperintensities and lacunar infarcts.

In summary, although total brain atrophy has been observed in those with T2DM, it occurs slowly over many years, at a rate which only slightly exceeds normal age-related brain volume loss. Nevertheless, atrophy contributes to the observed accelerated cognitive decline in those with T2DM. The smaller volumes of grey and white matter have been associated with, and/or mediate the relationship between T2DM and decrementation in memory, processing speed and executive function.

Table 3.2 summaries the studies investigating cognitive function and the mechanisms in people with T1DM and T2DM.

Table 3.2 Summary table of studies investigating cognitive function and the mechanisms in people with T1DM and T2DM, organised by proposed mechanism of cognitive dysfunction

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Brands et al. (2005)	People with T1DM	Nondiabetic or different T1DM patient groups	Hypoglycaemia	Meta-analysis of 33 studies	Various	Most commonly found decrements in the domains of crystallised IQ, psychomotor efficiency and cognitive flexibility. Majority of deficits modest. Memory and learning not consistently affected. Recurrent severe hypoglycaemic episodes do not cause impairment.	Diminished cognitive flexibility and slowing psychomotor efficiency and may explain crystallised IQ impairments.
Tonoli et al. (2014)	People with T1DM	Healthy subjects	Hypoglycaemia	Meta-analysis of 32 adult studies	Various	Small to modest performance decrements on tests of IQ (VIQ, PIQ and FSIQ), mental flexibility, spatial memory and motor speed.	
Awad et al. (2004)	People with T2DM	Various	Hypoglycaemia	Systematic review	Various	Most common impairments in treated T2DM are brief screening measures, verbal memory and processing speed. Less consistent results for executive function. Small-moderate effects in relatively younger adults (<60 yrs), while older adults (>65 yrs) have moderate to large effects, particularly in the presence of poor glycaemic control (i.e. higher HbA1c). Insulin increases the occurrence of hypoglycaemic episodes which could affect cognition.	High impairment risk in those with insulin therapy compared to diet or oral agents. Depression can lead to deficits, with cerebro- and cardio vascular disease increasing these impairments.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Palta et al. (2014)	Study samples were of middle aged to older adults (50-85 yrs old with T2DM.	Non-diabetic	Hypoglycaemia	Meta-analysis of six cognitive domains reported in 24 studies	Various	T2DM revealed impairments with small to moderate effect sizes in 5 of 6 cognitive domains assessed. Impairments in motor function had the largest effect size followed by executive function, processing speed, verbal and visual memory, with the smallest for attention.	50% of studies included T2DM samples with a mean age over 65 yrs, and the authors did not report the results stratified by age.
van den Berg (2009)	People with T2DM	Non-diabetic	Hypoglycaemia	27 studies; 50% of cross-sectional studies had a case–control design	Various	T2DM worse in one or more cognitive domains in 13/20 cross-sectional and 5/7 longitudinal studies. Most commonly found impairments were for processing speed (63%) followed by attention (50%), memory (44%), cognitive flexibility (38%), language (33%), general IQ (31%), and perception and construction (22%). For the most commonly affected domains, effect sizes were small to medium. Cross sectional studies show that older adults (>65 yrs) are more likely to demonstrate larger effect sizes than younger adults.	Not all studies distinguished between T1DM and T2DM; given the age of the populations, the majority of participants are likely to have had T2DM.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Jacobson et al. (2007, 2011)	N=1144 with T1DM. Mean age of entry to the DCCT: 27yrs.	None	Hypoglycaemia, glucose control, Macro-vascular	DCCT and EDIC study.	WAIS RINTB WMS Digit Vigilance, Grooved Pegboard Test, Verbal Fluency Test, Four-Word STMT, Symbol-Digit Learning Test, Embedded Figures Test	At least one severe hypoglycaemic episode reported in 40%. No association between the occurrence of one or more episodes of severe hypoglycaemia or prescribed treatment (intensive/ standard) and a decline in cognitive function after 18yr follow-up. Higher HbA1c associated with worse psychomotor efficiency and moderately slower motor speed. No evidence that macrovascular complications were associated with cognitive decline.	Relatively young sample with good glucose control. No mention whether T1DM who had diabetic microvascular complications were included in the follow-up.
Cox et al. (2009)	N=452 with T1DM, mean age 42.4 yrs, duration of disease: 25.9 yrs, estimated HbA1C 61.7 mmol/mol.	None	Hypoglycaemia	Prospective	Number of hypoglycaemia-related driving incidents	Over 12 months, 52% had at least one hypoglycaemic-related driving incident and 5% had six or more. Mishaps were related to insulin pump therapy, history of severe hypoglycaemic episodes, previous collisions and mild hypoglycaemia symptoms whilst driving in previous 6 months & hypoglycaemic related driving incidents in the past 2 yrs.	Average number of miles driven per yr: 16,000.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Chabriat et al. (1994)	N=9, T1DM with a history of more than 10 hypo-glycaemic comas, mean age 47.6 yrs (30-71 yrs).	N=6 with T1DM but no hypo-glycaemic comas. Mean age 42.8 yrs (20-63 yrs).	Hypoglycaemia	Cross-sectional	TMT (A,B), the Letter Cancellation Test, Stroop, WAIS (Digit Span), AVLT, Lexical Fluency Test.	No significant difference between those with and without hypoglycaemic comas. Intensive insulin therapy, although increasing the frequency of hypoglycaemic coma, may not always be detrimental for cognitive function.	Limited duration of hypoglycaemic coma induced by conventional insulin therapy may have contributed to the non-significant finding.
Chalmers et al. (1991)	Male, 34 yrs old, T1DM duration= 16yrs	N/A	Hypoglycaemia	Case study	WMS	Suffered severe amnesia after prolonged hypoglycaemia (6-8hrs). General cognitive function was largely intact except for a marked impairment of verbal learning and delayed recall, which was still apparent at 6 and 10 months later.	Hypoxic temporal lobe damage was secondary to hypoglycaemia
de Galan et al. (2009)	N=11140, ≥55 yrs, with T2DM (from the age of ≥30 years) and a history of micro- or macrovascular disease or at least one other cardiovascular risk factor.	N/A	Hypoglycaemia	ADVANCE trial	MMSE	In those with severe cognitive dysfunction (MMSE score ≤ 23), there was a twofold increased risk of severe hypoglycaemia compared to those with normal cognitive function. The increased risk was not a result of older age, low HbA1c, longer diabetes duration or cardiovascular risk.	Cognitive function was suggested to be an independent predictor of clinical outcomes.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Feinkohl et al. (2013, 2014)	N=831 (430M) with T2DM, mean age 67.7 yrs (60-75 yrs old).	N/A	Hypoglycaemia, macrovascular complications	ET2DS; longitudinal	WMS-III (Logical Memory, Faces), BVFT, TMT (A, B). WAIS-III (Digit Symbol Coding, Letter-Number Sequencing, Matrix Reasoning), MHVS	Having severe hypoglycaemia at 4 yr follow-up was associated with worse cognitive function (cognitive flexibility, visual spatial problem solving, processing speed) at baseline. History of severe hypoglycaemia at both baseline and follow-up was associated with greater cognitive decline (cognitive flexibility and visual spatial). Stroke, subclinical markers of cardiac stress and generalised atherosclerosis, ankle branchial index, and carotid intima-media thickness were all significantly associated with cognitive decline over 4 yrs whereas non-stroke vascular events were not.	
Punthakee et al. (2012)	N=2,956 adults, aged ≥55 yrs with T2DM and additional cardiovascular risk factors.	N/A	Hypoglycaemia	ACCORD trial	DSST, RAVLT, Stroop Test, MMSE	After a 3.25 yr median follow-up, the first severe hypoglycaemia episode requiring medical assistance was predicted by a lower score at baseline on the DSST. Whether individuals were on an intensive or standard glycaemic control intervention had no effect on the relationship between cognitive function and severe hypoglycaemic risk.	No effect of therapy type on the relationship between cognition and risk of severe hypoglycaemia; consistent with ADVANCE. Poor cognition increases the risk of severe hypoglycaemia.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Cox et al. (2005)	N=105 (5F, 40M) adults with T1DM, mean age 37.5 yrs, mean duration of diabetes 19.7 yrs.	N/A	Hyperglycaemia	Repeated measures	Mental subtraction, 4 CRT, Psychomotor	T1DM exhibited significantly slower psychomotor performance, mental subtraction speed and increased subtraction errors, and there was a trend for slowing of CRT, when blood glucose >15 mmol/L. There was a small-moderate effect for hyperglycaemia frequency (higher HbA1c and percentage of self-monitored blood glucose readings >15mmol/L) and the number of impaired tests. Greater impairment during hyperglycaemia if performance was poor with normal glucose levels.	High blood glucose can affect cognitive function differently. Hyperglycaemia is associated with mental slowing and increased errors, particularly when blood glucose levels exceed 15mmol/L
Sommer-field et al. (2004)	N=20, with T2DM, median age 61.5 yrs (53.1–72.0 yrs), known duration of diabetes 5.9 yrs (2.8–11.2 yrs), BMI 29.8 kg/m^2 (22.0–34.6 kg/m^2), and HbA1c 58.5 mmol/mol (49.7-68.3 mmol/mol).	N/A	Hyperglycaemia	Repeated measures, randomized and counter-balanced.	TMT (B), SRT, DSST, 4CRT, AVLT, Logical Memory, Digit Span, Letter /Number Sequencing, Visual Reproduction, Benton Visual Retention, TEA.	Acute hyperglycaemia (16.5 mmol/L) significantly impaired their ability on tasks of speed of information processing, working memory, and some aspects of attention. Decrements in performance were seen predominantly on tasks which have a degree of complexity. Acute hyperglycaemia was also found to negatively affect mood, with increased feelings of agitation, anxiety, tiredness and decreased feelings of happiness.	There was a speed-accuracy trade off, with accuracy preserved at the expense of speed. Mood was not a significant covariate for cognitive performance.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Green-wood et al. (2003)	N=19, T2DM, mean age 63.9 yrs, mean BMI 26.1 kg/m².	N/A	Hyperglycaemia	Repeated measures, crossover design	Verbal declarative memory (word and paragraph recall; (immediate and delayed), TMT (B)	When fasted, elevated HbA1c was negatively associated with immediate and delayed paragraph recall performance and higher fasting blood glucose trended toward poorer word list recall. Subsequent food ingestion did not improve immediate recall but did so for delayed; recall was improved at 15 min post ingestion but was impaired at 30 min. Cognitive flexibility or processing speed, and mood were influenced by food consumption.	Worse glycaemic control is associated with poorer performance on tests of declarative memory. Acute ingestion of high GI foods does not alleviate this deficit.
Cukierman-Yaffe et al. (2009)	N=2977 (1388 F), mean age 62.5 yrs, T2DM duration 10.4 yrs.	N/A	Hyperglycaemia; Glycaemic control	MIND ACCORD	DDST, MMSE, RAVLT, Stroop	A 1% increase in HbA1c score was associated with a 1.75 point decrease on the DSST, a 0.2 point decease on the MMSE , a 0.11 score decrease in memory score, and a worse score (>0.75) on the Stroop task.	HbA1c levels only explained a small amount of cognitive test score variability.
Munshi et al. (2006)	N=58 T2DM, 58% F, mean age 79 yrs (70-93 yrs), diabetes duration 14 yrs, mean HbA1c 62.8 mmol/mol.	N/A	Hyperglycaemia; Glycaemic control	Cross-sectional	MMSE, Clock Drawing Test	38% had low clock drawing performance and 34% had low clock drawing in a box performance. MMSE correlated with clock drawing ability. Performance on both clock drawing tasks was inversely correlated with HbA1c.	Cognitive impairment is associated with poor glycaemic control

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Reaven et al. (1990)	N=29 (19M,10F), older adults, T2DM, mean age 69.8 yrs.	N=30 (16M,14F)Non-diabetic, community volunteers mean age 68 yrs.	Hyperglycaemia	Cross- sectional	WAIS-R (vocabulary and digit span, block design and digit symbol), TMT (A, B), CVLT, WCST, finger-tapping test.	T2DM perform worse than controls on more difficult cognitive tests i.e. Learning, abstract reasoning, and complex psychomotor functioning. No difference on simple verbal and motor functioning. Of those with T2DM, people with poor glycaemic control performed worse on tasks involving learning, reasoning, and complex psychomotor performance compared to healthy controls.	
Geijselaers et al. (2015)	T2DM	N/A	Glycaemia, hypoglycaemic events, insulin concentration, insulin resistance, and glucose-lowering treatment	Systematic review; 86 studies	Various	Although high HbA1c (and glucose variability) was associated with worse cognitive function in people with T2DM, HbA1c accounted for less than 10% of the variability. A minority of studies have measured long-term cerebral outcomes, such as dementia and structural brain changes on MRI, and the effect of glucose-lowering treatment on cognitive function.	More RCTs are needed to establish the effect of glucose-lowering treatment on long-term cognitive function in T2DM.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Ryan (2006)	N=145,T2DM Rosiglitazone: N=69, mean age 60.7 yrs, 43% F. Glyburide: N=72, mean age 59.6 yrs, 36% F.	N/A	Hyperglycaemia	Randomized double blind trial	DSST, RAVLT, CANTAB (RTI, SWM, PRM, PAL, RVP)	Treatment with either rosiglitazone (thiazolidinedione insulin sensitizer) or glyburide (sulphonylurea insulin secretagogue) significantly improved FPG levels within 24 weeks. This improved glycaemic control led to a significant reduction in errors (25-31%) on a CANTAB working memory task.	Working memory appear particularly sensitive to improvements in FPG levels possibly due to the task complexity and the wide range of brain structures activated.
West et al. (2014)	N=897, mean age 72 yrs, 59.3% M, mean HbA1c 50.8 mmol/mol (20.2-86.9 mmol/mol).	N/A	Hyperglycaemia	Cross- sectional	TMT (A,B), DSST, Episodic memory, Letter and category fluency, Digit Span (forward, backwards), Constructional praxis, Similarities, Diamond cancellation	An association between the duration of diabetes with cognitive function was modulated by glycaemic control. Performance on tasks of executive functioning, attention, working memory, semantic categorisation and overall cognition were worse in those with a longer diabetes duration, but only if they had higher HbA1c levels as well.	Diabetes duration per se does not result in cognitive dysfunction but interacts with poor glycaemic control. Intensive treatment might be beneficial to reduce decline.
Tuligenga (2015)	T2DM	N/A	Hypoglycaemia	Meta-analysis; 5 RCTs	Various	No benefit of conforming to intensive glycaemic control to prevent the increased rate of cognitive decline. Intensive control may increase hypoglycaemia, which is associated with cognitive dysfunction	A small number of diabetes control trials including cognition endpoints.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Ferguson et al. (2003)	N=25 (14M, 11F) developed T1DM in childhood or adolescence, mean age 31.5 yrs (21-44 yrs).	N=46, (23M, 23F) developed T1DM in childhood/ adolescence, without retinopathy, mean age 26.4 yrs (20-36 yrs).	Microvascular complications	Cross-sectional	WAIS-R (block design, picture completion, digit symbol object assembly), CRT, NART, BVFT, PASAT, Inspection Time	People with T1DM who had developed retinopathy had worse spatial ability, mental flexibility, psychomotor speed, processing speed and sustained attention compared to those without retinopathy. Magnitude of these differences was moderate (0.4-0.7 SD) and could not be explained by years of education, estimated premorbid cognition or the effects of developing retinopathy as the visual aspect of information processing was not affected.	It is proposed that retinopathy is a consequence of chronic hyperglycaemia and suboptimal glucose control also leads to the development of microangiopathy which affects cognitive function.
Wessels et al. (2007)	N=25, T1DM, Proliferative retinopathy n=10 (3M, 7F), mean age 42.3 yrs (37-53 yrs). No retinopathy N=15, (7M, 8F), mean age 42.1yrs (34-50 yrs).	N=9 (3M, 6F) mean age 40.9 yrs (31-52 yrs). Sex, age and education matched.	Microvascular	Cross-sectional	Digit span (forward, backward), 15 Words test, WAIS (DSST, block design) incidental learning, ROCF, TMT (A, B), D2 test, Stroop, WCST, WISC (Mazes), GIT, Category Word Fluency.	T1DM performed worse on information processing and visuoconstruction compared to controls. However, while those without proliferative retinopathy performed worse on information processing, those with retinopathy performed worse on visuoconstruction. Diminished performance on tasks of speed of information processing, attention and executive functioning was associated with smaller white matter volume. There was no correlation observed between grey matter volume and cognitive function.	The development of proliferative retinopathy may alter the pattern of dysfunction in people with T1DM.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Ryan et al. (1993)	N=82 (41M, 41F), mean age 33.4 yrs (21-50 yrs), middle aged adults with T1DM (mean diabetes duration >26 yrs).	N=82 (41M, 41F), Gender, age and education matched controls (spouse, sibling, "significant other," or close friend)	Interaction between hypoglycaemia and neuropathy	Cross-sectional	WAIS-R, TMT (A,B), ROCF, Lafayette Clinic Repeatable Test Battery (digit vigilance), Grooved pegboard, Boston Embedded Figures, Verbal Paired Associates Learning, Digit Symbol Paired Associates, Four Word STMT, WMS (logical memory)	Learning and memory not impaired. T1DM had significantly worse psychomotor efficiency. Presence of dysfunction was predicted by having developed clinically significant diabetic complications, and not by having diabetes itself. Those who had one or more diabetic complication had significantly worse performance than group without complications (on tasks of visual scanning, rapid decision making and dexterity) and controls (on tasks of sustained attention, visual scanning, rapid decision making and hand-eye coordination). The diagnosis of DSP was the best predictor of performance on sustained attention, visual scanning, rapid decision making, mental flexibility and hand-eye coordination tasks but not memory.	Hypoglycaemia was not associated with cognitive dysfunction but the findings suggest it may interact with neuropathy to increase the extent of cognitive impairment.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Ryan et al. (2003)	N=103 young and middle-aged adults, 58.3%F, mean age 40.4 yrs with childhood-onset T1DM.	N=57, 61.4% F, mean age 41.8 yrs, demographically similar adults without diabetes	Micro- & Macro-vascular complications	Cross sectional	Verbal Paired-Associate Learning Test, Symbol-Digit Paired-Associate Learning Test, Four-Word STMT, ROCF, Tactual Performance, TMT(B), WAIS-R (Object Assembly, Block Design DSST),WCST, Digit Vigilance, Grooved Pegboard	T1DM had significantly slower psychomotor performance at baseline compared to controls, and the degree of decline was greater in those with diabetes 7 yrs later. Psychomotor slowing was predicted by the presence of microvascular complications at baseline, and microvascular complications, SBP and duration of diabetes at follow-up. Those who developed retinopathy between baseline and follow-up showed greater psychomotor slowing compared to those without retinopathy, with performance similar to those who had retinopathy at baseline. Same pattern in those who developed autonomic neuropathy during the study. Conversely, the development of either DSP or overt nephropathy predicted psychomotor slowing at baseline but not at follow-up. Prevalence of macrovascular complications increased significantly over the 7 yr period. Increase in psychomotor slowing was associated with the development of macrovascular complications.	A greater decline in psychomotor slowing over a 7 year period in those with T1DM compared to controls. Proliferative retinopathy and autonomic neuropathy have a more pronounced effect of cognitive decline.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Bresser et al. (2010)	N=68, elderly adults with T2DM.	N/A	Microvascular	Longitudinal 4yr interval	Various	Presence of retinopathy or neuropathy was not associated with cognitive performance at baseline or cognitive decline. Albuminuria, was found to be a predictor of accelerated cognitive decline.	
Ding et al. (2010)	N=1,046 T2DM, aged 60–75 yrs. No retinopathy: N=705, mean age 67.3 yrs. Mild retinopathy: N=292, mean age 67.4 yrs. Moderate/ Severe retinopathy: N=47, mean age 67.1 yrs.	N/A	Microvascular	ET2DS; cross sectional	WMS-III (Faces and Family Pictures and Logical Memory), WAIS-R (Matrix Reasoning, Letter-Number Sequencing, DSST), BVFT, TMT (B), MHVS, MMSE	Moderate to severe diabetic retinopathy was associated with worse general cognitive ability. This was particularly evident in men. Measures of verbal fluency, information processing speed, and mental flexibility were affected, after adjusting for vocabulary, depression, sociodemographic characteristics, cardiovascular risk factors, and macrovascular disease.	
Barzilay et al. (2013)	N=2977 (1377M) with T2DM, mean age 62.5 yrs.	N/A	Microvascular	ACCORD-MIND; Longitudinal; baseline, 20 months, and 40 months	RAVLT, DSST, MMSE	Persistent and progressive albuminuria were associated with a greater than 5% decline in scores for processing speed, but not performance of verbal memory or executive function. In terms of information processing, speed decline relative to 1 yr of ageing. Having persistent albuminuria was equivalent to 7.2 yrs of ageing, while progressive albuminuria was equivalent to 3.2 yrs.	Persistent albuminuria is associated with greater information-processing speed decline.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Manschot et al. (2006)	N=113 (56M,57F) with T2DM, mean age 66.1 yrs.	N=52 (22M,29F) spouses or acquaintances of the T2DM people, mean age 65.1 yrs.	Macrovascular	Utrecht Diabetic Encephalopathy Study; cross sectional, population based	RPM, WAIS-III, (Digit span (forward, backward), DSST), Corsi, RAVLT, LLT, TMT (A,B), Stroop, Brixton Spatial Anticipation, ROCF, DART	Deep and punctate white matter lesions, cortical and subcortical atrophy and silent infarcts were significantly associated with processing speed ability, whereas subcortical atrophy was associated with attention and executive function abilities. Adjustment for hypertension did not affect the results. There was also a modest association between cognitive dysfunction, HbA1c and diabetes duration. Age was related to atrophy and severity of white matter lesions, and was also significantly associated with memory and processing speed decrements in the group with T2DM.	Impairments in T2DM are not only associated with subcortical ischemic changes in the brain, but with increased brain atrophy.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Manschot et al. (2007)	N=122 (62M,60F), T2DM, mean age 66.0 yrs.	N=56 (25M,31F) mean age 65.1 yrs. Controls were spouses or acquain- tances.	Macrovascular	Utrecht Diabetic Encephalo- pathy Study; cross sectional, population based	RPM, WAIS-III (Digit span (forward, backward), DSST), Corsi, RAVLT, DART, TMT (A, B), LLT, Stroop, ROCF, Brixton Spatial Anticipation Test	T2DM had more cortical and subcortical atrophy and deep white matter lesions and worse cognitive function. People with T2DM who had hypertension and a history of vascular events had impaired processing speed and memory, while statin use was associated with better performance. Association was attenuated by the exclusion of patients who had a history of stroke. Retinopathy and brain infarcts on MRI were associated with more severe cortical atrophy, and statin use with less atrophy. Insulin level and brain infarcts were associated with more severe white matter lesions, and statin use with less severe white matter lesions.	Groups were comparable for age, gender and educational level.
Ruis et al. (2009)	N=183, T2DM, 61.2% M, mean age 63 yrs (50–70 yrs).	N=69 peers of T2DM, 47.8% M, mean age 62.7 yrs. Groups matched on age, gender and education level.	Macrovascular	ADDITION	RPM, Corsi, Dutch RAVLT and NART, WAIS-III (Digit span (forward, backward), DSST), LLT, ROCF, TMT (A, B), Stroop, Brixton Spatial Anticipation Test, Category naming, Lexical fluency	After adjusting for IQ, only memory was significantly different between T2DM and controls. In T2DM, a history of macrovascular disease and current smoking were significant determinants of slower information-processing speed but not memory performance.	Modest impairments are already present at the early stage of T2DM. Significant risk factors for early decrements are macrovascular disease and smoking.

Authors (year)	Diabetes group (Experimental group)	Control Group	Proposed mechanism of cognitive dysfunction	Study design	Cognitive assessment	Results	Comments
Schoenle et al. (2002)	N=64 children with T1DM (38F, 26M).	N/A	Age of onset, hypoglycaemia, and degree of metabolic control.	The Zurich longitudinal study on growth and development in children with type 1 diabetes diagnosed at a young age; Longitudinal	German version of WPPSI (HAWIVA) and WISC-R (HAWIK-R), Adaptives Intelligenz Diagnostikum	Although the IQ of children with T1DM and healthy controls is similar, by the age of 7yrs, there is a significant decline in VIQ and PIQ between the age of 7 and 16 years in boys with T1DM who were diagnosed before 6 years of age. This decline was not prevalent in girls either diagnosed before or after the age of 6 years.

The decline in VIQ was correlated with the degree of metabolic control (degree of ketoacidosis) at 7 years of age. | Presence of severe hypoglycaemia was not found to affect cognitive development. Boys who have early T1DM onset and have poor metabolic control may be vulnerable for cognitive dysfunction. |
| Gaudieri et al. (2008) | People with T1DM | Various | Age of onset | Meta-analysis; 19 studies. T1DM=1,393 Controls= 751 | Various grouped into intelligence, learning and memory, psychomotor activity and speed of information processing, attention/ executive function, academic achievement, and visual motor integration | Learning and memory was similar between both diabetics and controls. Children with early T1DM onset (< 7 years) were more likely to exhibit lower verbal and visual learning and memory, crystallised IQ, attention, executive function skills and academic attainment than those who had late-onset. Effect sizes were small. When children with early and late onset T1DM were compared to controls, the impairment decrements between those with early T1DM onset and controls was larger, particularly for learning and memory. | Diabetes in children generally relates to mildly poorer performance on most cognitive domains. |

KEY: 4CRT, Four Choice Reaction Time; AVLT, Auditory Verbal Learning Test; BMI, body mass index; BNT, Boston Naming Test; BVFT, Borkowski Verbal Fluency Test; CANTAB, Cambridge Neuropsychological Test Automated Battery; COWA, Controlled Oral Word Association Test; CRP, c-reactive protein; CRT, choice reaction time; CVLT, California Verbal Learning Test; CWAT, Controlled Word Association Test; DART, Dutch Adult Reading Test; DSP, Distal symmetric polyneuropathy; DSST, digit symbol substitution test; Fasting Plasma Glucose; FSIQ, full scale IQ; GDS, Global Deterioration Scale; GI, Glycaemic Index; GIT, Groninger Intelligence Test; HDL, high density lipoprotein; HPA, hypothalamic-pituitary-adrenal; IL-6, interleukin-6; IQ, intelligence quotient; IV, intravenous; LDL, low density lipoprotein; LLT, Location Learning Test; M, male(s); MHVS, Mill Hill Vocabulary Scale; MMSE, Mini Mental State Examination; NART, National Adult Reading Test; PAL, Paired Associates Learning; PASAT, Paced Auditory Serial Addition Task. PIQ, performance IQ; PRM, Pattern Recognition Memory; RAVLT, Rey Auditory Verbal Learning Test; RCT, Randomised Control Trial; ROCF, Rey-Osterrieth Complex Figure; RPM, Raven's Progressive Matrices; RTI, Reaction Time; RVP, Rapid Visual Information Processing; SBP, systolic blood pressure; SD standard deviation; SDLT, Serial Digit Learning Test; SILS, Shipley Institute of Living Scale; SRT, Simple reaction time; STMT, Short-Term Memory Test; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 Diabetes Mellitus; TEA, Test of Everyday Attention; TMT (A,B), TNF-α, tumor necrosis factor-α; Trail Making Test (Part A, Part B); TOH, Tower of Hanoi; VIQ, Verbal IQ; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS, Wechsler Adult Intelligence Scale; WISC-III, Wechsler Intelligence Scale for Children; WMS –R/III, Wechsler Memory Scale- Revised/3rd edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence-II.

3.3.4   Summary of diabetes and cognitive function

- The regulation of both glucose and insulin are instrumental in cognitive functioning.

- People with T1DM commonly exhibit modest deficits in the domains of crystallised IQ, psychomotor efficiency and cognitive flexibility. There is minimal decline in cognitive function over time, but early onset of disease is associated with greater impairment.

- Before the development of T2DM, people experience pre-diabetes (IGT) and features of the metabolic syndrome (hypertension, obesity, dyslipidaemia and inflammation) which have all been found to be independently associated with cognitive dysfunction.

- T2DM is associated with accelerated cognitive decline and deficits have been most commonly observed in verbal memory, processing speed and executive function.

- In T1DM, recurrent acute severe episodes of hypoglycaemia do not result in cognitive dysfunction, but could cause subclinical brain damage.

- In T2DM, although hypoglycaemia is not thought to be a primary cause of cognitive dysfunction, decline in cognitive function is a risk factor for severe hypoglycaemia, and the risk may be particularly heightened for those who already have poor cognitive function.

- In both T1DM and T2DM, acute hyperglycaemia can have negative effects on cognition. Chronic hyperglycaemia is not only associated with poor cognitive outcomes, but also leads to the development of micro- and macro-vascular complications, which have also been associated with cognitive impairments.

- The development of microvascular complications in T1DM increases the rate of cognitive deterioration while in T2DM, the findings are mixed.

- In contrast, the development of macrovascular complications in T2DM has consistently been shown to cause cognitive dysfunction (although there is some heterogeneity regarding domains) whilst for T1DM, the findings are mixed.

- Early T1DM onset of disease is associated with greater cognitive impairment. Before the age of 70 years old, T2DM probably has little effect on cognitive function if good glycaemic control is achieved and maintained.

- People with T1DM have reductions in brain volume which are associated with increased episodes of severe hypoglycaemia or chronic hyperglycaemia and early onset of T1DM.

- In T2DM, CNS dysfunction occurs more rapidly, possibly the result of diabetes-specific factors (e.g. glycaemic control) interacting with co-morbid conditions (e.g. hypertension, obesity). T2DM is associated with cerebral atrophy and lacunar infarcts and less consistently with cerebral white matter hyperintensities.

3.4   Conclusion

Compared to non-diabetic people, those with T1DM are characterised as having poor cognitive flexibility and slowing in psychomotor speed, while people with T2DM commonly show deficits in (verbal) memory, executive function and, like people with T1DM, a slowing in processing speed. As CFRD is neither T1DM nor T2DM but shares clinical characteristics with both these forms of diabetes, it is plausible that people with CFRD may exhibit the same cognitive impairments observed in adults with T1DM and T2DM.

Chapter 4

Aims of the thesis

It is clear from Chapter 1 that CF could impact on cognitive function given its effects on lung function and glucose regulation. Impaired glucose regulation leads to diabetes (CFRD) in CF and the research reviewed in Chapter 3 has shown that diabetes (T1DM and T2DM) is also associated with cognitive impairment in some domains. The overall aim of this thesis is therefore to examine cognitive function in CF. To this end the following objectives will be examined:

1. Does CF impact on cognitive function?

This aim is addressed in Study 1 (Chapter 5) where people with CF were compared to matched healthy controls.

2. Is cognitive function worse in people with CFRD than people with CF who are not diabetic?

This aim is addressed in Study 1 (Chapter 5) where people with CFRD were compared to people with CF who are not diabetic (CFND).

3. Does cognitive function decline over time in people with CFRD?

This aim is addressed in Study 2 (Chapter 6) where people with CFRD were followed up after a period of 1 to 3 years.

4. Does transplantation improve cognitive function in people with CFRD?

This aim is addressed in Study 3 (Chapter 7) where people with CFRD who had received a transplant (CFRDTx) were compared to people with CFRD who have not undergone transplantation and matched healthy controls.

5. Does cognitive function decline over time in people with CFRD who are post transplant?

This aim is addressed in Study 4 (Chapter 8) where people with CFRDTx were followed up after a period of 18±6months.

Figure 4.1 provides an overview of the studies presented in this thesis and describes the nature and number of participants included in each.
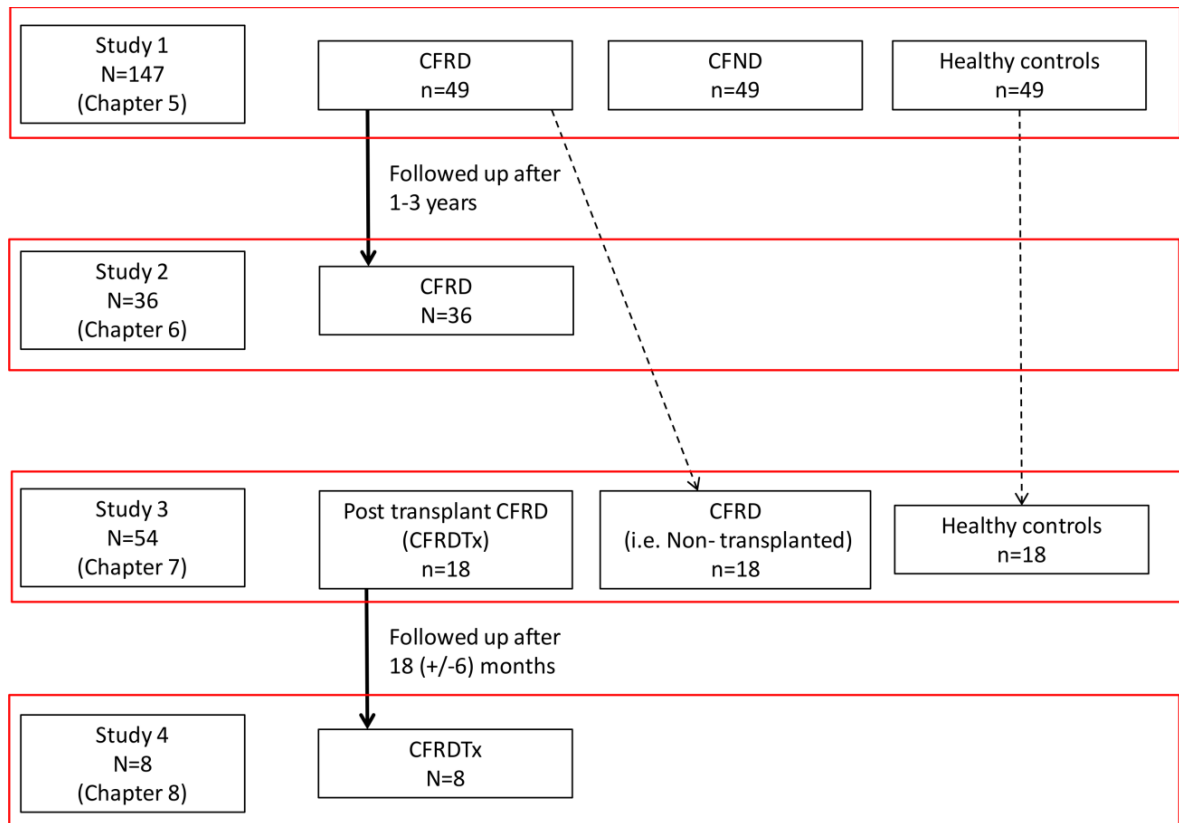
Figure 4.1 Overview of the studies included in this thesis showing participant type and number in each.

Chapter 5

Cognitive function in people with cystic fibrosis (CF), with and without CF related diabetes (CFRD), relative to healthy controls (Study 1)

5.1 Introduction

Chapter 1 reviewed the abnormalities in glucose tolerance in CF. Section 1.4 showed that glucose tolerance is variable but worsens over time (Sterescu et al., 2010), and that people with CF experience delayed onset of insulin secretion, hypoglycaemia and hyperglycaemia irrespective of glucose tolerance status (Holl et al., 1995; Armaghanian, Brand-Miller, Markovic, & Steinbeck, 2016; Moran et al., 2014). Section 1.5 reviewed CFRD which is caused by pancreatic abnormalities (Meacham et al., 1993) and defective CFTR function (J. H. Guo et al., 2014) and has an insidious onset (Lanng et al., 1995). It is neither T1DM nor T2DM but shares clinical characteristics with both (Konrad et al., 2013). Sections 1.6.5 and 1.6.6 showed that, despite a high treatment burden in CF, the educational and employment attainments are currently similar to their peers (Targett et al., 2014; Hodson, Bush, & Geddes, 2007), but this has not always been the case (see Walters, 2001; Claxton et al., 2012; Taylor-Robinson et al., 2014). Chapter 3 reviewed the profile of cognitive function in people with T1DM and T2DM (and features of what has been termed the metabolic syndrome). Figure 5.1 summarises sections 3.3.1 and 3.3.2, and shows the commonality and differences between the cognitive impact of both of the more common types of diabetes. Compared to non-diabetic people, those with T1DM are characterised as having poor cognitive flexibility and slowing in psychomotor speed, while people with T2DM commonly show deficits in (verbal) memory, executive function and, like people with T1DM, a slowing in processing speed (Awad et al., 2004; Brands et al., 2005; Palta et al., 2014). It is therefore plausible people with CFRD may exhibit similar impairments to those seen in both T1DM and/or T2DM.
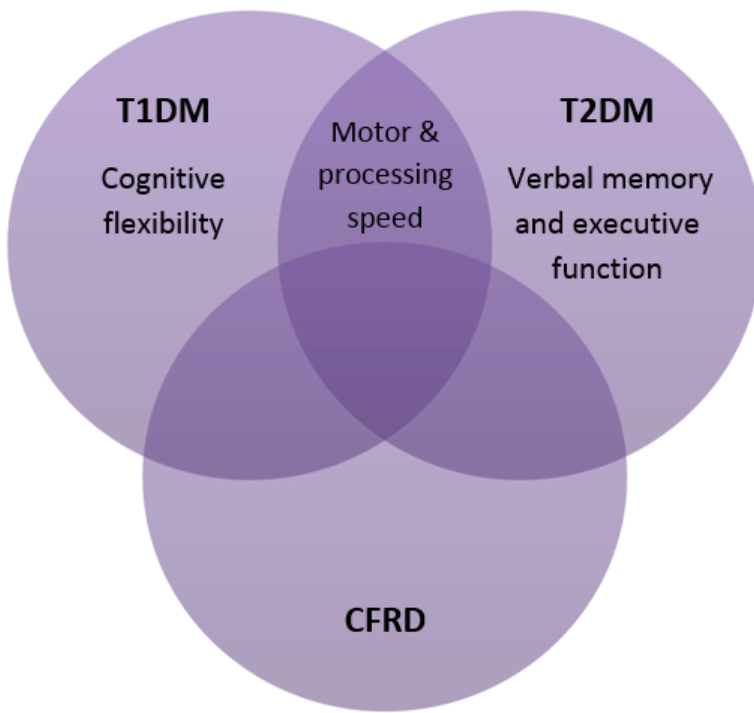
Figure 5.1Venn diagram showing the cognitive impairments commonly seen in people with T1DM and T2DM. The cognitive impairments observed in adults with CFRD are likely to be similar to those observed in T1DM and T2DM.

Chapter 2 showed that people with CF, who have not undergone lung transplantation commonly exhibit impaired cognitive function in memory, processing speed and executive function domains. However, various aspects of CF related disease could plausibly affect performance (for example, see Crews, Jefferson, Broshek, Barth, and Robbins (2000); Dancey, Tullis, Heslegrave, Thornley, and Hanly (2002); Dobbin, Bartlett, Melehan, Grunstein, and Bye (2005); Holley (2011); Koscik et al. (2004); Koscik et al. (2005)). There have been no large scale studies objectively measuring the effect of CFRD on cognitive function in adults. The only study reported in the literature which makes reference to diabetes having an effect on cognition in CF (section 2.3.7;Wong et al. (2011)) is reported as part of a conference abstract and has not been formally peer reviewed. The study was very small and based on the propositon that in CF, the combined effects of hypoxia in lung failure and diabetes causes cognitive dysfunction although the association between diabetes and cognition was not formaly investigated. Cognitive function was measured in six children with chronic end stage organ failure as part of standard protocols for transplant assessments but there was no reference in the abstract to the diabetic status of the patients. The lack of research into the effect of CFRD on cognitive function is surprising for three reasons. Firstly, CFRD is the most common comorbidity of CF. Secondly, there is a wealth of literature showing cognitive dysfunction in people with T1DM and T2DM. Finally, Crews et al. (2000), in the only study to investigate the effects of end stage CF lung disease on cognitive function specifically, proposed that although the prevalence of diabetes wasn't recorded in their study, it may have contributed to the degree of impairment observed in their sample.

Chapter 1 (Section 1.5.3.2.1) reported how some CF centres advocate the use of insulin therapy before WHO confirmation CFRD diagnosis. This is an attempt to alleviate clinical deterioration in the pre-diabetic period, or during periods of acute deterioration in glucose control. However, insulin therapy is associated with some clinical cost including an increased risk of hypoglycaemia. Research has shown that hypoglycaemia is associated with cognitive impairment in people with T2DM (Chapter 3, section 3.3.3.2.2). Therefore, it can be hypothesised that early initiation of insulin in CFRD, or CF-related non-diabetic hyperglycaemia could potentially cause unintended harm by impairing cognition. Hypoglycaemia does have significant clinical impact as observed in a patient attending the Leeds adult CF unit who developed enduring cognitive impairment thought clinically most likely to be as a result of hypoglycaemia (D Peckham and M. Mansfield, personal communication). However, this hypothesis was based on clinical judgement within a CF population and a clinical objective study is needed (Kimberg, 2011). As mentioned in Chapter 2 (section 2.2.5), appropriate control groups are needed when investigating the impact of chronic disease on cognitive function. This includes having a matched healthy control group. Therefore, the first aim of the study was to objectively investigate cognitive function in adults with insulin treated CFRD, compared to adults with CF who do not have diabetes (CF non-diabetics; CFND) and healthy adult controls. It is possible that people with CFRD may share the same cognitive impairments observed in people with T1DM and T2DM respectively given the shared clinical characteristics.

The study by Epker and Maddrey (1999) reported in Chapter 2 (section 2.3.3) showed that people with CF have some degree of cognitive impairment and are also aware of these deficits. Therefore, the second aim of this study was to investigate whether people with CF, regardless of glucose tolerance (i.e. CFRD or CFND) report subjective cognitive impairments compared to a healthy control group.

Factors related to CF disease described in Chapter 2 such as severity (2.3.1), lung function (2.3.5 and 2.3.8), quality and disturbances of sleep (section 2.3.4) and PEs (section 2.3.5) have been shown to have a negative effect on cognitive functioning. Psychological comorbidities associated with CF have also been shown to affect cognitive functioning. For example, levels of anxiety and depression have been associated with cognitive impairment (McDermott & Ebmeier, 2009; O. J. Robinson, Vytal, Cornwell, & Grillon, 2013). It is therefore possible that people with CFND may also show impaired cognitive function. The third aim was to investigate whether there were any differences in participant characteristics (which have been associated with cognitive functioning), subjective evaluations of sleep, stress, mood and mental alertness between the people with CF (CFRD and CFND) and healthy controls.

5.2 Method

5.2.1 Design

A between subjects design with three matched groups; (i) people with CFRD, (ii) people with CFND and (iii) healthy controls.

5.2.2 Participants

Ninety-eight PI people with CF (49 CFRD, 49 CFND) were recruited from the Regional Adult CF Unit in Leeds. A group consisting of 49 healthy control people was recruited through the partners and relatives of patients and from the general population. Inclusion and exclusion criteria are specified below (Sections 5.2.2.1 and 5.2.2.2). Those with CFRD were insulin treated and had been confirmed to have diabetes by OGTT and confirmatory blood glucose profiling. People with CFND had received a normal OGTT result within the past 12 months. Partners and relatives of people with CF were recruited for the control group where possible in order to match for lifestyle and SES. People with CF were matched as closely as possible on at least one genotype. Across all three groups, participants were matched as closely as possible on gender, age and education level (assessed on the Recruitment Information Questionnaire (RIQ) and defined as the highest educational qualification awarded).

5.2.2.1 Inclusion criteria

Table 5.1 shows the inclusion criteria for people with CF (CFRD and CFND) and healthy controls.

Table 5.1 Study 1. Inclusion criteria for people with CF (CFRD and CFND) and healthy control group

People with CFRD	People with CFND	Healthy control group
Aged over 16 years of age	Aged over 16 years of age	Aged over 16 years of age
PI	PI	Be in good health and not taking any regular medication (excluding contraceptive preparations)
Diabetes/ positive OGTT result and treated with insulin	Normal OGTT result within the past 12 months	No known IGT or diabetes
Adequate comprehension of English (written and verbal)	Adequate comprehension of English (written and verbal)	Adequate comprehension of English (written and verbal)
Able to provide Informed Consent	Able to provide Informed Consent	Able to provide Informed Consent

These inclusion criteria were required for the following reasons. Chapter 1 (section 1.1.2) showed that people with CF who are PI are more likely to have gene mutations from class I, II or III, a more severe disease phenotype and to develop CFRD as a consequence of disease progression. It is these individuals who are likely to receive insulin treatment before a diagnosis of diabetes as their pulmonary and nutritional status declines. The OGTT is seen as the gold standard test for detecting glucose tolerance abnormalities in CF and is performed at a time of clinical stability (see section 1.4). OGTT screening is performed annually in those who had previously received a normal OGTT result. The Leeds CF Unit conforms to a strict diabetes diagnosis which requires home blood glucose monitoring to confirm an OGTT diabetic result (according to defined WHO criteria) and the commencement of insulin therapy.

The cognitive tests required participants to understand verbal instructions and one test required them to learn a list of English words hence adequate comprehension of English was required. The control group included the partners and relatives of patients from the same SES, since schooling and educational attainment can be affected by having CF and by SES (see Chapter 1 and 2, sections 1.7, 2.2.1 and 2.2.3). Only participants whose first language was English were recruited for the control group to match for the majority of patients in the sample whose first language is English; three patients were bilingual. This is because research shows that different cognitive processes are applied when learning words from a non-native language (Wong, Parsons, Martinez, & Diehl, 2004).

5.2.2.2 **Exclusion criteria**

Table 5.2 shows the exclusion criteria for people with CF (CFRD and CFND) and healthy controls.

Table 5.2 Study 1. Exclusion criteria for people with CF (CFRD and CFND) and the healthy control group

People with CFRD	People with CFND	Healthy control group
Pregnant or been pregnant within the past 6 months	Pregnant or been pregnant within the past 6 months	Pregnant or been pregnant within the past 6 months
Continuous oxygen therapy	Continuous oxygen therapy	Diabetic or known impaired glucose tolerance
Overnight oxygen therapy	Overnight oxygen therapy	Not a match to people with CF based on gender, age, and education level
Recipient of a transplant	Recipient of a transplant	

These exclusion criteria were required for the following reasons. Glucose tolerance is affected by pregnancy with a risk of gestational diabetes, especially in women with CF (Buchanan, Xiang, Kjos, & Watanabe, 2007; Cystic Fibrosis Trust Diabetes Working Group, 2004). Research has shown that oxygen therapy can improve cognitive function (Moss & Scholey, 1996). For this reason, individuals with CF who were on either continuous or overnight oxygen were excluded. Organ transplantation can also impact on cognitive functioning (see Chapter 7, e.g. Cohen et al., 2014) and recipient of any form of organ transplant were therefore excluded.

5.2.3 **Cognitive Tests**

5.2.3.1 **Selection of the cognitive testing system**

The Cambridge Neuropsychological Test Automated Battery (CANTAB; CANTAB, 2012) was chosen for cognitive test administration. The battery was originally developed by Trevor Robbins and colleagues at the University of Cambridge in 1986, initially assessing subtypes of dementia, but has since gained popularity in the assessment of functional deficit related

cognitive impairment (Luciana & Nelson, 2000; Morris, Evenden, Sahakian, & Robbins, 1987; Robbins et al., 1994). This test system is used worldwide (Gonçalves, Pinho & Simoes, 2016) and provides a comprehensive cognitive assessment which has been shown to be sensitive to normal cognitive ageing (Robbins et al., 1994) and neurodegenerative changes in brain function (Rabbitt and Lowe, 2000 and Fray and Robbins, 1996). CANTAB tests are able to map onto specific brain regions, unlike screening tests, which look at global cognition. Tests are shown to have high to adequate test-retest reliability (Goncalves et al., 2016; Fowler et al., 1995; Lowe & Rabbitt, 1998), proven brain-behaviour reliability (Lucinana & Nelson, 2002), and activate brain regions which may be affected by changes in the CNS (Robbins et al., 1994), and immune function (Lynch, 1998) with age. Neuroimaging tests (PET and fMRI) have also confirmed the accuracy and sensitivity of CANTAB in people exhibiting brain dysfunction (Lee et al., 2000). Construct validity of CANTAB has been obtained from studies using both patients with long term health conditions, including diabetes (Ba –Tin et al., 2011, Lasselin et al, 2012); Epilepsy, (Witt, Alpherts & Helmstaedter , 2013, Torgersen et al., 2012); ADHD (Gau & Shang 2010); psychiatric disorders such as schizophrenia (Levaux et al., 2007), people with brain lesions (Fowler et al., 1997), degenerative disorders (such as Parkinson's disease, Owen et al., 1997) as well as healthy, normal functioning, adult populations (De Luca et al., 2003, Robbins et al., 1998); However, measuring validity has been largely based on the ability to discriminate cognitive functioning of a clinical population compared to that of a healthy control group. CANTAB also stores standardised and validated normative test data for individuals aged 4-90 years of age, which can be used for comparison purposes and analysis (Luciana & Nelson, 1998; Luciana & Nelson, 2000).

CANTAB also shows high sensitivity to positive and negative pharmacological effects (Harmer et al., 2001; Ryan et al., 2006; Attwood et al., 2007; Elliot et al., 1997; Rusted & Warbuton, 1988) and so may be able to detect the impact of early insulin administration before a confirmed diabetes diagnosis in people with CF. People with CF may have struggled with schooling and achieving educational qualifications which can often lead them to feel embarrassed (A. Morton, personal communication). Taking this into account, the more game-like appearance of the CANTAB tests, rather than pencil and paper type school tests, which may be anxiety provoking and affect recruitment rates, was deemed preferable. Ease of administration was also important as flexibility is needed for testing in hospital situations. As CANTAB is administered using a touch screen tablet (Tablet Kiosk i400series), with some tests requiring the use of a response box (Cambridge Cognition 2-button press pad version 2.0) for responding, this also influenced the choice of test system.

5.2.3.2 Cognitive test selection from the CANTAB and piloting the tests

The CANTAB cognitive test battery was chosen and piloted to ensure an appropriate level of difficulty for people with CF.

5.2.3.2.1 Cognitive test selection

The tests were selected on the basis of: previous diabetes literature which had used CANTAB, commonly found cognitive impairments in non-transplanted people with CF (memory, processing speed and executive function; see chapter 2), and exploratory considerations

given the lack of literature investigating the effect of CFRD upon cognition. CANTAB tests which have been found to be sensitive in detecting a significant difference between healthy individuals and people with diabetes are: Pattern Recognition Memory (PRM), Rapid Visual Processing (RVP), Paired Associates Learning (PAL), Reaction Time (RTI), Spatial Working Memory (SWM) and One Touch Stocking of Cambridge (OTS; Ba-Tin, Strike, & Tabet, 2011; Lasselin et al., 2012; Ryan et al., 2006; Saczynski et al., 2008). The tests which were included in this study and the order of test administration are described in Table 5.3 below with the test outcomes described in Table 5.4. The tests assessed a wide range of cognitive domains which together formed a long and demanding battery. The battery lasted on average 45 minutes, but may have been slightly longer or shorter depending on the participant's level of ability. CANTAB recommends a number of test outcomes (CANTAB (2012) test administration guide, manual version 5.0.0). However, many of these outcome measures are functions of each other (see Appendix A) and return the same results. Therefore, only non-duplicated outcome measures are considered in this thesis to reduce the type 1 error rate due to multiplicity of outcomes. Where applicable, outcome measures which have been recalculated using a different formula to CANTAB to permit appropriate analysis or expressed as proportion correct to this end, are reported as a footnote.

Table 5.3 The order of administration of the CANTAB tests, the cognitive domain (and subcomponents) assessed, and test duration

Test	Cognitive domain (subcomponents)	Mode of test	Test duration (minutes)
Motor Screening Test (MOT)	Motor Speed (Index of motor skill; speed and accuracy)	Clinical	2
Paired Associates Learning (PAL)	Memory (visual and new learning)	Clinical	5
Verbal Recognition Memory (VRM)	Memory (verbal; immediate free recall and recognition)	Clinical- immediate 18 words	7
Pattern Recognition Memory (PRM)	Memory (visual; immediate recognition)	Immediate	4
Rapid Visual Processing (RVP)	Attention and processing speed (vigilance, processing speed)	Clinical	7
Spatial Span (SSP)	Executive function (spatial working memory)	Clinical	6
Attention Switching Task (AST)	Executive function (cognitive flexibility)	Version 5.0.0 Press pad	7
Delayed Verbal Recognition Memory (VRM)	Memory (verbal; delayed free recall[28] and recognition)	Clinical- delayed 18 words	5
Delayed Pattern Recognition Memory (PRM)	Memory (visual; delayed recognition)	delayed	2
			45

[28] The delayed aspect of free recall is not available on CANTAB. Therefore, a pencil and paper version was included in the cognitive battery. Participants verbally recalled words into a digital voice recorder, and responses entered on a score sheet.

Table 5.4 CANTAB cognitive test outcomes measures

Cognitive Test	Outcome measures	Description
Motor Screening Test (MOT)	Total correct	The total number of correct responses made by the subject over the assessed trials in the test; higher is better
	Mean error	Measurement of accuracy. The mean distance between the centre of the cross and the location the subject touched on the screen; lower is better
	Reaction time for correct responses	Time taken to touch the cross after it appeared on the screen; lower is better
Paired Associates Learning (PAL)	Stages completed[29]	Key indicator in overall success, recording how many stages were successfully completed; higher is better. There are 8 stages: 2 stages locating one pattern (stages 1 and 2), 2 stages locating 2 patterns (stages 3 and 4), 2 stages locating 3 patterns (stages 5 and 6), 1 stage locating 6 patterns (stage 7), and 1 stage locating 8 patterns (stage 8)
	Stages completed on first trial[30]	Number of stages successfully completed on the first trial; higher is better
	First trial memory score[30]	Related to 'stages completed on first trial'. Number of patterns correctly located on the first trial, summed across the stages completed; higher is better
	Total trials[30]	Total number of trials taken to locate all the patterns correctly, summed across the number of stages completed; lower is better
	Proportion of total trials at n-patterns[31]	Related to 'total trials'. Proportion number of trials taken at n- patterns (1,2,3,6,8) to locate the required number; lower is better
	Total errors[30]	Total number of errors required to locate all the patterns correctly, summed across the number of stages completed
	Proportion of total errors at n-patterns[31]	Related to 'total errors'. Proportion number of errors made at n- patterns (1,2,3,6,8) to locate the required number

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[29]Progression through the stages on the Paired Associates Learning (PAL) test is dependent on ability. Participants only progress to the next stage if they successfully locate the required number of patterns within 10 trials. If, after 10 trials, the participant has not located the patterns correctly for that particular stage, the test terminates.

[30] This measure is affected by the number of stages completed. Therefore, 'stages completed' was added as a covariate in the analysis to control for this.

[31] A proportion of total trials for n-patterns were calculated because this outcome measure is affected by the unequal number of stages for each number of patterns (see 'stages completed' outcome measure). Calculating a proportion makes the within subject factor levels comparable in the ANCOVA/ANOVA.

Cognitive Test	Outcome measures	Description
Verbal Recognition Memory (VRM)	Number of correctly recalled words[32]	Total number of distinct words correctly free recalled from the presentation phase; higher is better
	Number of novel words (free recall)[32]	Total number of words recalled that did not appear in the presentation phase; lower is better
	Number of perseverations (free recall)[32]	Total number of times the subject repeats the recall of a previously correctly recalled word from the presentation phase; lower is better
	Number of correctly recognised target words[32]	Total number of words correctly recognised from the presentation phase; higher is better
	Number of false positives (recognition)[32]	Total number of times the subject responded 'yes' incorrectly to a distractor word; lower is better
Pattern Recognition Memory (PRM)	Number of correct patterns[32]	Total number of patterns correctly recognised
	Reaction time for correct patterns[32]	Mean time taken to respond (in milliseconds) to correctly recognised patterns
Rapid Visual Information Processing (RVP)	Total hits	Total number of occasions upon which the target sequence is correctly detected (within a response window of 1800 milliseconds); higher is better
	Total hits at each minute	Total number of occasions upon which the target sequence is correctly detected at each minute of the test
	Total false alarms	Total number of times the subject incorrectly detected a target sequence as a correct sequence; lower is better
	Total false alarms at each minute	Total number of times the subject incorrectly detected a target sequence as a correct sequence at each minute of the test
	Mean reaction time for hits	Mean time taken to respond (in milliseconds). Only includes correct responses made within the response window of 1800ms
	Reaction time for hits at each minute	Mean time taken to respond (in milliseconds) at each minute. Only includes correct responses made within the response window of 1800ms

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[32] Outcome measure applies to both the immediate and delayed aspects this test

Cognitive Test	Outcome measures	Description
RVP *continued*	A Prime (A')[33]	Sensitivity to the target, regardless of response tendency. Range from 0.00 to 1.00. A high detection rate with no false alarms would be indicated by an A' value of 1, while a low detection rate with many false positives would have a sensitivity of 0.
	B Prime (B')[33]	The tendency to respond regardless of whether the target sequence is present. Range 0.00 to +1.00. It is a measure of bias; a score of 1 reflects no bias, a score close to 1 indicates that the participant made few false alarms, while a value of 0 indicates constant key pressing (guessing) and therefore maximum bias.
Spatial Span (SSP)	Span Length[34]	Longest sequence successfully recalled; higher is better. Span lengths range from 2 (a sequence of two boxes changing colour) to 9 (a sequence of 9 boxed changing colour).
	Total numbers of attempts[35]	Total number of attempts made to successfully recall a sequence, summed across all span lengths.
	Numbers of attempts at each level (span lengths 2-9)	Number of attempts made for the span length specified. A maximum of 3 attempts can be made at any level; lower is better
	Mean time to first response[35]	Mean time taken to initiate recalling the sequence across all assessed span lengths. Reaction time measured from the end of the presentation phase until subject touches the screen to initiate recalling the sequence
	Mean time to last response[35]	Mean time taken to complete recalling the sequence across all assessed span lengths. Reaction time measured from the end of the presentation phase until the participant makes their final response on a given attempt
	Total errors[35]	Total number of times an incorrect box (wrong sequence order or not part of the sequence) is selected
	Total usage errors[35]	Number of times a box not in the sequence is selected; lower is better

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[33] CANTAB calculates this measure on a scale of -1 to +1. Participants score between 0 and +1, but if a participant correctly detects all of the target sequences and makes no false alarms, CANTAB scores this as -1. However, this is not suitable for data analysis. Therefore, this has been corrected so that participant scores are on a scale of 0 to +1.
[34] Spatial Span (SSP) starts at span length 2, and progression to the next span length is dependent on ability. If the sequence is correctly recalled on the first attempt, the participant advances to the subsequent span length. If after three attempts the participant has failed to successfully recall the sequence at that span length, the test is terminated.
[35] This measure is affected by the 'span length'. Therefore, 'span length' was added as a covariate in the analysis to control for this.

Cognitive Test	Outcome measures	Description
Attention Switching Task (AST)	Total number of correct trials[36]	Total number of trials for which the trial outcome was a correct response; higher is better
	Total number of commission trials	Total number of trials where a participant responded too soon, either prior to the end of the pre-empt window or prior to the appearance of the stimulus; lower is better
	Total number of omission trials	Total number of trials where the participant responded too late, after the end of the response window; lower is better
	Reaction time for correct trials[37]	Reaction time of response (from stimulus appearance to button press) for correct trials; lower is better
	Congruency cost	Subtraction of the reaction time for correct congruent trials from the reaction time for correct incongruent trials. A positive score indicates the subject is faster on congruent trials and a negative score indicates that the subject is faster on incongruent trials
	Switch cost	Subtraction of the reaction time for correct switched trials from the reaction time for correct non-switched trials. A positive score indicates that the subject is faster on non-switched trials, and a negative score indicates that the subject is faster on switched trials.

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[36] Total correct trials can be further analysed by type of trial (number of correct direction and side trials), congruency (number of correct congruent and incongruent trials) and switching (proportion of switched and non switched trials). There were an unequal number of switched and non-switched trials and therefore a proportion of correct switched and non switched trials were calculated to adjust for this CANTAB error.

[37] Reaction time can be further analysed by type of trial (reaction time for number of correct direction and side trials), congruency (reaction time for number of correct congruent and incongruent trials) and switching (reaction time for number of switched and non switched trials). No correction can be applied to reaction time data to adjust for the unequal number of switched and non switched trials.

5.2.3.2.2 Piloting of the cognitive tests

During the study design phase, the cognitive tests were piloted on a CF research nurse working on the Leeds Adult CF Unit. She was approached to give her opinion about the tests and test difficulty due to her patient awareness and knowledge of ability of the patients registered to the Leeds Unit. As some patients suffer from sight and hearing problems, either as a result of their condition or treatment, it was important to consider this with regards to the stimuli used. Based on feedback, it was agreed that the font size in the word tests, the loudness of the tone played during the tests to signal participant response, the pace of the tests in general and the duration of the test battery were appropriate for people with CF.

5.2.3.3 **Descriptions of each cognitive test included in the battery**

This section describes the cognitive tests which were chosen for inclusion in the cognitive test battery.

5.2.3.3.1 Motor Screening Test (MOT)

This test assesses difficulties in vision, movement and comprehension. It introduces the participant to the CANTAB system and the touch screen aspect. CANTAB advise that it is always completed at the beginning of a test session. A series of 10 crosses appear in different locations on the screen one at a time (see Figure 5.2). The task of the participant is to touch the centre of each cross as quickly as possible with their dominant hand whilst it is alternatively flashing pink and green. If it is touched properly, the cross disappears and a sound is played. If the cross is not touched properly, it will stay on the screen and no sound will be played. Reaction time is recorded in milliseconds.

Figure 5.2 Motor Screening Test: An example of a cross

5.2.3.3.2 Paired Associates Learning (PAL)

This test assesses visual memory and learning. White boxes, with a pattern contained behind some of them, are displayed on the screen, and open up in a randomised order (see Figure 5.3). Patterns are displayed for 3200 milliseconds. Once all boxes have been opened, the patterns which were displayed in the boxes appear in the middle of the screen. The task of the participant is to touch the box where the patterns were located. If an error is made, the patterns are re-presented where they were originally located (display duration 2200 milliseconds). As reported in Table 5.4, the test involves two stages of locating one pattern

(stages 1 and 2), two stages of locating two patterns (stage 3 and 4), two stages of locating three patterns (stage 5 and 6), one stage locating six patterns (stage 7) and one stage of locating 8 patterns (stage 8). The participant must correctly locate all the original pattern locations in a particular trial within 10 attempts otherwise the test is terminated
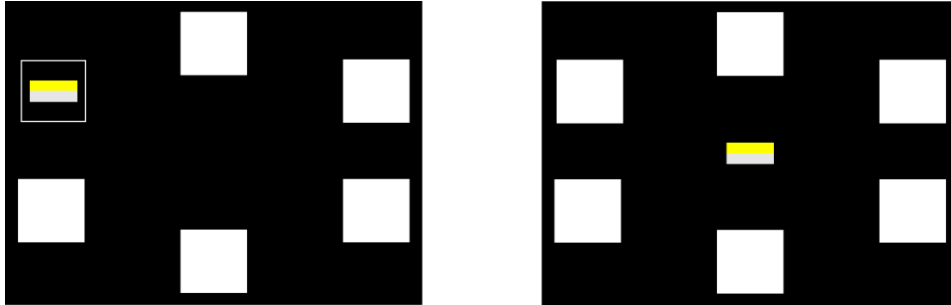
Figure 5.3. Paired Associates Learning Test: An example of a pattern being presented (left) and, once all the patterns have been presented, located in the middle of the screen, prompting the participant to locate where the pattern was displayed (right)

5.2.3.3.3 Verbal Recognition Memory (VRM)

This test assesses the immediate and delayed memory for verbal information. It is assessed under conditions of free recall (recall of words in any order) and forced choice recognition (responding with yes or no as to whether a word was in the word list which participants had to remember). During the presentation phase, the participant is shown a word list of 18 words in the centre of the screen, one at a time for 3 seconds, with a 2 second delay in between words (see Appendix B for word list). Participants are required to read each word aloud once and remember as many words as possible (see Figure 5.4). Reading the words aloud ensures the participant does not try to remember a word not in the list due to reading error; any incorrectly remembered words may produce novel words during the free recall task.

5.2.3.3.3.1 VRM- Immediate

Once all 18 words have been presented, the screen is turned away from the participant. At this point, the participant is subsequently required to freely recall as many of the words as possible in one minute, and the researcher records these responses on the CANTAB programmed response sheet. After the minute has elapsed, the screen is then turned back to face the participant and they are instructed to identify, from a list of 36 words (18 target and 18 distractor), which words were presented in the presentation phase (see Figure 5.4). There is no time limit for participant response on the recognition task.

Figure 5.4 Verbal Recognition Memory: An example from the word presentation phase (left) and recognition phase (right)

5.2.3.3.3.2   VRM- Delayed

After a 30 minute delay, during which other tests were performed (see Table 5.3), the participant is asked to verbally and freely recall as many of the list of 18 words they can remember from the presentation phase, in a minute, without seeing the words again. The delayed aspect was scored on a score sheet as the delayed aspect is not programmed into CANTAB. Participants are then required to recognise which words were shown in the presentation phase from another list of 36 words (18 target and 18 distractor). The 18 distractor words are different to those presented in the immediate recognition task. There is no time limit for participant response on the recognition task.

5.2.3.3.4   Pattern Recognition Memory (PRM)

This test assesses visual pattern recognition memory in a two-choice forced discrimination paradigm. Twelve patterns, which cannot be verbalised (see Figure 5.5), are shown one at a time, in the centre of the screen, at a pace of every 3 seconds.

Figure 5.5 Pattern Recognition Memory: An example of the presentation phase (left) and recognition phase (right)

5.2.3.3.4.1   PRM- Immediate

In the immediate tasks, a set of 12 patterns is presented in the centre of the screen one at a time. The participant is subsequently asked to recognise the stimuli when presented with distractors in a two choice forced paradigm. There are 3 phases in the immediate model; first presentation phase, first forced choice recall phase (see Figure 5.5), and the second

presentation phase (different stimuli to the first presentation phase). There is no time limit for participant response on the recognition task.

5.2.3.3.4.2 PRM- Delayed

After a 30 minute delay, the participant is required to recognise the patterns shown in the second presentation phase when shown with additional distractors. The distractors are different to those presented in the immediate (first) forced choice recall phase. There is no time limit for participant response on the recognition task.

5.2.3.3.5 Rapid Visual Processing (RVP)

This is a test of visual sustained attention. Single digits, ranging from 2-9, are presented inside a white box in a pseudo-random order at a rate of 100 digits per minute. The task of the participant is to detect target sequences of 3 digits, and press the right button on the response box when they have seen the last number of the sequence. There is a practise phase lasting 2 minutes, and an assessed phase lasting 4 minutes. In the practise phase, participants are instructed to find the target sequence of 3-5-7, initially with the help of cues (see Figure 5.6). Digits appear in white, but when the target sequence is presented (i.e. 3 is immediately followed by 5, immediately followed by 7), numbers are coloured red, underlined in yellow and an instruction of 'press now' appears on the screen instructing the participant to press the button on the response box to record a hit i.e. a correct detection. As the practise phase advances, the cues disappear and the test resembles the assessed phase. In the assessed phase, numbers are only presented in white and there are no cues as to when the target sequences will appear. Participants have to detect three pre-set target sequences: 2-4-6, 3-5-7, and 4-6-8. There are a total of 36 target sequences in the assessed phase (9 target sequences per minute).
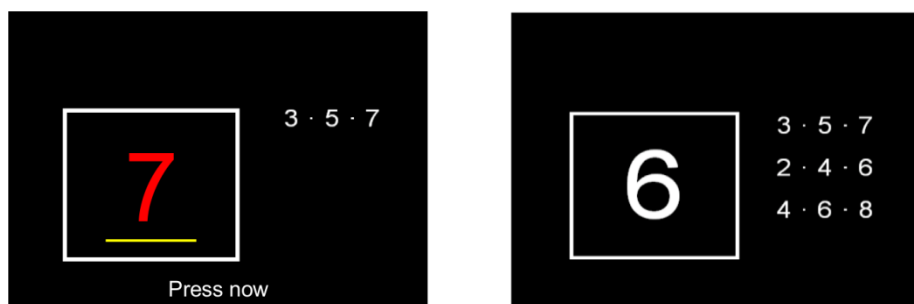
Figure 5.6 Rapid Visual Processing: An example of the practice phase (left) and assessed phase (right)

The principles of Signal Detection Theory (Stanislaw & Todorov, 1999) can be applied to RVP. The optimal pattern of response on the RVP test is to maximise sensitivity so that no target sequences are missed (i.e. 100% hit rate; detecting 36 target sequences) or false alarms committed. Participants who place more importance on speed than accuracy tend to be less accurate in detecting target sequences and making correct rejections (not responding to stimuli which are not part of any target sequences). Measures of A prime (A')

and B' prime are included within this thesis. A' refers to a participant's sensitivity to detecting the target, regardless of response tendency (see Table 5.4). B' refers to the tendency to respond regardless of whether the target sequence is present.

5.2.3.3.6 Spatial Span (SSP)

This test assesses working memory capacity. It is a computerised version of the Corsi Block Tapping Test and a visuospatial analogue of the Digit Span test. A pattern of white boxes is displayed on the screen with a number of boxes (ranging from 2 to 9) turning a different colour one at a time (see Figure 5.7). Within a span length, each box changes colour for 3000 milliseconds. The task is for the participant, when instructed by a tone, to click on the boxes in the order that they changed colour as quickly as possible. The test starts at span length 2 (two box sequence to recall). The subject has three attempts at each level. If the sequence is correctly recalled on the first attempt, the participant advances to the subsequent span length (number box sequence). If after three attempts the participant has failed to successfully recall the sequence at a particular span length, the test is terminated.
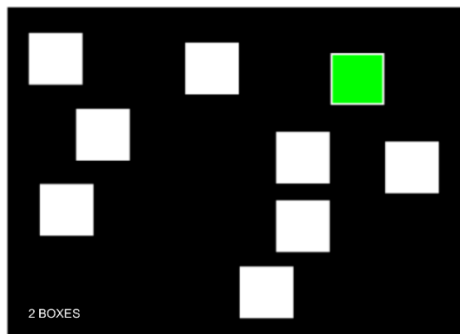
Figure 5.7 Spatial Span: An example of a 2 box sequence being presented

5.2.3.3.7 Attention Switching Task (AST)

This test assesses cognitive flexibility. An arrow, pointing either left or right, appears in either the left or right hand side of the screen on each trial. The participant is directed by a rule as to what they should attend and respond to; either the direction of the arrow, or the side of the screen where the arrow is displayed. There are 4 practise stages and one assessed stage. These range from the participant being instructed to respond to the direction of the arrow when it is placed in the centre of the screen (stage 1), then to the direction of the arrow when it is placed either side of the screen (stage 2), then to which side the arrow is on (regardless of the direction of the arrow; stage 3), then to respond to either the side the arrow is displayed or the direction of the arrow as cued (stage 4; see Figure 5.8). The assessed stage (stage 5) follows the same procedure as stage 4. There are 160 assessed trials.
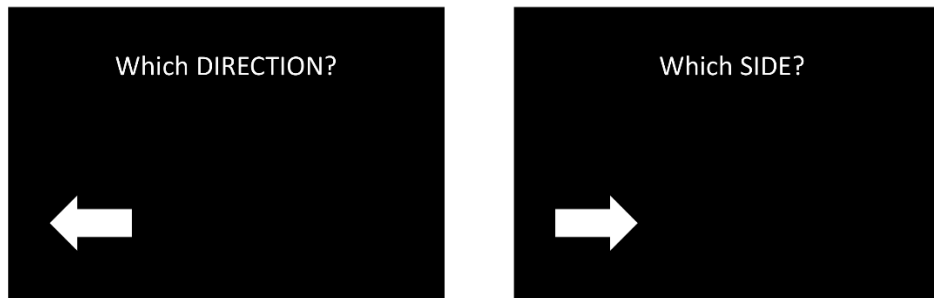
Figure 5.8 Attention Switching Task: An example of the two rules

Within the 160 trials, trials can be switched (n=80+/-10% trials; rule differs to previous trial) or non-switched (n=80+/-10% trials; rule is the same as the previous trial), and congruent (n=80; arrow is on the same side as the direction it is pointing; see Figure 5.8, left) or incongruent (n=80; arrow is on one side but pointing in the opposite direction; see Figure 5.8, right). Task difficulty is increased by including congruency as a factor, with incongruent trials being more difficult.

5.2.4   Questionnaires

Potential confounding variables and subjective sensations relevant to the study were monitored at the testing session using questionnaires. Responses were recorded using pencil and paper.

5.2.4.1   Leeds Sleep Evaluation Questionnaire (LSEQ) - adapted version

Glycaemic response and cognitive function can be affected by sleep quality (Morgan, Hampton, Gibbs, & Arendt, 2003). Hence subjective sleep quality was measured using an adapted version of the Leeds Sleep Evaluation Questionnaire (LSEQ; Parrott & Hindmarch, 1978). Eight of the original 10 questions were used, and sleep quality was measured using visual analogue scales (VAS). Participants were asked to give their answers to questions concerning sleep by drawing a vertical mark on a 100mm horizontal line anchored at each end by two extreme descriptors. For example, for the question of 'In a typical night, how EASY was it to get to sleep?' the descriptors used were 'very easy' (on the left, score = 0) and very difficult (on the right, score 100). The distance (mm) of the vertical line from the left descriptor was measured using a ruler, yielding a score in the range of 0-100. The LSEQ was adapted to measure sleep quality from the previous night's sleep (see Appendix C) and over the last week (see Appendix D), respectively, using the same method. A lower score indicated better sleep quality.

5.2.4.2   Perceived stress scale (PSS-10)

Research has suggested that stress has effects on cognitive function (McEwen & Sapolsky, 1995). Hence stress was measured using the Perceived Stress Scale-10 (PSS-10; Cohen, Kamarck, & Mermelstein, 1983). Participants answered various questions to determine how stressed they have felt by using semantic differentials for the past month (see Appendix E).

Possible responses were between 0 – 4, with 0 corresponding to 'Never', 1 'almost never', 2 'sometimes', 3 'fairly often and 4 'Very Often', to answer the questions. The questionnaire was also modified into a weekly version (see Appendix F). Scores on each questionnaire were summed taking into account reversed items, and a constant added, to provide a total perceived stress score for the month and week respectively on a scale from 0-34. A higher score indicated higher stress.

5.2.4.3 Hospital Anxiety and Depression Scale (HADS)

Severity of depression and anxiety can influence cognitive functioning as mentioned in section 5.1 and Chapter 3 (sections 3.3.2 and 3.3.3.4.2). Levels of depression and anxiety were assessed using the HADS (Zigmond & Snaith, 1983; see Appendix G). This questionnaire is designed specially for people with chronic diseases. It does not include items which relate to somatic symptoms such as fatigue and trouble sleeping, which individuals with chronic diseases are likely to experience (Quittner et al., 2008). The HADS consists of 14 questions; 7 for anxiety and depression respectively. Participants completed the questionnaire based on how they have felt in the past week. It takes on average 2-5 minutes to administer. Participants chose from possible answers on a 4 point scale. For example, for the statement of 'I feel tense or wound up', responses ranged from 'most of the time' to 'no, not at all' to indicate the experiencing each symptom. Scores on each scale can be interpreted in ranges: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) anxiety and depression.

5.2.4.4 Ratings of mood and mental Alertness

Cognitive function correlates highly with, and can be affected by, mood states (Blaney, 1986; Bolmont, Thullier, & Abriani, 2000). Therefore, it is important to measure subjective mood states when assessing cognitive function. Just before completing the cognitive tests, ratings of contentedness, irritability, sleepiness, mental alertness and feeling energetic were measured using VAS (see Appendix H). Participants responded to each item by placing a vertical line through the horizontal line to indicate the intensity of the subjective sensation, between the descriptors of 'not at all' (score of 0) to 'very' (score of 100). The sensations were then scored in the same way as for the LSEQ (see section 5.2.4.1).

5.2.4.5 Cognitive test evaluation questionnaire (CTEQ)

Ratings of subjective performance and mental effort in relation to the cognitive tests were completed after the test battery (see Appendix I) using VAS adapted from the NASA TLX (Task Load Index) mental workload measure (Hart & Staveland, 1988). For example, 'How much did you concentrate during these tests?' with the descriptor of 'a small amount' on the left (score of 0) and 'a large amount' on the right (score of 100). Scoring followed the same procedure as the LSEQ (see section 5.2.4.1). Participants also identified the test which they found to be the most and least difficult.

5.2.4.6 **Cognitive Failures Questionnaire (CFQ)**

The Cognitive Failures Questionnaire (Broadbent, Cooper, FitzGerald, & Parkes, 1982) is a measure of self reported failures occurring in everyday life. Participants report how often errors in perception, memory and motor function (i.e. minor daily cognitive errors) have happened to them within the past 6 months (see Appendix J). For example, 'Do you find you forget whether you've turned off a light or a fire or locked the door?', 'Do you find you confuse right and left when giving directions?' and 'Do you find you forget appointments?' A higher score indicates a higher amount of subjective minor daily cognitive errors occurring, with a maximum score of 100.

5.2.4.7 **Debriefing Questionnaire**

A debriefing questionnaire (see Appendix K) was given at the end of the testing session before participants were verbally debriefed. It asked questions such as 'Why did you decide to take part in the study?', 'During the study was there anything in your personal life which may have affected your performance (e.g. concentration) on any of the tests of mental performance?' and 'Did the tests make you think about your memory and/or attention in day-to-day life?'

5.2.5 Physiological Measures

Blood glucose and carbon monoxide levels were measured during the testing session.

5.2.5.1 **Blood glucose (mmol/L)**

Participants were asked to fast for two hours before the testing session because blood glucose levels can affect cognitive performance (see Chapter 3, section 3.3). A single blood glucose measurement was taken using a GlucoMen® LX blood glucose meter (A. Menarini Diagnostics Ltd) using the capillary finger prick blood glucose technique. Finger prick capillary blood samples using a GlucoMen® Meter have been shown to have good correspondence with plasma blood glucose measured from arterialised venous samples (Dye et al., 2010). The coefficient of variance for reference venous whole-blood samples in the range 2·1–22·0 mmol/l are 0–4·3%. The GlucoMen® LX system is calibrated with venous plasma values using a Yellow Springs 2300 glucose analyzer, and shows very good accuracy when tested by hexokinase method on a Roche laboratory analyser, according to the manufacturer's information. The finger prick testing kit underwent regular laboratory calibration checks.

People with CF were required to have a blood glucose level which was ideally euglycaemic, but definitely lower than 12mmol/L. People with CF experience delayed insulin secretion in response to a glucose load irrespective of glucose tolerance (see Chapter 1, section 1.4) and this can be exacerbated by factors such as PEs (see Chapter 1, section 1.4.2.1). Furthermore, some patients from the Leeds CF Unit have poor glucose control and either cannot safely achieve a blood glucose level in the normal range or choose to have their blood glucose levels in the hyperglycaemic range (A Morton, personal communication).

Therefore, a cut-off of 12 mmol/L was used. If a patient's blood glucose was higher than the cut off value, the testing session was either delayed until their blood glucose was lower than 12mmol/L or rescheduled. Participants in the control group were required to have a blood glucose level within the normal range. After a 2 hour fast, this would be expected, and a result above 7.8 mmol/L may indicate impaired blood glucose tolerance or failure to comply with fasting. This did not occur at any point throughout the study; all values were <7.8mmol/Ĺ. If any participant was hypoglycaemic at the time of testing, a snack and drink were to be provided to restore their blood glucose levels to within the normal range and they were withdrawn from the study. This did not occur at any point throughout the study. The finger prick blood glucose standard operating procedure (SOP) details the step-by-step procedure (see Appendix L) and was explained to all participants before consenting.

5.2.5.2 Carbon monoxide (CO)

Research has shown that the exhaled carbon monoxide levels of people with CF who are in a stable condition are higher compared to those of healthy, non-smokers, and even higher in those suffering from a PE (Antuni, 2000). Furthermore, despite having a chronic respiratory disease, there are some patients registered to the Leeds CF Unit who smoke cigarettes. Smokers were not excluded but were required not to smoke for the two hours before the testing session. Carbon monoxide levels were monitored in all participants using the Micro+ Smokerlyzer gold standard CO breath test monitor (Bedfont Micro+ advance package Smokerlyzer). This equipment detects breath carbon monoxide which is measured in parts per million (ppm; COppm) and blood carboxyhaemoglobin which is measured as a percentage (%COHb). COppm relates to inhaled CO, both the amount of CO in the lungs and on the breath. COHb is when CO has been inhaled, and CO has displaced oxygen in the bloodstream. Values between 0-6ppm indicated a non-smoker, 7-9ppm were borderline, and over 10ppm indicated signs that people were a smoker.

5.2.6 Procedure

5.2.6.1 Screening

5.2.6.1.1 People with CF

People with CF registered to the Leeds Adult Unit were screened against the inclusion and exclusion criteria (see section 5.2.2.1 and 5.2.2.2) with the assistance of either a CF specialist clinical dietitian or a research nurse using EMIS (Egton Medical Information Systems; the CF electronic patient register). The clinical staff advised whether it was a suitable time to approach a patient about taking part in the study i.e. whether the person was going through any personal issues or health issues which could have affected their ability to complete the testing. People with CF were approached either as an inpatient or outpatient and given an information sheet explaining who the chief investigator was (see Appendix M) and a Participant Information Sheet (PIS) for patients with CF (see Appendix N). They were made aware that there were no consequences to their clinical care whether they participated or not and informed about the possibility of their unaffected family

members or friends taking part in the control group in the PIS. People with CF were given at least 7 days to consider the information, ask questions and to express their interest in the study.

If people with CF agreed to take part in the study, written informed consent was obtained (see Appendix O) and a RIQ which asked for their information such as demographic (including age, education level, occupation, postcode to calculate a Townsend score, occupation), health (relevant CF gene mutation, height, weight, BMI, subjective health rating, diabetes diagnosis and insulin therapy) and behaviour (e.g. smoking behaviour, caffeine consumption, physical activity levels) was completed. Townsend score is a measure of material deprivation based on a participant's postcode and used as an indicator of SES in this study. The score is calculated from rates of unemployment, household overcrowding, non car- and non home ownership in an area. Other clinical characteristics were collected from EMIS: age at CF diagnosis (years), FEV_1, FEV_1%predicted, FVC, FVC% predicted, pulse, SBP, diastolic blood pressure (DBP), oxygen saturation level, HbA1c (International Federation of Clinical Chemistry (IFCC) measurement), CRP, year of CFRD diagnosis, OGTT history, vitamin A, D, and E, serum creatinine and urea (indicators of renal disease), albumin (indicator of liver disease), and gene mutation if unknown to the patient.

5.2.6.1.2 Healthy control group

Participants in the control group were recruited through the partners and relatives of patients with CF, and the general population (posters, leaflets and School of Psychology Participant Pool scheme, University of Leeds; a mailing list of people willing to participate in psychological research). Both methods of recruitment were used as it was thought an appropriately matched sample of healthy controls may not be realistically recruited through people with CF. If interested, healthy controls were given a Participant Information Sheet (PIS) with information about the study (see Appendix P). The healthy controls completed the testing in the Human Appetite Research Unit (HARU) within the School of Psychology, University of Leeds. If the control participant was known to a person with CF, they had the option of completing the testing whilst the person with CF completed their health assessment providing if this did not affect the running of the CF clinics (i.e. not using an outpatient room needed by a patient). Inclusion and exclusion criteria were checked following the completion of the relevant questions on the RIQ (see Appendix Q) to confirm they were a match to people with CF on gender, age and educational level. If they were a match, written informed consent was obtained (see Appendix R) and the remaining questions on the RIQ were completed: demographic (including age, education level, postcode to calculate a Townsend score, occupation), health (height, weight, BMI, subjective health rating, medication history) and behaviour (e.g. smoking behaviour, caffeine consumption, physical activity levels).

5.2.6.2 **Testing Session**

For people with CF, the testing session was arranged at a time convenient to them. Ethics was initially approved for testing to coincide with one of their clinic appointments or during

their stay if they were an inpatient. A subsequent submission to the NHS ethics committee allowed testing to take place at a patient's home either to reduce the inconvenience of having to extend their hospital appointment or to allow them to fit taking part in around their family and work commitments. Testing therefore took place either in the morning or afternoon, and the time of day was recorded. For the control participants, their session was arranged at a time convenient to them, but where possible, arranged so that testing took place at the same time of day as the patient they were matched to.

The procedure for each testing session was the same regardless of participant group (see figure 5.9). The informed consent of each participant was obtained in writing prior to commencement of the study. Participants completed questionnaires relating to sleep quality, perceived stress, and mood and mental alertness. Physiological measures (carbon monoxide and blood glucose) were then collected. During clinic appointments, patients routinely have their blood glucose measured. If it was measured near the time of the testing procedure, this reading was used to avoid the patient having it done twice in quick succession. The cognitive testing took approximately 45 minutes to complete (see Table 5.3). After the cognitive testing, participants completed the CTEQ, CFQ and finally the debriefing questionnaire. All participants received a £10 Love2Shop Voucher for participating. Travel expenses were also reimbursed (up to the value of £10) for controls, and for people with CF if testing was completed on the Unit outside of their allocated appointment (i.e. if it was not feasible to complete it during their routine appointment, and if participants preferred not to complete it at home).

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┌─────────────────────────────────────────────┐      ┌──────────────┐
│        Written informed consent obtained     │──┐   │ Recruitment  │
└─────────────────────────────────────────────┘  │   │     and      │
                                                  │   │  screening   │
┌─────────────────────────────────────────────┐  │   │    visit     │
│   Recruitment Information Questionnaire (RIQ) │──┘   └──────────────┘
└─────────────────────────────────────────────┘
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┌─────────────────────────────────────────────┐
│    LSEQ (Typical night's sleep last night)   │──┐
│  LSEQ (Typical night's sleep over past week) │  │
│    PSS-10 (Perceived stress over past week)  │  │
│   PSS-10 (Perceived stress over past month)  │  │
│                    HADS                      │  │
│   VAS Ratings of mood and mental alertness   │  │
└─────────────────────────────────────────────┘  │
                      ↓                           │
┌─────────────────────────────────────────────┐  │
│   Finger prick blood glucose measurement taken│ │
│        using a GlucoMen® LX meter            │  │
└─────────────────────────────────────────────┘  │
                      ↓                           │
┌─────────────────────────────────────────────┐  │   ┌──────────────┐
│     Carbon monoxide level measured using a   │  │   │              │
│                Smokerlyzer                   │  │   │   Test day   │
└─────────────────────────────────────────────┘  │   │              │
                      ↓                           │   └──────────────┘
┌─────────────────────────────────────────────┐  │
│   Cognitive test assessment using CANTAB     │  │
│             (7 tests in total)               │  │
└─────────────────────────────────────────────┘  │
                      ↓                           │
┌─────────────────────────────────────────────┐  │
│                    CTEQ                      │  │
│                    CFQ                       │  │
│           Debriefing Questionnaire           │  │
└─────────────────────────────────────────────┘  │
                      ↓                           │
┌─────────────────────────────────────────────┐  │
│     Debriefed and compensated with a £10     │  │
│              Love2Shop Voucher               │  │
│                                              │  │
│ Travel expenses (up for £10) paid for controls and│
│          people with CF if required          │──┘
└─────────────────────────────────────────────┘
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Figure 5.9 Study 1 flow diagram to indicate the order of screening and test day procedures

5.2.7 NHS Ethical Approval

This study was approved by the Leeds West NHS Research Ethics committee (REC) on 20th August 2013 (REF: 13/YH/0219). Approval from Leeds Teaching Hospitals NHS Trust Research and Development (R&D) was gained on 22nd August 2013. Following approval

from both NHS REC and R&D, the study was added to the National Institute for Health Research Clinical Research Network (NIHR CRN) Portfolio database.

An amendment was subsequently submitted on 26th September 2014 to allow testing to be performed in patients' homes (i.e. home visits) as an option instead of a hospital setting (inpatient or outpatient). This amendment was approved on 6th October 2014 and R&D study approval was subsequently gained on 27th October 2014.

At screening, participants were given written and verbal information about the purpose of the study, and all procedures involved including the capillary finger prick blood glucose technique, and what was required of them during participation. Participants were made aware they could withdraw at any point without having to give a reason. It was made explicit to people with CF that withdrawing from the study had no consequences to their clinical care. The informed consent of each participant was obtained in writing prior to commencement of the study.

There was the risk of hypoglycaemia occurring on the test day, particularly in some people with CF due to fasting for two hours and glucose tolerance being affected by factors in CF such as PEs. As control participants who did not have any known glucose tolerance normalities or diabetes were recruited, the risk of hypoglycaemia was lower in this participant group. If hypoglycaemia was detected (<3.9mmol/L) or symptoms were reported by a participant, food and drink were immediately provided to restore a person's blood glucose level to within the normal range and they were withdrawn from the study. This did not happen at any point during the study.

5.2.8   Statistical analysis

5.2.8.1   Power analysis

There are approximately 400 people registered to the Leeds Regional Adult CF Unit. However, it was acknowledged that not all these people would be eligible to take part in the study (e.g. PS, post-transplant, diabetic but not taking insulin etc.). An a priori power calculation was performed to consider how many people with CF would be needed to power the experiment in order to detect any cognitive dysfunction. The calculation was performed in collaboration with an independent statistician (Quadt Consultancy BV, The Netherlands).

As CANTAB had been chosen as the cognitive test system, the CANTAB bibliography was initially searched. Initially the study by Ba-Tin, Strike, and Tabet, (2011) was chosen due to its similar sample (clinical diabetic population (T1DM and T2DM) compared to a healthy control group), and it had used four of the seven tests chosen for inclusion in this study. However, the data were log transformed, and presented using median scores and percentiles. Despite communication with several of the authors, the means and standard deviation for the data were not obtained. However, Ba-Tin et al., (2011) stated in their paper that power was calculated for a 10% shift in median value. As transforming the data, in theory brings the median and mean closer to the same value, it was decided to use a 10% shift applied to the transformed averages as a definition of the difference between groups.

Papers were sourced to find an estimate of the mean and standard deviation for the healthy control group. Three papers were selected from the CANTAB bibliography. Values for the PRM test calculation were taken from Lasselin et al., (2012). Not only did this paper differentiate between different types of diabetes (T1DM and T2DM), it also separated the people with T2DM as to whether they were on insulin therapy or not. SSP test normative values were taken from De Luca et al., (2003). Finally, values for the PAL test power calculation were taken from Collie, Maruff, and Currie, (2002). This paper investigated the pattern of cognitive dysfunction in people with MCI relative to a healthy control group. Cognitive function in MCI was found to be most impaired on the PAL test compared to controls, and participants with MCI were not aware of this deficit.

The outcome measure of PRM was chosen as the primary outcome measure on which to base the power calculation. The power calculation indicated that 33 participants would be required in each group, based on a one-sided test, in order to detect a difference of 5% on the number of correct patterns at the immediate forced choice recall phase on the PRM test (see Appendix S). As there are approximately 110 people with CFRD on insulin therapy registered to the Leeds Adult CF Unit, it was decided to aim to recruit approximately 50% of these patients in order to have a representative sample. Therefore, we aimed to recruit 50 people with insulin treated CFRD, 50 people with CFND and 50 healthy controls.

5.2.8.2 Method of analysis

Cognitive test data were extracted from CANTAB, entered into Excel and checked for accuracy. The delayed VRM data were recorded on a score sheet for each participant's session prior to entry into Excel, where it was checked. All subjective data were scored, entered and checked for accuracy in Excel.

The analytical approach was reviewed by the independent statistician (Quadt Consultancy BV, NL). A p-value of .05 was considered statistically significant. P values below 0.1 were considered trends. All data were analysed using SPSS version 22.0 (IBM Corp Inc., Armonk, NY, USA) or SAS 9.4 (SAS Institute Inc, IL, USA) as appropriate. All plotted data represent individual data points and means unless otherwise stated. Where data were transformed in order to normalise the distribution of residuals, the raw data scores are plotted for clarity.

Participant characteristic data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Analysis of participant characteristics was performed to test for adequate matching between all 3 groups in terms of age, using between subjects one-way ANOVAs with participant group as the between subjects factors, and gender and education using a Chi squared for frequency data or Fisher's Exact test (when the expected cell frequencies were small). Groups were also compared on Townsend score, height, weight, BMI, health rating, capillary finger prick blood glucose, carbon monoxide (COppm and %COHb), anxiety, depression and cognitive failures data. The two groups of people with CF (CFND and CFRD) were compared on age at CF diagnosis, FEV_1, FEV_1%predicted, FVC, FVC%predicted, oxygen saturation, HbA1c, SBP, DBP, pulse, CRP, vitamins A, D

and E, serum creatinine, serum urea, and albumin. Chi-Square or Fisher's Exact tests were also used to compare the two CF groups for occurrence of F508del mutation, microbiology and the number of people receiving IV treatment at the time of testing.

Cognitive data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Accuracy data is often negatively skewed and therefore a either a square root logarithm, or inverse transformation was applied depending on the severity of the skew (and a constant added where the data contained zeros). Reaction time data is often positively skewed and a square root transformation was applied. All reaction time analysis was for correct responses only.

Univariate ANOVA's were performed on the cognitive test data using group as the between subjects factor. Age varied across the three groups, with CFRD being older as a function of disease status. Thus age was included as a covariate to improve model fit. On tests where progression through the different stages/levels of the test was dependent on participant ability, other covariates were added where appropriate. For example, on the PAL test, stages completed was added as a covariate for outcome measures of stages completed on the first trial, total trials and total errors; on the SSP, span length was added as a covariate for the outcome measures of total number of attempts, reaction time and errors. Standardised residuals greater than (+/-) 3 were considered outliers and the analysis was repeated excluding these participants. If age was not a significant covariate, the analysis was re-run without the covariate. The final model was considered to be the model which explained the greatest proportion of the variance. If covariates were not included in the final model, and the homogeneity of variance was violated for the one way ANOVA, the Welch F statistic (Welch, 1951) was calculated. In this instance, it is denoted with 'Wadj' before reporting the F values. However, the original F value is reported where one group has zero variance and a Welch F statistic cannot be calculated.

Where other factors were added, as appropriate for each cognitive test, a mixed ANOVA was calculated in SAS. This is because SAS takes into account missing values which are often present when analysing cognitive data by level. For example: for the proportion of errors produced, and trials taken, locating each number of patterns on the PAL, the factor 'pattern' with 5 levels (patterns 1,2,3,6 and 8) was included in the ANOVA as a repeated measures factor; for hits, false alarms and reaction time at each minute on the RVP, the factor 'minute' with 4 levels (minute 1,2,3,4) was included in the ANOVA as a repeated measures factor (see sections 5.2.3.3.2, and 5.2.3.3.5). Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS and confidence intervals examined to determine within factor differences where interactions were significant. In SAS Tukey-Kramer adjustment was used to correct for familywise type 1 error (Roberts & Russo, 1990).

Univariate ANOVA's were performed on the subjective data in SPSS using group as the between subjects factor with age as a covariate since this differed significantly between groups. Subjective data were checked for homogeneity of variance and skewness and

appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). If Mauchley's test of Sphericity was significant, a correction was applied, and the Sphericity assumed degrees of freedom are reported. If the Greenhouse Geisser estimate of Sphericity (ε) was below .75, Greenhouse-Geisser was reported (denoted by GGadj before reporting the F values) and if ε was above .75, Huynh-Feldt was reported (denoted by HFadj before reporting the F values). Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS and confidence intervals examined to determine within factor differences where interactions were significant.

5.3 **Results**

5.3.1 **Participant Characteristics**

Table 5.5 below shows the participant characteristics for CFRD, CFND and healthy control groups and Table 5.6 shows the clinical characteristics of people with CF.

Table 5.5 Study 1. Participant characteristics (CFRD, CFND and healthy controls) at screening

	CFRD group n=49 Mean (SE)	CFND group n=49 Mean (SE)	Healthy control group n=49 Mean (SE)	F (2,144)	p value	η_p^2
Gender (n = males)	30	23	24		.31[38]	
Age (years)	32.10 (1.03)	27.33 (1.00)	31.12 (1.23)	5.33	.006	.069
Education (n= degree or higher)	16	11	15		.92[39]	
Occupation (n= employed full time)	12	14	31		<.001[40]	
Townsend	-.65 (.37)	-.34 (.38)	.36 (.53)	1.19	.31[41]	.02
Height (cm)	168.34 (1.18)	166.22 (1.20)	170.38 (1.45)	2.16	.08	.04
Weight (kg)	66.19 (1.85)	62.56 (1.83)	70.48 (1.78)	4.75	.010	.06
BMI (kg/m^2)	23.28 (.57)	22.52 (.52)	24.08 (.44)	.871	.10	.03
Health rating (1-10)	6.61 (.25)	6.75 (.27)	7.73 (.18)	5.06	.008[42]	.07
Blood glucose (mmol/L)	7.9 (.30)	6.2 (.19)	5.7 (.09)	28.42	<.001[43]	.31
COppm	3.53 (.19)	3.73 (.26)	3.16 (.22)	2.49	.09[44]	.03
%COHb	1.21 (.03)	1.24 (.04)	1.16 (.03)	1.75	.18[44]	.02
Anxiety score	6.31 (.57)	6.17 (.54)	5.35 (.46)	.932[20]	.38[45]	.01
Depression score	4.24 (.50)	4.02 (.50)	2.35 (.41)	4.91	.009[45]	.06

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[38] Chi Square test, χ^2(2, N=147) = 2.35, p = .31
[39] Fishers Exact test, χ^2(14, N=147) = 8.08, p = .92
[40] Chi Square test, χ^2(12, N=147) = 36.98, p < .001
[41] Assumption of homogeneity of variance was violated; the Welch F-ratio is reported. F(2, 94.11) = 1.19, p = .31
[42] Data were reverse and logarithm transformed due to substantial negative skewness; F, p and η_p^2 are reported on the transformed data. For clarity, means (SE) are raw data.
[43] Assumption of homogeneity of variance was violated; the Welch F-ratio is reported. F(2, 80.93) = 28.44, p < .001
[44] Data were logarithm transformed due to substantial positive skewness; F, p and η_p^2 are reported on the transformed data. For clarity means (SE) are raw data
[45] One person did not complete the HADS. Results are based on: CFRD n = 49, CFND n = 48, Controls n = 49; df(1, 143)

Table 5.5 shows groups were adequately matched on gender and education, but not age. Although not significantly different to the other groups, there was a larger percentage of males in the CFRD group because of survivor bias (see Chapter 1, section 1.5.2.3). The significant difference in ages between the groups reflects difficulty matching CFRD to CFND since CFRD typically develops with advancing age in CF. People in the CFND group were slightly, although significantly, younger than people with CFRD group ($p = .007$) and controls ($p = .046$) despite efforts to match groups (see Figure 5.10).
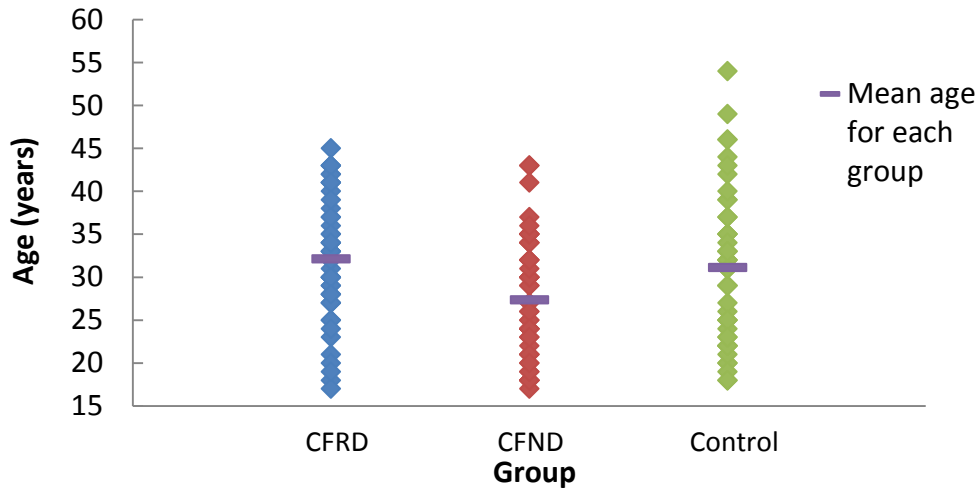
Figure 5.10 Study 1. Distribution of participants' ages for each experimental group (CFRD, CFND and healthy control)

For each group, the highest educational qualification achieved varied between no qualifications to PhD (see Figure 5.11). People with CFRD were more likely to be awarded with Diplomas, Degrees and Masters than CFND, but this may be an effect of age.
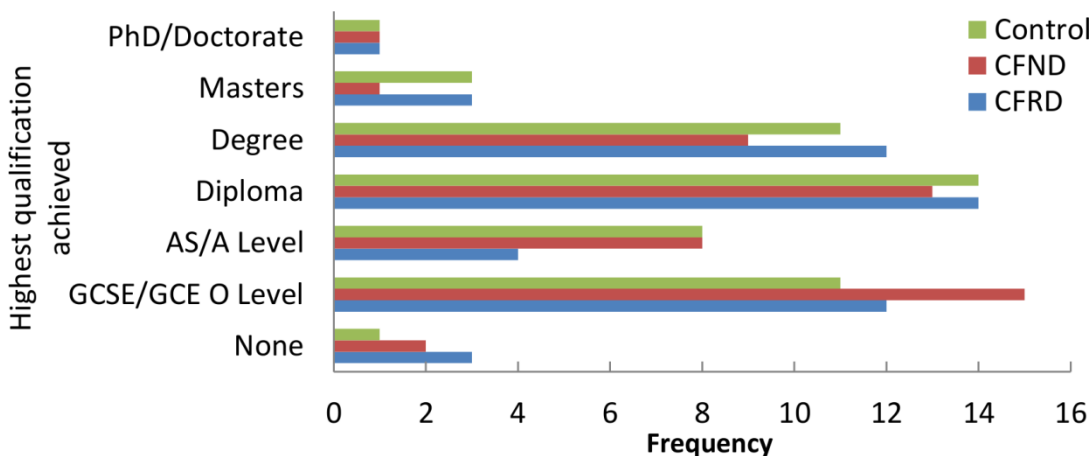
Figure 5.11 Study 1.Frequency of highest education qualification achieved by group (CFRD, CFND, Control)

In relation to other participant characteristics, there was no significant difference between Townsend score, BMI, %COHb, and anxiety score. There was a trend for a significant

difference for height and COppm. The participants in the control group tended to be taller than people with CFND ($p = .071$). There were no differences between groups for COppm. There was a significant difference between groups for occupation, weight, health rating, blood glucose (mmol/L), and depression score (HADS). More controls were in full time employment compared to the two groups of people with CF (see Figure 5.12). People with CFRD showed the highest frequency of unemployment.
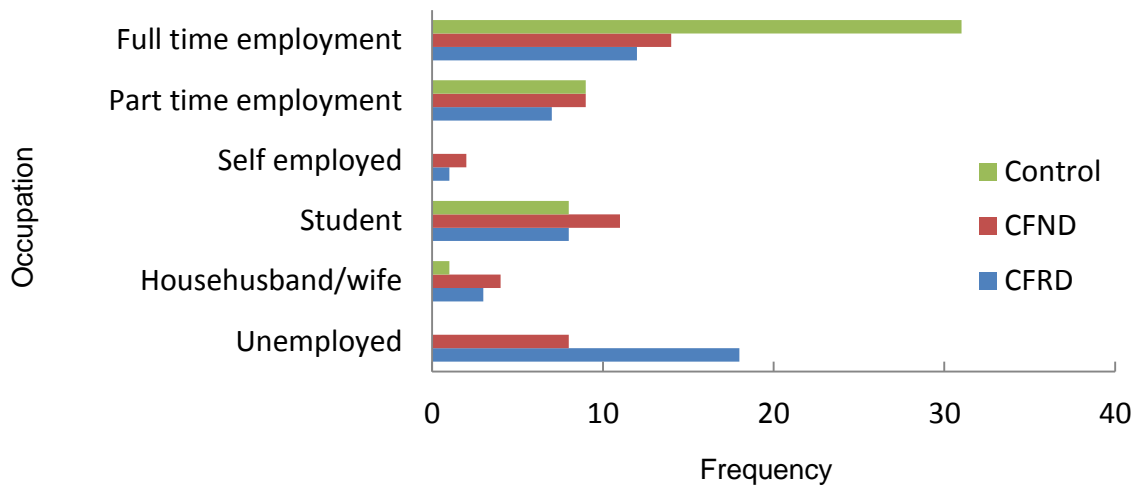
Figure 5.12 Study 1. Frequency of type of occupation in each group (CFRD, CFND and control)

As expected, blood glucose levels were significantly higher in the CFRD group relative to the CFND group ($p < .001$) and control group ($p < .001$; see Figure 5.13). The control group and most of the CFND group had blood glucose values within the normal range. However, some people with CFND had values similar to those in the CFRD group. There was more variation in blood glucose values in the CFRD group, with values ranging from normal to the cut off level of 12 mmol/L used in this study.
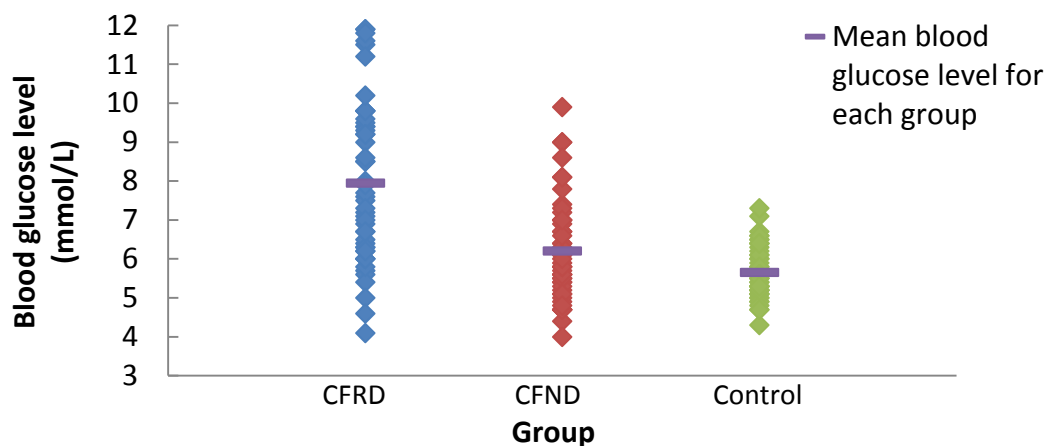
Figure 5.13 Study 1. Distribution of participants' blood glucose level for each experimental group (CFRD, CFND and control)

People in the CFND group weighed significantly less than those in the control group (*p* = .007; see Figure 5.14) and there was a trend for the CFND group to have a lower BMI than the control group (*p* = .096). People with CFND had the lowest weight and CFRD had the heaviest weight of all participants.
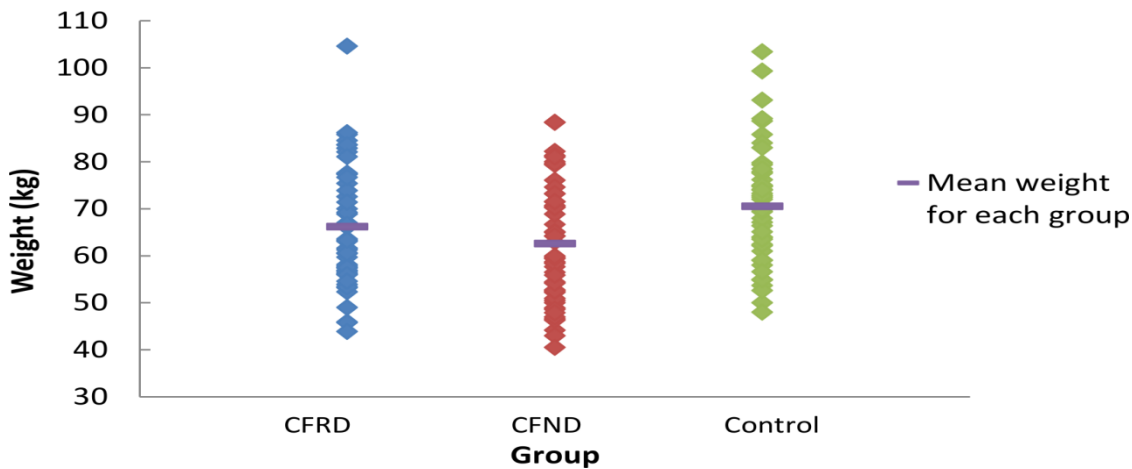
Figure 5.14 Study 1. Distribution of participants' weight for each experimental group (CFRD, CFND and control)

The control group subjectively rated their health as better than those with CFRD (*p* = .003) and CFND (*p* = .01), as expected (see Figure 5.15). Nevertheless some people with CF did rate their health as very well and/or healthy.
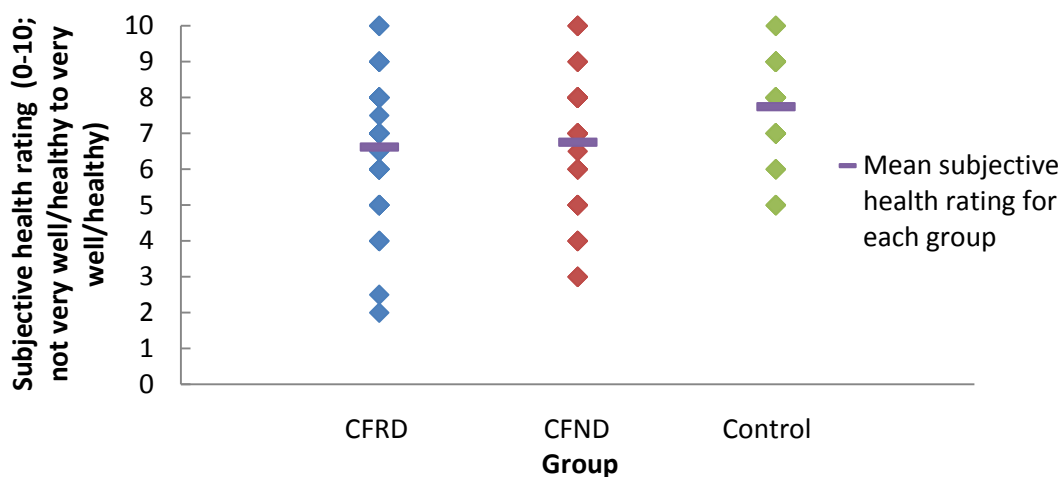
Figure 5.15 Study 1. Distribution of participants' subjective rating of health for each experimental group (CFRD, CFND and control)

The control group scored significantly lower on the depression aspect of the HADS compared to those in the CFRD (*p* = .01) and CFND group (*p* = .04; see Figure 5.16). While the majority of controls scored in the normal range (0-7), people with CF tended to score in the normal, mild (8-10), moderate (11-14) ranges. No participant scored in the severe depression range (15-21).
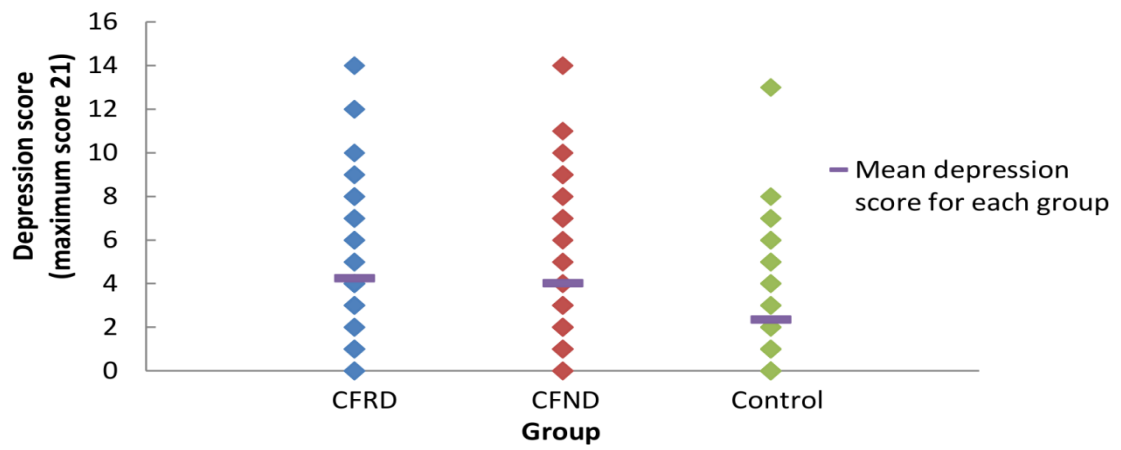
Figure 5.16 Study 1. Distribution of participants' depression scores (measured using the HADS) for each experimental group (CFRD, CFND and control)

Table 5.6 Study 1. Key clinical characteristics of the two CF groups; CFRD and CFND

	CFRD (n=49) Mean (SE)	CFND (n=49) Mean (SE)	F (1,96)	p value	η_p^2
Heterozygous F508del (n)	47	45		.68[46]	
P. aeruginosa infection (n)	35	31		.055[47]	
Age at CF diagnosis (yrs)	2.30 (.82)	1.65 (.47)	10.33	.002[48]	.097
FEV$_1$	1.90 (.14)	2.06 (.13)	.68	.41	.007
FEV$_1$%predicted	52.20 (3.46)	58.27 (3.25)	1.63	.21	.02
FVC	3.06 (.16)	3.23 (.17)	.50	.48	.005
FVC % predicted	71.78 (3.24)	77.69 (3.34)	1.62	.21	.02
Oxygen saturation (%)	96.08 (.31)	96.51 (.30)	.99	.32	.01
HbA1c (mmol/mol; IFCC)	61.90 (3.52)	39.47 (.66)	39.20	<.001	.29
CFRD duration (years)	10.50 (1.04)	-			
Patients with microvascular complications	0	-			
Number of previous impaired OGTTs [24]		1.20 (.19) [49]			
SBP (mmHg)	130.80 (2.18)	121.73 (2.71)	6.81	.01	.07
Diastolic blood pressure (DBP; mmHg)	77.98 (1.16)	73.74 (1.42)	5.35	.02	.05
Pulse (bpm)	96.00 (2.15)	90.49 (2.40)	2.93	.09	.03
Receiving IV's (%)	42.9	49		.53[50]	
CRP (mg/L)	14.54 (2.11)	12.05 (1.99)	.73	.40[51]	.008
Vitamin A (ng/mL)	1.67 (.070)	1.72 (.08)	.28	.60	.003
Vitamin D (ng/mL)	72.32 (3.65)	65.70 (4.36)	1.36	.25	.01
Vitamin E (ng/mL)	29.23 (1.37)	27.77 (1.37)	.57	.45	.006
Serum creatinine (µmol/L)	63.59 (2.43)	64.57 (2.36)	.08	.77	.001
Serum urea (mmol/L)	5.28 (.24)	5.16 (.21)	.14	.71	.002
Albumin (g/L)	41.88 (.59)	42.43 (.50)	.51	.48	.005

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[46] Fisher's Exact test, People with CF have two copies of CFTR mutations and are either homozygous or heterozygous. Matching was based on F508del as it is the most common mutation in CF.
Mutation 1, χ^2(6, N = 98) = 5.65, p = .68. mutation 2, χ^2(18, N = 98) = 17.30, p = .46
[47] Fishers Exact test, *P. aeruginosa* is the most common pathogen in CF and is associated with poorer survival, increased hospitalisation and a more rapid progression of lung disease,
χ^2(4, N = 98) = 8.57, p = .055
[48] Data were inversely transformed due to severe positive skewness; F, p and η_p^2 are reported on the transformed data. For clarity, means (SE) are raw data
[49] Using EMIS, the number of times a patient had received an impaired OGTT since 2007, or for patients born after 1991 since they have been registered to the Leeds Adult CF Unit, was recorded.
[50] Pearson Chi-Square, $\chi2$(2, N = 44)=1.29, p=.53
[51] Data were reflected and inversely transformed due to severe positive skewness; F, p and η_p^2 are reported on the transformed data. For clarity, means (SE) are raw data

As shown in table 5.6, there were no significant differences between CFRD and CFND groups on FEV_1, FEV_1%predicted, FVC, FVC% predicted, oxygen saturation, the number of people receiving IV treatment at the time of testing, CRP levels, vitamin A, D and E, serum creatinine, urea and albumin. The Chi-Square test showed there was also no difference between groups with regards to the stage of IV treatment, $\chi^2(2, N = 44)=1.29$, p=.53 (see Figure 5.17).
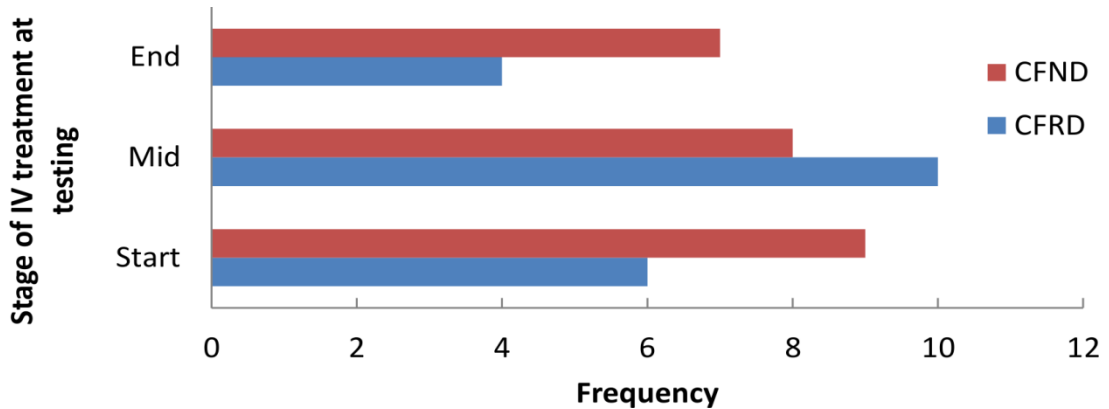
Figure 5.17 Study 1. Stage of IV treatment (start, mid, end) at testing, for each CF group (CFRD, CFND)

There was a significant difference between groups for age at CF diagnosis (see Figure 5.18), HbA1c, SBP and DBP. Figure 5.18 shows that while most people with CFRD and CFND were diagnosed before 5 years of age, a number of people received a diagnosis of CF later in life. This is particularly evident for one patient in the CFRD group.
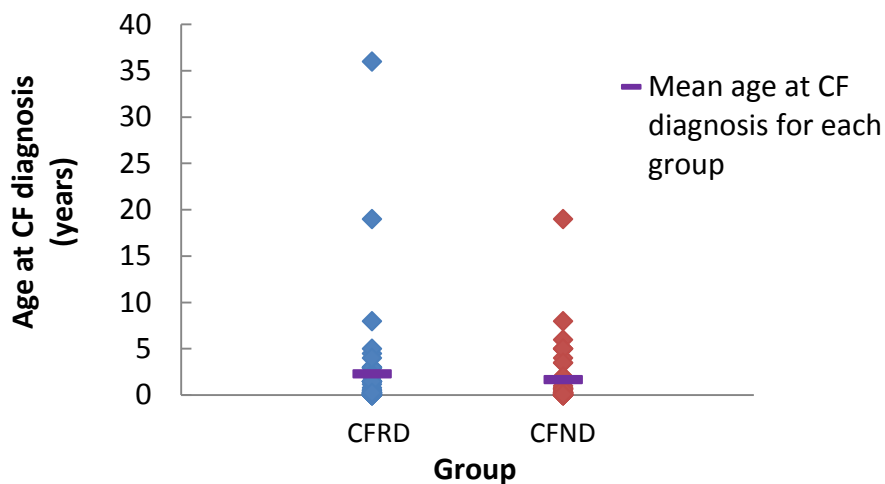
Figure 5.18 Study 1. Distribution of age at which CF was diagnosed for each CF group (CFRD, CFND)

As expected, HbA1c was significantly higher in those with CFRD (see Figure 5.19). One person with CFRD had a particularly high HbA1c value reflecting extremely poor glycaemic control.
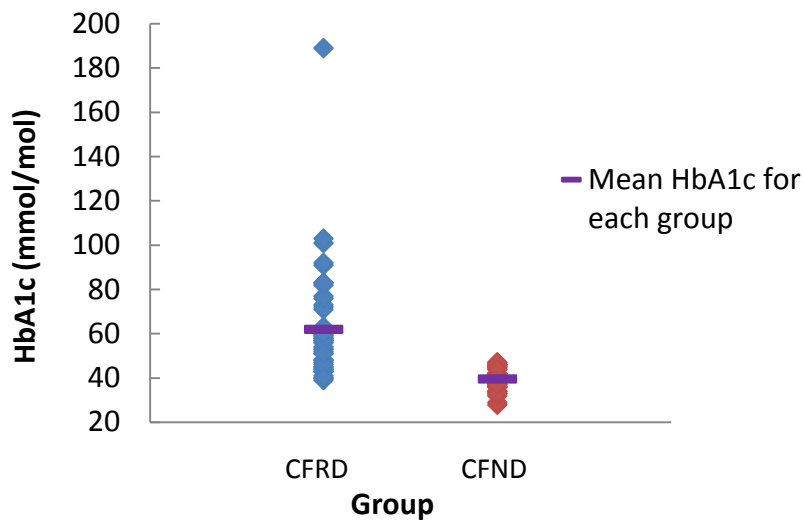
Figure 5.19 Study 1. Distribution of participants HbA1c values for each CF group (CFRD, CFND)

Those in the CFRD group also had significantly higher SBP and DBP relative to those in the CFND group (see Figure 5.20). There was more variation in the readings in the CFND group.

Figure 5.20 Study 1. Distribution of SBP readings (left figure) and DBP readings (right figure) for each CF group (CFRD, CFND)

There was also a trend for people with CFRD to have a faster pulse than CFND (see Figure 5.21), and for people with CFRD to be more chronically infected with *P. aeruginosa* than people with CFND (see Figure 5.22).
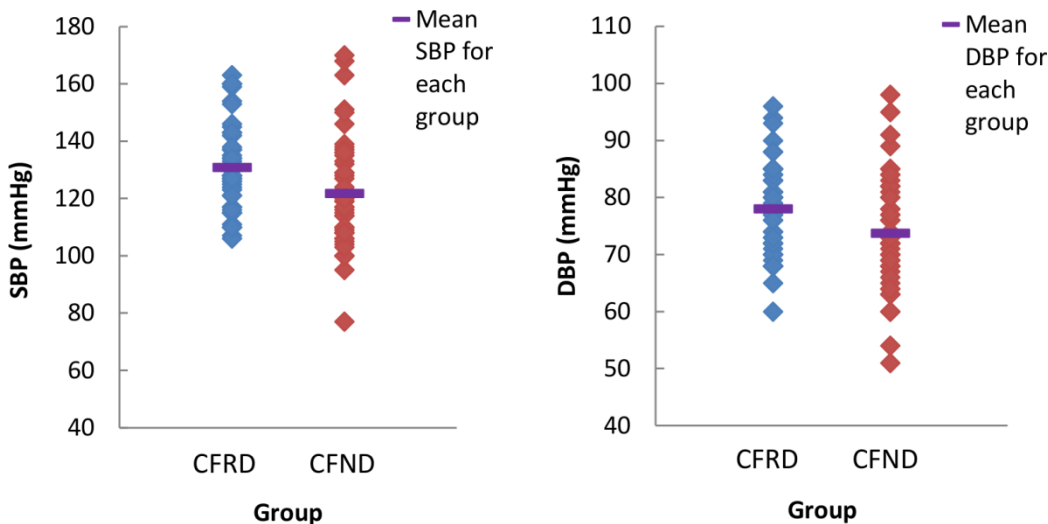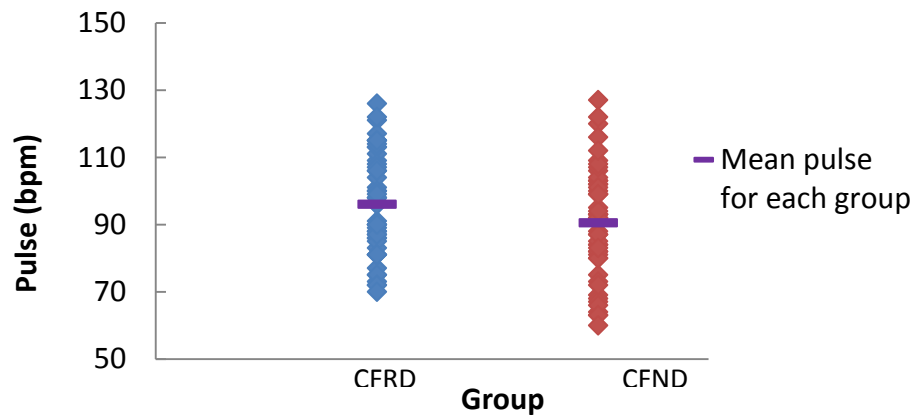
Figure 5.21 Study 1. Distribution of participants pulse readings for each CF group (CFRD, CFND)
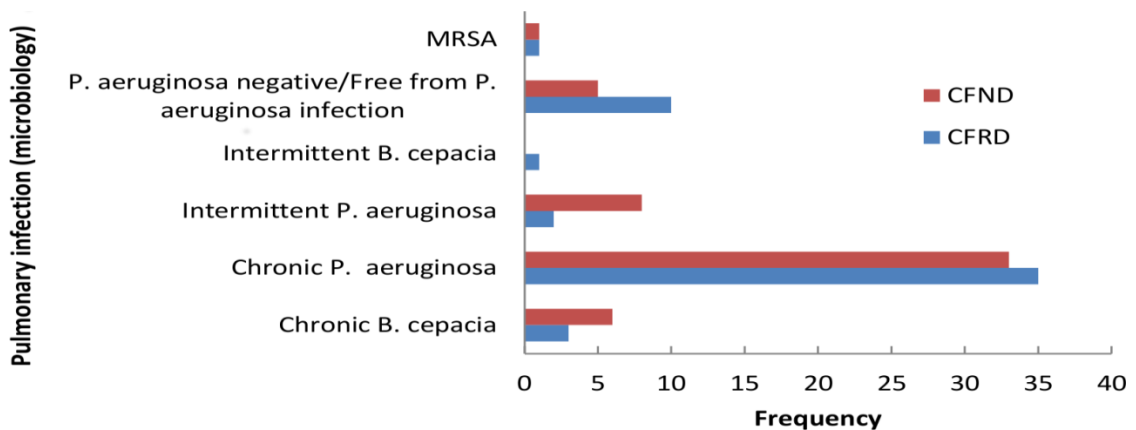
Figure 5.22 Study 1. Frequency of pulmonary infection for each CF group (CFRD, CFND)

5.3.2 Questionnaires

5.3.2.1 Sleep quality (LSEQ)

One person with CFRD and 5 people with CFND did not complete the LSEQ last week questionnaire due to time constraints. One person with CFRD had missing data for the outcome measures of ease of waking and waking duration.

5.3.2.1.1 Ease of getting to sleep

Data showed a bimodal distribution with a slight negative skew for both previous night and last week. Therefore, a square root transformation was applied to the data. Age was a significant covariate, $F(1, 137) = 4.65$, $p = .033$, $\eta_p^2 = .033$, such that older participants found it easier to get to sleep than younger participants. There was no significant main effect of time, $F(1, 137) = 0.001$, $p = .98$, $\eta_p^2 < .001$, therefore there was no difference in how easy it was to get to sleep the night before the testing session compared to the previous week (see Figure 5.23). There was no effect of group, $F(2, 137) = 2.12$, p = .12, $\eta_p^2 = .03$, or

time*group interaction, $F(2, 137) = 0.46$, $p = .64$, $\eta_p^2 = .007$, or time*age interaction, $F(1, 137) = 0.45$, $p = .50$, $\eta_p^2 = .003$.
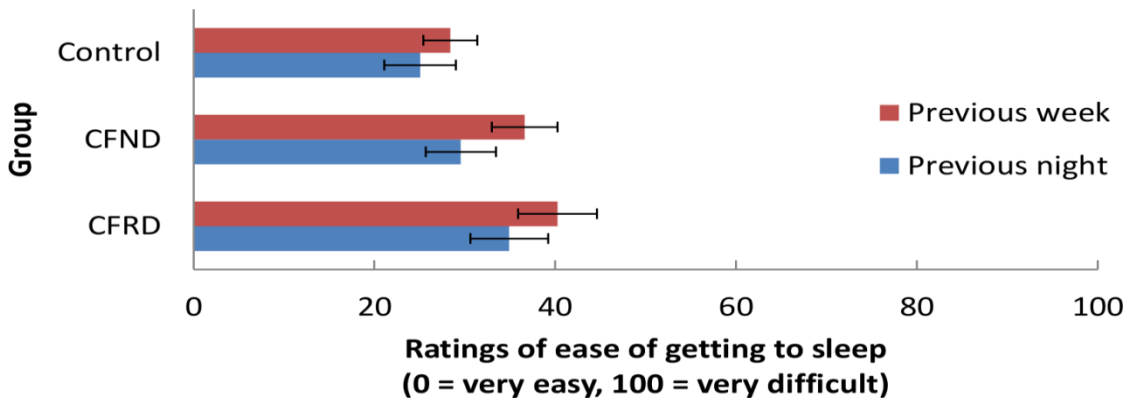
Figure 5.23 Study 1. Mean ratings of ease of getting to sleep (+/-SE) for the night before the testing session and previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.2 Time to get to sleep

Data were substantially negatively skewed for the previous night and moderately skewed for the last week. Therefore, a logarithm transformation was applied to the data. Age was a significant covariate, $F(1, 137) = 6.11$, $p = .015$, $\eta_p^2 = .043$, such that older participants found it quicker to get to sleep than younger participants. There was no significant main effect of time, $F(1, 137) = 0.44$, $p = .51$, $\eta_p^2 = .003$, therefore there was no difference in how quickly participants fell asleep the night before the testing session compared to the previous week (see Figure 5.24). There was no effect of group, $F(2, 137) = 1.54$, $p = .22$, $\eta_p^2 = .02$, or time*group interaction, $F(2, 137) = 0.06$, $p = .94$, $\eta_p^2 = .001$, or time*age interaction, $F(1, 137) = 0.05$, $p = .82$, $\eta_p^2 < .001$.
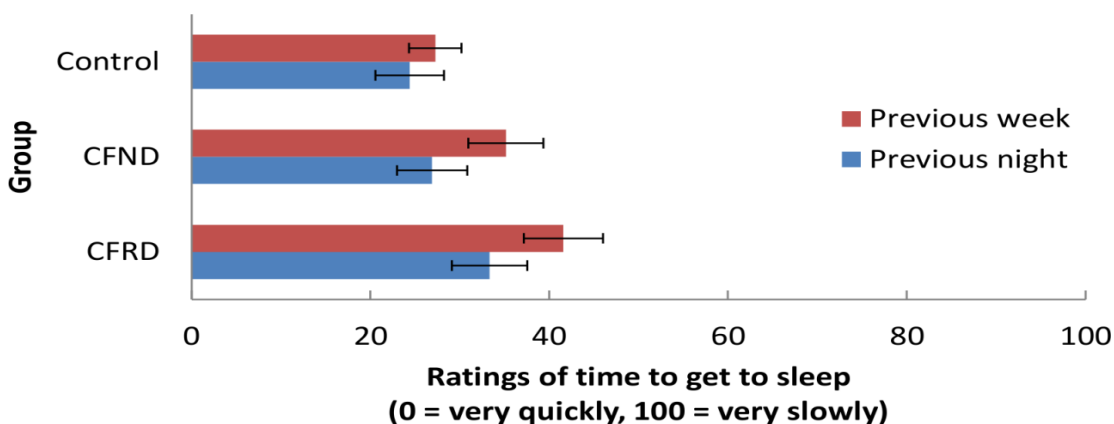
Figure 5.24 Study 1. Mean ratings of time to get to sleep (+/-SE) for the night before the testing session and previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.3 Restful

Age was not a significant covariate, $F(1, 137) = 0.54$, $p = .47$, $\eta_p^2 = .004$, and therefore age did not predict restfulness during sleeping. There was no significant main effect of time, $F(1, 137) = 1.59$, $p = .21$, $\eta_p^2 = .012$, therefore there was no difference in how restful participants reported their sleep was the night before the testing session compared to the previous week. There was a significant main effect of group, $F(2, 137) = 7.20$, $p = .001$, $\eta_p^2 = .095$, a trend for a time*group interaction, $F(2, 137) = 2.71$, $p = .07$, $\eta_p^2 = .038$, and a time*age interaction, $F(1, 137) = 3.23$, $p = .075$, $\eta_p^2 = .023$. People with CFRD reported their sleep was more restless than people with CFND ($p = .006$) and healthy controls ($p = .003$). People with CFRD and CFND reported that their sleep was less restless the night before the testing session compared to the previous week, whereas controls reported their sleep was more restless the night before the testing session (see Figure 5.25). Older participants reported their sleep was more restful the night before the testing session compared to younger participants, while younger participants reported their sleep to be more restful for the previous week compared to older participants.
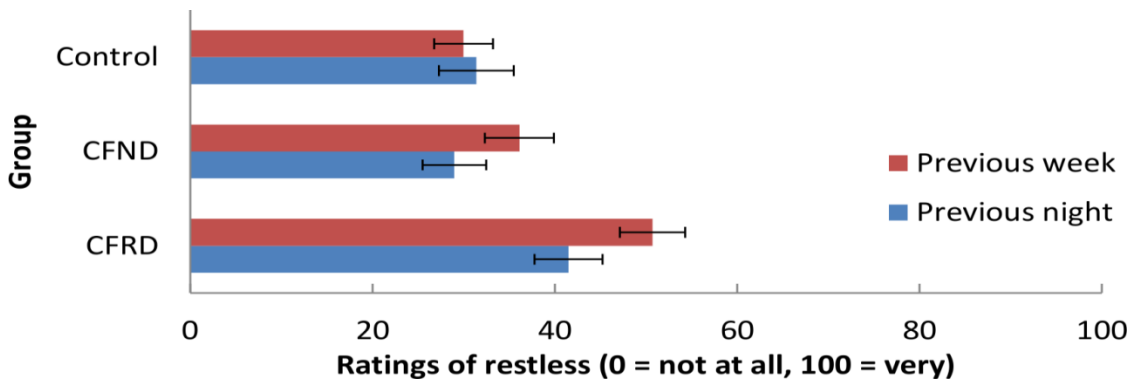
Figure 5.25. Study 1. Mean ratings of restfulness (+/-SE) during sleeping for the night before the testing session and previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.4 Wakefulness

Data were square root transformed due to moderate negative skew for both previous night and last week. Age was not a significant covariate, $F(1, 137) = 0.34$, $p = .56$, $\eta_p^2 = .002$, and therefore was not a predictor for periods of wakefulness during sleep. There was no significant main effect of time, $F(1, 137) = 0.53$, $p = .47$, $\eta_p^2 = .004$, therefore, participants did not report a difference in periods of wakefulness the night before the testing session compared to the previous week (see Figure 5.26). There was a significant main effect of group, $F(2, 137) = 4.86$, $p = .009$, $\eta_p^2 = .066$, such that people with CFRD reported significantly more periods of wakefulness relative to controls ($p=.008$). There was a trend for a time*age interaction, $F(1, 137) = 3.53$, $p = .062$, $\eta_p^2 = .025$, such that older participants reported less periods of wakefulness the night before the test session compared to the previous week while younger participants reported more periods of wakefulness for the night before the test session compared to the previous week. There was no time*group interaction, $F(2, 137) = 0.18$, $p = .84$, $\eta p^2 = .003$.
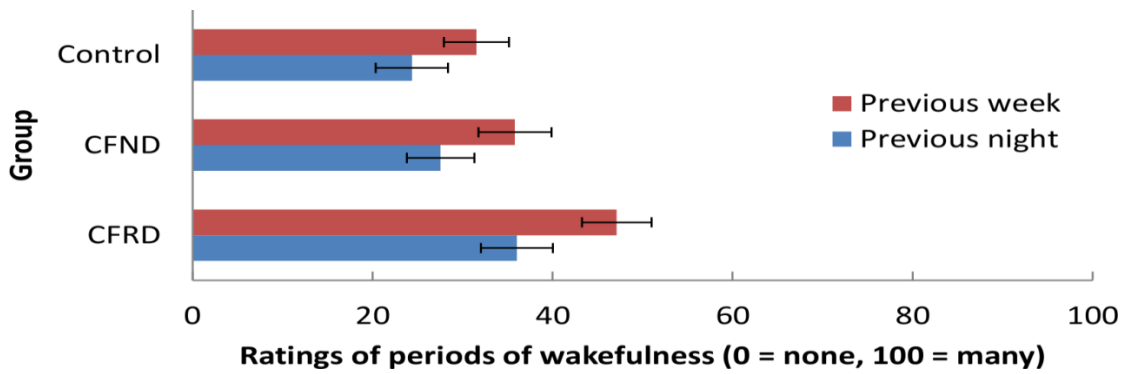
Figure 5.26 Study 1. Mean ratings of periods of wakefulness (+/-SE) during sleeping for the night before the testing session and previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.5   Ease of waking

There was missing data for one person with CFRD in addition to those who did not complete the last week questionnaire due to time constraints. Age was a significant covariate, $F(1, 136) = 8.34$ $p = .005$, $\eta_p^2 = .058$, such that older participants reported it was harder to wake up than younger participants. There was a significant main effect of time, $F(1, 136) = 4.55$, $p = .035$, $\eta_p^2 = .032$, but the post hoc test revealed there was no difference in ease of waking between participants for the morning of the test session compared to the previous week (see Figure 5.27). There was a significant main effect of group, $F(2, 136) = 3.04$, $p = .051$, $\eta_p^2 = .043$, such that people with CFRD tended to report that it was marginally harder to wake up in the morning than controls (p=.069). There was a time*age interaction, $F(1, 136) = 4.68$, $p = .032$, $\eta_p^2 = .033$, such that younger participants found it easier to wake up over the past week than the morning of the test session, whist older participants found it easier to wake up on the morning of the test session than during the previous week. There was no time*group interaction, $F(2, 136) = 1.76$, $p = .18$, $\eta_p^2 = .025$.
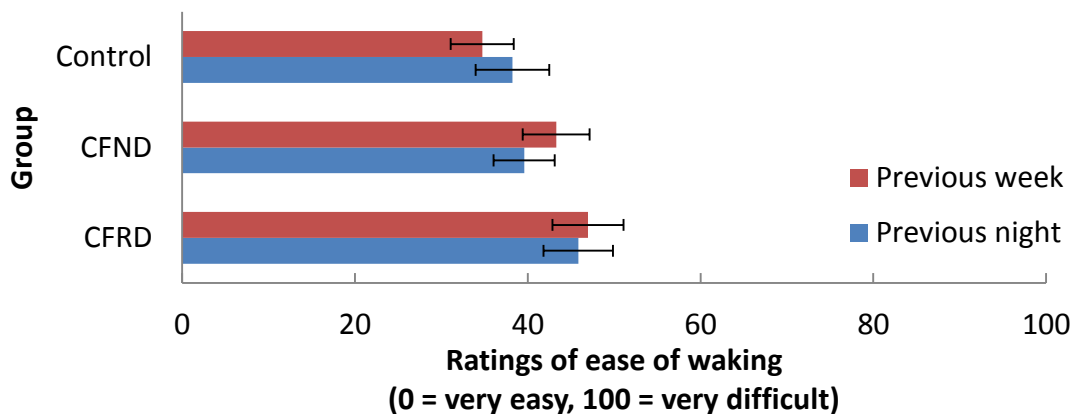
Figure 5.27 Study 1. Mean ratings of ease of waking (+/-SE) for the morning of the testing session and previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.6 Waking duration

There was missing data for one person with CFRD in addition to those who did not complete the last week questionnaire due to time constraints. Data were square root transformed due to moderate negative skew for both previous night and last week. Age was a significant covariate, $F(1, 136) = 8.65$ $p = .004$, $\eta_p^2 = .060$, such that older participants took less time to wake up than younger participants. There was a trend for a time*group interaction, $F(2, 136) = 2.49$, $p = .087$, $\eta_p^2 = .035$, such that participants in all groups reported it took less time to awake on the morning of the testing session compared to the previous week (see Figure 5.28). There was a trend for a time*age interaction, $F(1, 136) = 3.58$, $p = .061$, $\eta_p^2 = .026$, such that that older participants reported it took less time to wake up than younger participants on the morning of the test session, while younger participants reported it took less time to wake up for the previous week compared to older participants. There was no significant main effect of time, $F(1, 136) = 1.38$, $p = .24$, $\eta_p^2 = .010$ or no significant main effect of group, $F(2, 136) = 2.07$, $p = .13$, $\eta_p^2 = .030$.
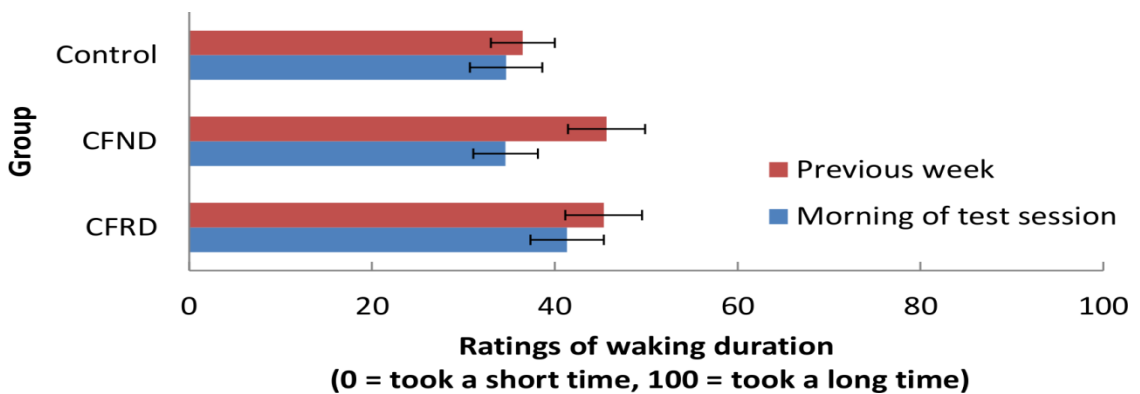
Figure 5.28 Study 1. Mean ratings of waking duration (+/-SE) on the morning of the testing session and for the previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.7 Alertness on waking

Age was a significant covariate, $F(1, 137) = 5.93$, $p = .04$, $\eta_p^2 = .04$, such that older participants reported they were more alert on waking than younger participants. There was a significant main effect of group, $F(2, 137) = 8.08$, $p < .001$, $\eta_p^2 = .106$, such that people with CFRD reported feeling significantly less alert than people with CFND ($p = .021$) and controls ($p < .001$; see Figure 5.29). There was no main effect of time, $F(1, 138) = 1.27$, $p = .26$, $\eta_p^2 = .009$, no time*group interaction, $F(2, 138) = 1.05$, $p = .35$, $\eta_p^2 = .015$, nor time*age interaction, $F(1, 138) = 0.84$, $p = .36$, $\eta_p^2 = .006$.
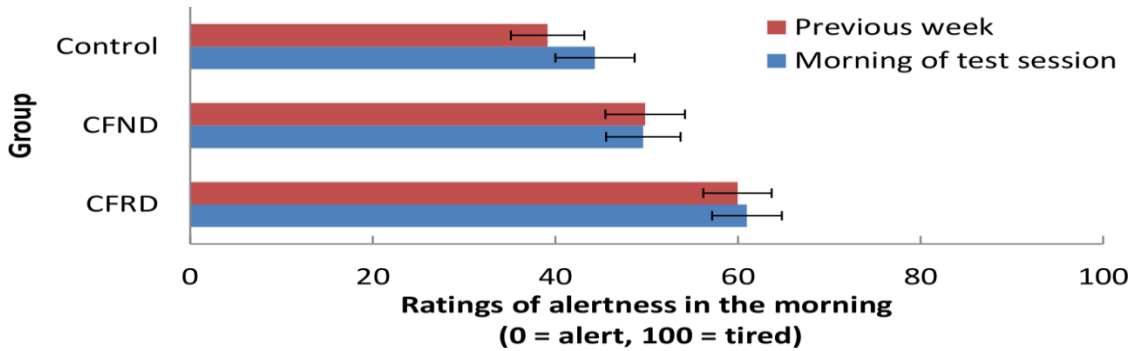
Figure 5.29 Study 1. Mean ratings of alertness (+/-SE) on the morning of the testing session and for the previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.1.8 Alertness 1hour after waking

Data were logarithm transformed due to substantial negative skew for both previous night and last week. Age was not a significant covariate, $F(1, 137) = 1.38$, $p = .24$, $\eta_p^2 = .010$, and therefore age was not a predictor of how alert participants felt one hour after waking. There was no significant main effect of time, $F(1, 137) = 0.10$, $p = .75$, $\eta_p^2 = .001$ (see Figure 5.30). There was no time*group interaction, $F(2, 137) = 1.19$, $p = .31$, $\eta_p^2 = .017$, or time*age interaction $F(1, 137) = 0.43$, $p = .51$, $\eta_p^2 = .003$. There was a trend for a significant main effect of group, $F(2, 137) = 2.82$, $p = .063$, $\eta_p^2 = .040$, such that the people with CFRD tended to report feeling more tired one hour after waking compared to control participants ($p = .058$; see Figure 5.28).
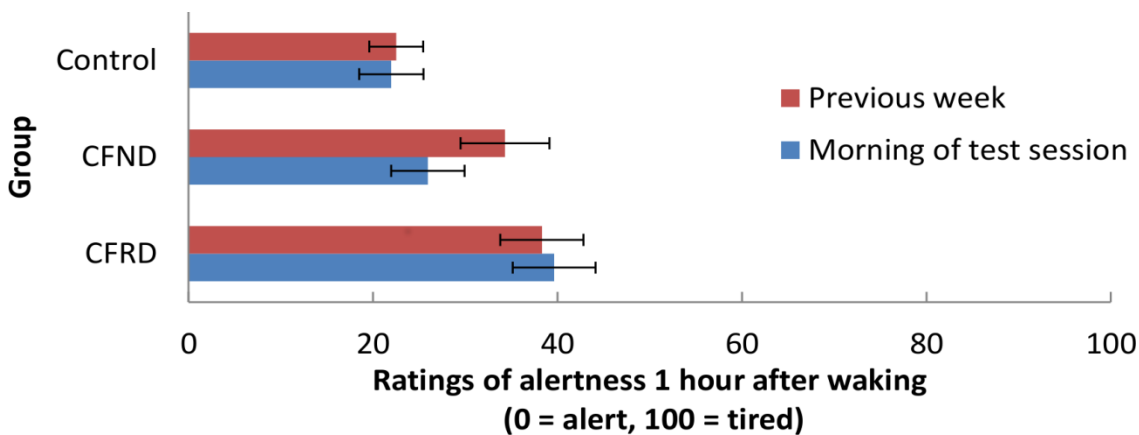
Figure 5.30 Study 1. Mean ratings of alertness 1 hour after waking (+/-SE) on the morning of the testing session and for the previous week, for each experimental group (CFRD, CFND and healthy control)

5.3.2.2 **Perceived stress (PSS)**

One person with CFRD and 5 people with CFND did not complete the stress month questionnaire due to time constraints. Age was not a significant covariate, $F(1, 143) = 0.11$, $p = .74$, $\eta_p^2 = .001$. There was a trend for a significant main effect of time, $F(1, 138) = 2.90$, $p = .091$, $\eta_p^2 = .02$, such that participants reported feeling more stressed during the past month compared to the past week (see Figure 5.31). There was a trend for a main effect of group, $F(2, 143) = 2.95$, $p = .055$, $\eta_p^2 = .04$, such that people in the CFRD group tended to

be more stressed than those in the control group (p = .085). There was no time*group interaction, $F(2, 138) = 1.17$, $p = .31$, $\eta_p^2 = .016$ or time*age interaction, $F(1, 138) = 1.18$, $p = .28$, $\eta_p^2 = .008$.
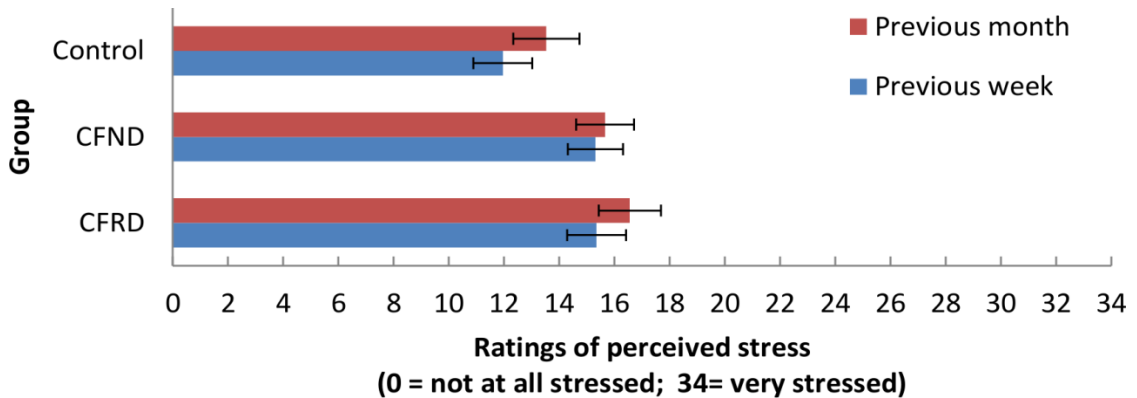
Figure 5.31 Study 1. Perceived stress ratings for the previous month and week before the test session for each group (CFRD, CFND, Control)

5.3.2.3 VAS Ratings of mood and mental alertness

5.3.2.3.1 Contentedness

Data were reflected and square root transformed due to moderate negative skewness. Age was not a significant covariate, $F(1, 143) = 0.02$, $p = .89$, $\eta_p^2 < .001$. There was a significant main effect of group for contentedness, $F(2, 143) = 3.91$, $p = .022$, $\eta_p^2 = .052$ such that those in the CFRD group were significantly less contented than those in the control group ($p = .028$; see Figure 5.32).
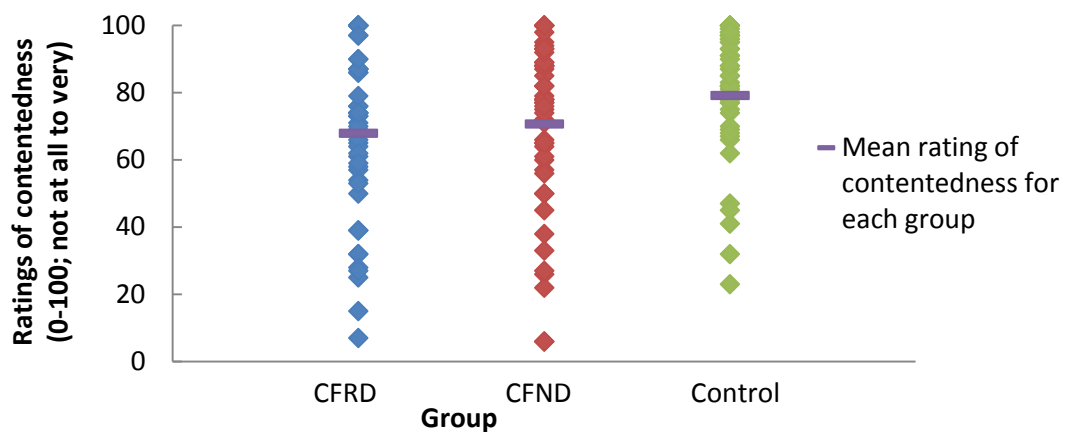
Figure 5.32 Study 1. VAS ratings of contentedness for each experimental group (CFRD, CFND and healthy control)

5.3.2.3.2 Irritability

Data on irritability were log transformed to correct for positive skewness. Age was not a significant covariate, $F(1, 143) = 0.96$, $p = .33$, $\eta_p^2 = .007$ and there was no effect of group on irritability, $F(2, 143) = 1.48$, $p = .23$, $\eta_p^2 = .02$ (see Figure 5.33).
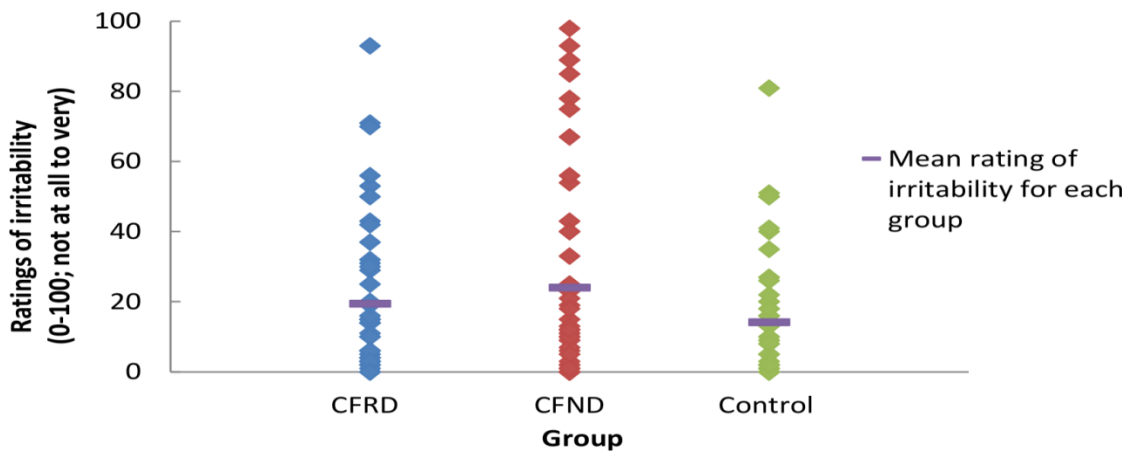
Figure 5.33 Study 1. VAS ratings of irritability for each experimental group (CFRD, CFND and healthy control)

5.3.2.3.3 Sleepiness

Data were reflected and square root transformed due to moderate negative skewness. Age was a significant covariate, $F(1, 143) = 6.08$, $p = .015$, $\eta_p^2 = .041$. Older participants reported feeling less sleepy just before the cognitive tests than younger participants. There was a significant main effect of group on sleepiness, $F(2, 143) = 4.81$, $p = .010$, $\eta_p^2 = .63$, such that controls were significantly less sleepy than those with CFRD ($p = .010$) and there was a trend for controls to feel less sleepy than people with CFND ($p = .091$; see Figure 5.34).
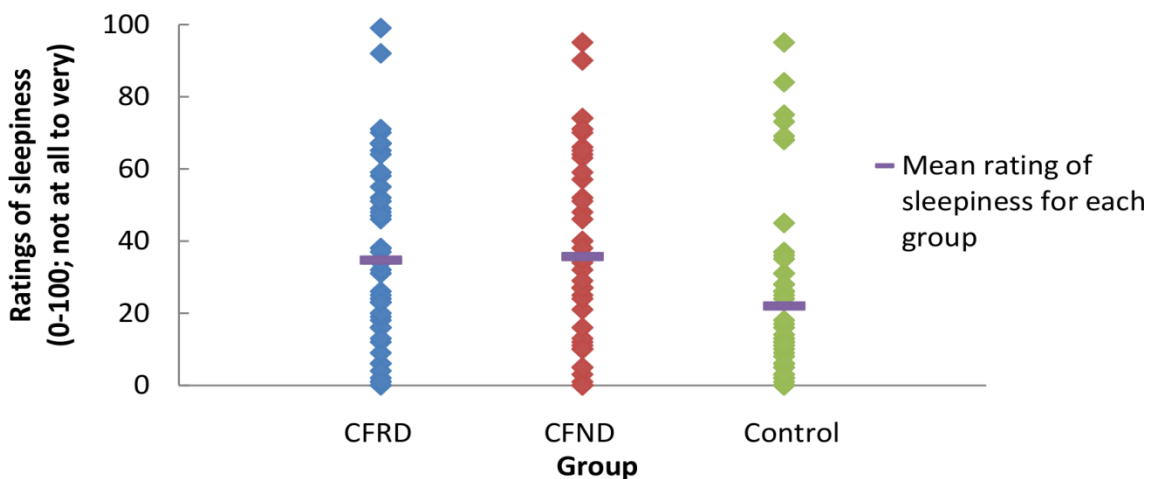
Figure 5.34 Study 1. VAS ratings of sleepiness for each experimental group (CFRD, CFND and healthy control)

5.3.2.3.4 Mental alertness

Data were reflected and square root transformed due to moderate negative skewness. Age was not a significant covariate, $F(1, 143) = 0.13$, $p = .72$, $\eta_p^2 = .001$. There was a main effect of group on mental alertness, $F(2, 143) = 3.05$, $p = .050$, $\eta_p^2 = .041$, which is explained by the tendency for controls to report being more mentally alert than those in the CFRD group ($p = .069$; see Figure 5.35).
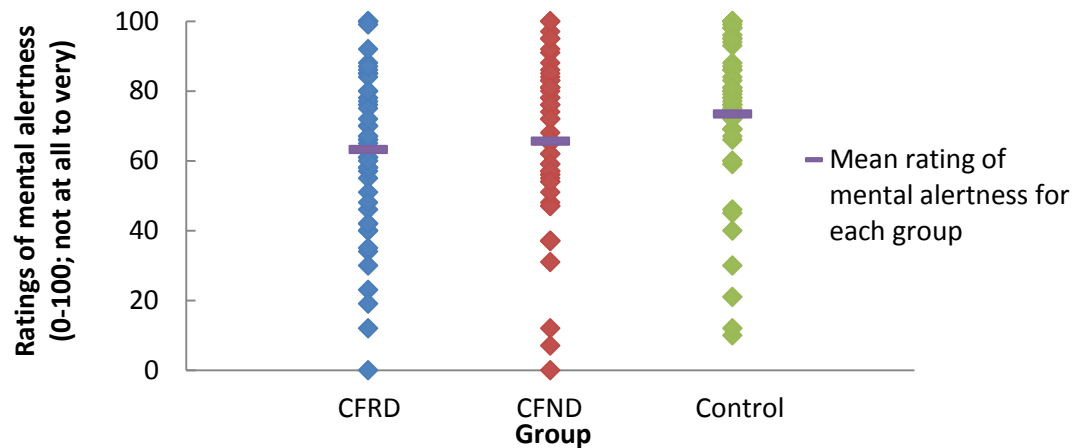
Figure 5.35 Study 1. VAS ratings of mental alertness for each experimental group (CFRD, CFND and healthy control)

5.3.2.3.5 Ability to concentrate

Data were reflected and square root transformed due to moderate negative skewness. Age was not a significant covariate, $F(1, 143) = 0.03$, $p = .88$, $\eta_p^2 < .001$. There was a significant main effect of ability to concentrate, $F(2, 143) = 9.40$, $p < .001$, $\eta_p^2 = .116$ such that people with CFRD reported a significantly lower ability to concentrate relative to the controls ($p < .001$) and a marginally significant difference relative to those with CFND ($p = .053$; see Figure 5.36).
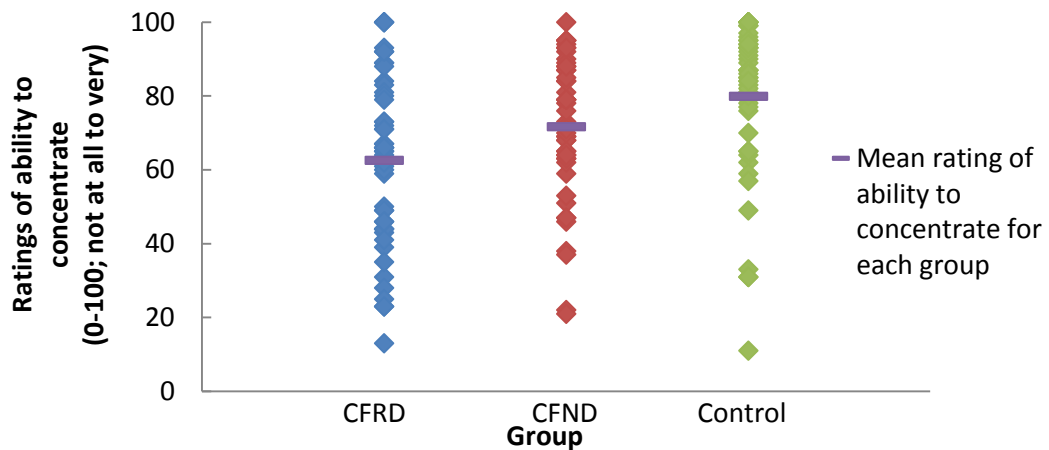
Figure 5.36 Study 1. VAS ratings of ability to concentrate for each experimental group (CFRD, CFND and healthy control)

5.3.2.3.6 Feeling energetic

Age was not a significant covariate, $F(1, 143) = 0.36$, $p = .55$, $\eta_p^2 = .002$. There was a significant main effect of group for feeling energetic, $F(2, 143) = 3.85$, $p = .024$, $\eta_p^2 = .051$, such that those in the control group reported feeling significantly more energetic than those with CFRD ($p = .019$; see Figure 5.37).
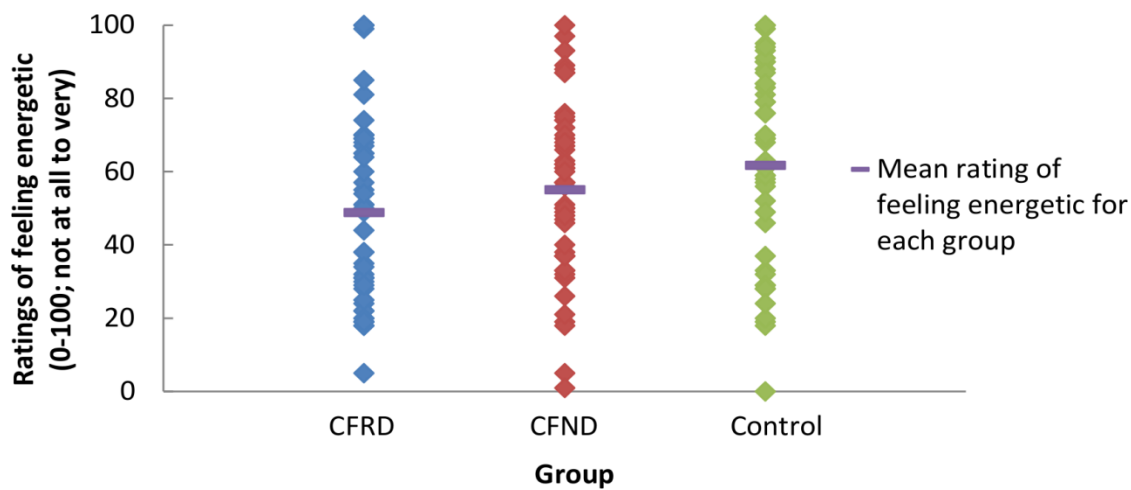
Figure 5.37 Study 1. VAS ratings of feeling energetic for each experimental group (CFRD, CFND and healthy control)

5.3.3 Subjective occurrences of minor daily cognitive errors

Figure 5.38 shows the mean number of subjective occurrences of minor daily cognitive errors which occurred in the previous 6 months reported on the CFQ by each group. Age was a not a significant covariate, $F(1, 143) = 1.06$, $p = .35$, $\eta_p^2 = .015$, therefore age was not a predictor of the number of minor daily cognitive errors reported by participants. There was no significant main effect of group, $F(2, 143) = 0.95$, $p = .39$, $\eta_p^2 = .01$.
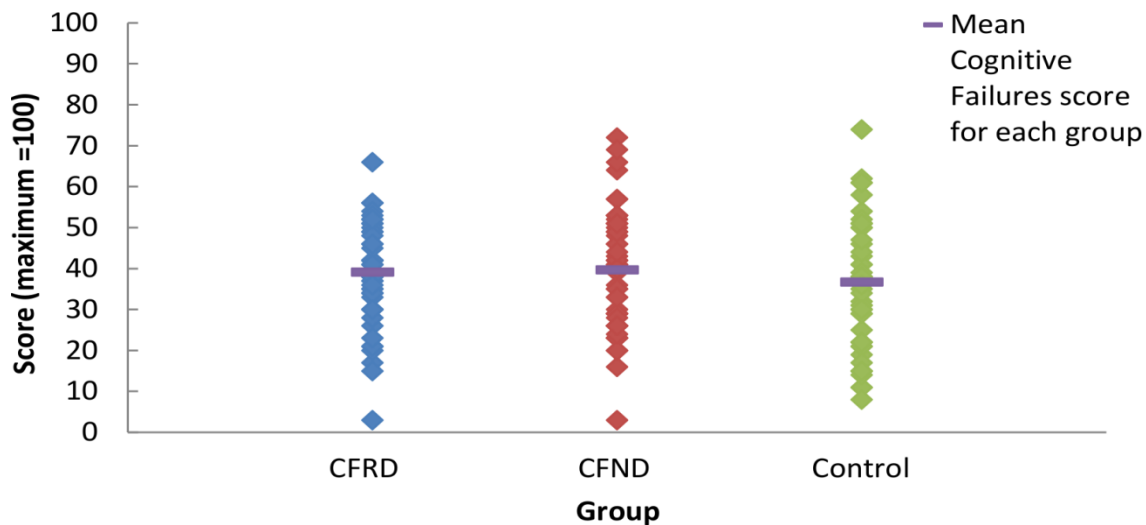
Figure 5.38 Study 1. Cognitive Failures Questionnaire scores for each experimental group (CFRD, CFND and healthy control)

5.3.4 Cognitive Tests

Time of day can affect cognitive functioning (Schmidt et al., 2007). The time of day at which testing was completed did not differ between groups, $\chi^2(2, N = 147) = 0.39$, $p = .87$; see Figure 5.39. The majority of participants in each group completed the testing in the afternoon.
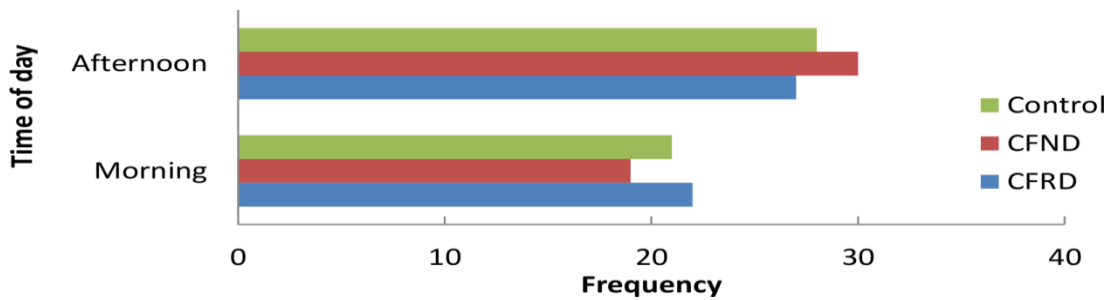
Figure 5.39 Study 1. Frequency of time of day testing was completed for each experimental group (CFRD, CFND and healthy control)

5.3.4.1 Motor Screening Test (MOT)

This test is an index of motor skill assessing both speed and accuracy (see section 5.2.3.3.1). For the outcome measure of total correct, people with CFRD and CFND correctly responded to all 10 crosses. All but one control correctly responded to the 10 presentations. This participant scored 9 correct responses.

5.3.4.1.1 Mean error

Mean error is a measurement of accuracy (see Table 5.4; the mean distance between the centre of the cross and the location the subject touched on the screen). Data for one participant included data points which met the criteria for outliers (see section 5.2.8.2) and was removed from the analysis. Age was not a significant covariate, $F(1, 142) = .07$, $p = .80$, $\eta_p^2 < .001$. Therefore, age was not a significant predictor of mean error performance. There was no main effect of group, $F(2, 142) = 1.50$, $p = .23$, $\eta_p^2 = .021$, ($R^2 = .021$) although Figure 5.40 indicates that both patient groups were more variable than controls.
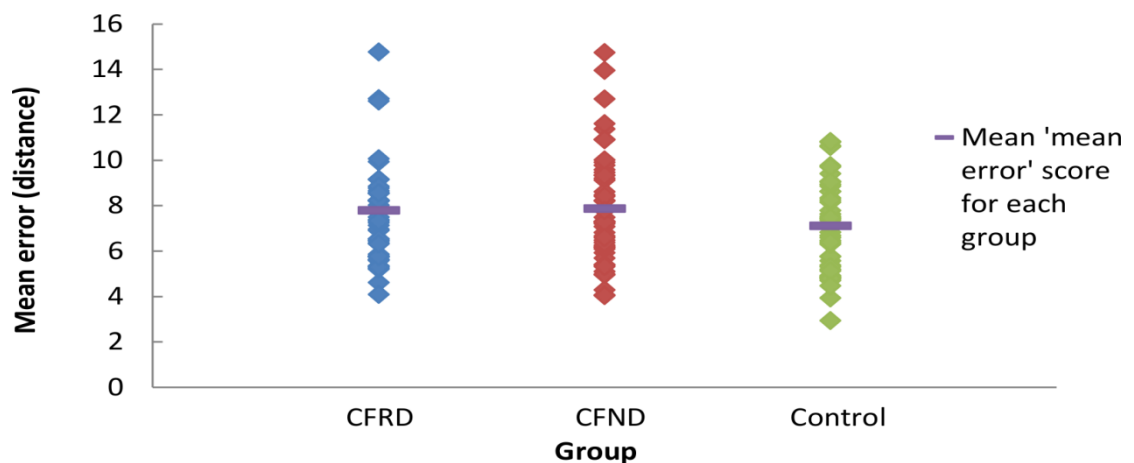
Figure 5.40 Study 1. Mean error (distance; measurement of accuracy) on the MOT (excluding one outlier)

5.3.4.1.2 Reaction time for correct responses

Data were square root transformed due to moderate positive skewness, and data for one participant was removed from the analysis as an outlier. Age was not a significant covariate

and did not improve model fit so was removed from the final model There was a trend for a significant main effect of group, $F(2, 143) = 2.58$, $p = .08$, $\eta_p^2 = .035$, ($R^2 = .035$; see Figure 5.41). However, post hoc tests revealed no significant differences between groups.
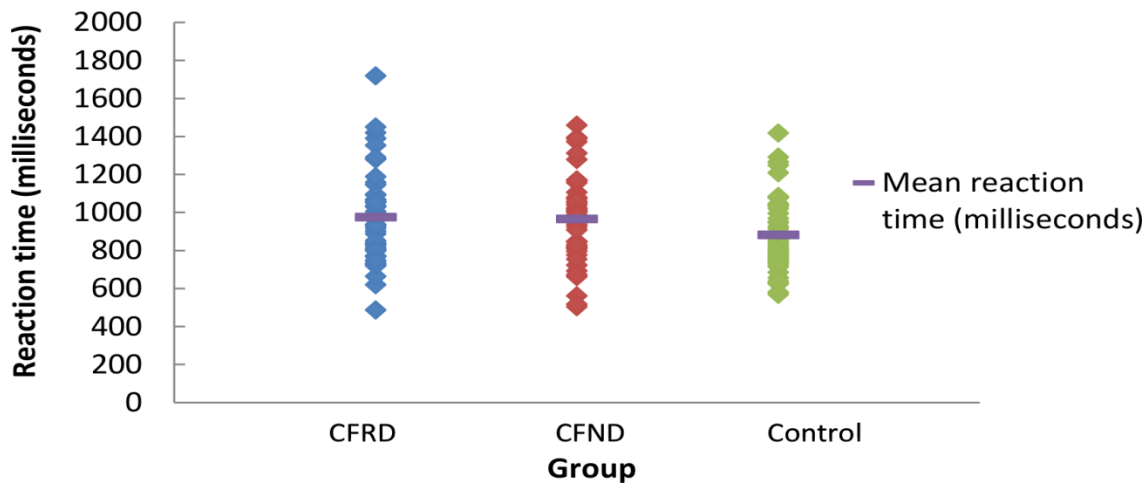
Figure 5.41 Study 1. Reaction time (milliseconds) for correct responses on the MOT (excluding one outlier)

5.3.4.2 Paired Associates Learning (PAL) test

The outcome measures for the PAL tests are stages completed, stages completed on the first trial, first trial memory score, total trials, total trials at n-patterns, total errors and total errors at n-patterns (see section 5.2.3.3.2, and Table 5.4 for a definition of each outcome variable). As the degree of test completion varies as a function of individual performance, number of stages completed was included as a covariate where applicable.

5.3.4.2.1 Stages completed

Data were reflected and an inverse transformation applied due to severe negative skewness. Age was a significant covariate, $F(1, 143) = 8.09$, $p = .005$, $\eta_p^2 = .054$, such that younger participants completed more stages than older participants. There was no significant main effect of group, $F(2, 143) = 1.07$, $p = .35$, $\eta_p^2 = .015$ ($R^2 = .057$; see Figure 5.42).
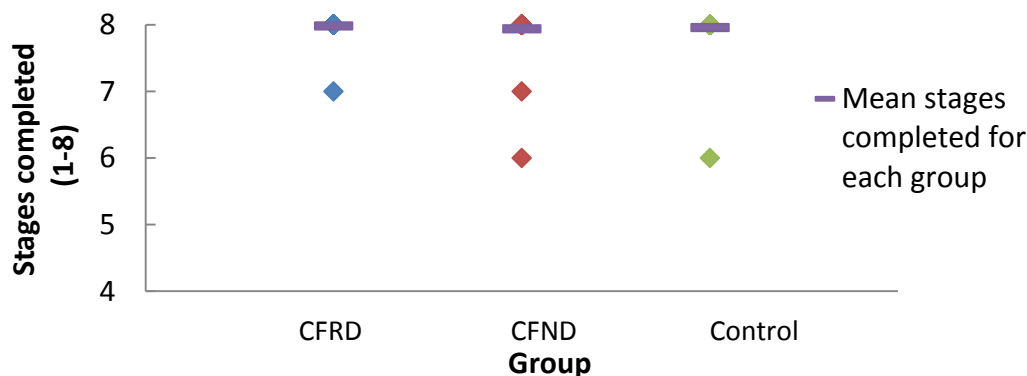
Figure 5.42 Study 1. Number of stages completed on the PAL test

5.3.4.2.2 Stages completed on first trial

Age was a significant covariate, $F(1, 142) = 31.06$, $p < .001$, $\eta_p^2 = .176$. Younger participants completed more stages on the first trial than older participants. Stages completed was not a significant covariate, $F(1, 142) = 0.35$, $p = .55$, $\eta_p^2 = .002$. There was a significant main effect of group, $F(2, 142) = 10.36$, $p < .001$, $\eta_p^2 = .13$ ($R^2 = .256$), such that controls completed significantly more stages on the first trial than those with CFRD ($p = .040$) and CFND ($p < .001$; see Figure 5.43).
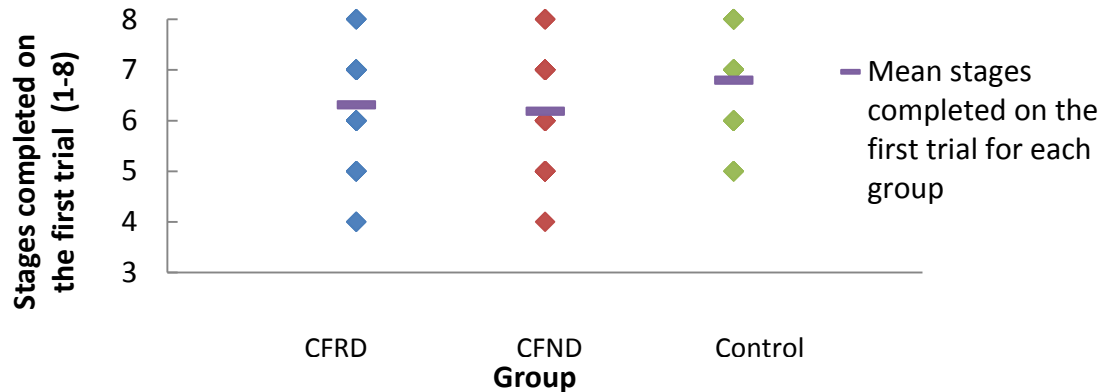
Figure 5.43 Study 1. Number of stages completed on the first trial on the PAL test

5.3.4.2.3 First trial memory score

Data were reflected and a logarithm transformation applied due to substantial negative skewness. Age was a significant covariate, $F(1, 142) = 22.13$, $p < .001$, $\eta_p^2 = .135$ and stages completed showed a trend, $F(1, 142) = 3.42$, $p = .067$, $\eta_p^2 = .024$. As expected, that participants who completed more stages have a higher first trial memory score, and younger participants located more patterns on the first trial of each stage. There was a significant main effect of group, $F(2, 142) = 9.45$, $p < .001$, $\eta_p^2 = .118$ ($R^2 = .244$) such that the control group correctly located more patterns on each first trial compared to those in the CFND group ($p < .001$) and the CFRD group ($p = .015$; see Figure 5.44).
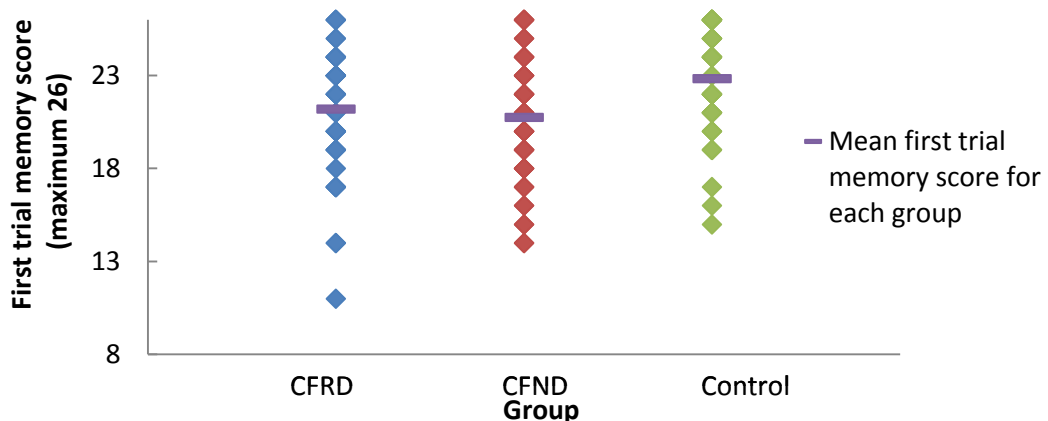
Figure 5.44 Study 1. First trial memory score on the PAL test

5.3.4.2.4 Total trials

Data were square root transformed due to moderate positive skewness. Data for one participant was removed from the analysis as an outlier. Age was a significant covariate, $F(1, 141) = 20.58$, $p < .001$, $\eta_p^2 = .127$, and stages completed was a significant covariate, $F(1, 141) = 25.27$, $p < .001$, $\eta_p^2 = .152$. These indicated that younger participants performed better than older participants. As stages completed was a significant covariate, this was taken into account when the effects of group were considered. There was a significant main effect of group, $F(2, 141) = 11.45$, $p < .001$, $\eta_p^2 = .140$ ($R^2 = .358$), such that the control group took significantly less trials to complete the test compared to those in the CFND group ($p < .001$) and the CFRD group ($p = .006$) even when stages completed were taken into account (see Figure 5.45).
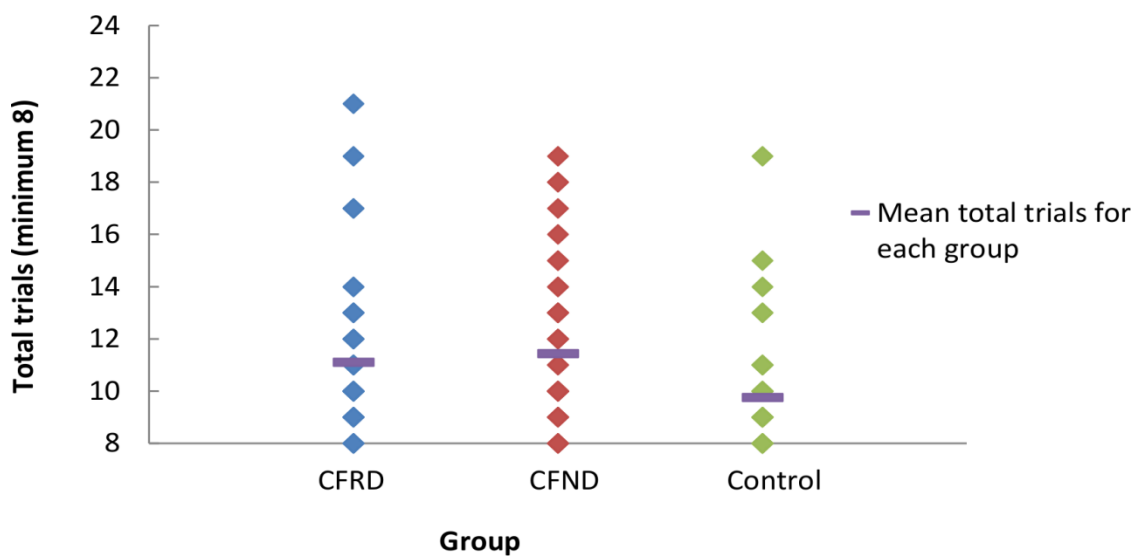
Figure 5.45 Study 1. Total trials on the PAL test (excluding one outlier)

5.3.4.2.5 Total trials at n-patterns

16 data points were excluded as outliers. Age was a significant covariate, $F(1, 143) = 38.46$, $p < .0001$, which indicated that younger participants performed better than older participants. There was no group*level interaction $F(8, 560) = 1.40$, $p = .20$. There was a significant main effect of group, $F(2, 143) = 7.62$, $p = .0007$ (AICC = 1515.9), such that there was a trend for the control group to need less trials than the CFRD group ($p = .07$) and CFND group ($p = .0004$; see Figure 5.46). As expected, there was a significant main effect of level, $F(4, 560) = 101.10$, $p < .0001$, such that the control group needed significantly less trials at locating 8 patterns ($p = .01$), and there was a trend for less trials at locating 6 patterns ($p = .057$), compared to the CFND group.
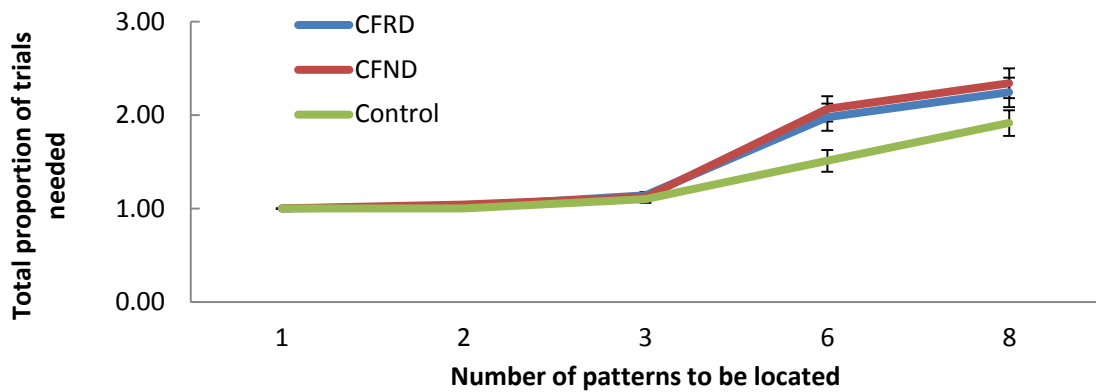
Figure 5.46 Study 1. Total number of trials at each at n-pattern (1,2,3,6,8; outliers excluded) on the PAL test

5.3.4.2.6 Total errors

Data were square root transformed due to moderate positive skewness. Age was a significant covariate, $F(1, 142) = 20.55$, $p < .001$, $\eta_p^2 = .126$ as was stages completed, $F(1, 142) = 12.77$, $p < .001$, $\eta_p^2 = .082$. Younger participants performed better than older participants. As stages completed was a significant covariate, this was taken into account when the effects of group were considered. There was a main effect of group, $F(2, 142) = 11.47$, $p < .001$, $\eta_p^2 = .139$ ($R^2 = .304$), such that the control group made significantly less errors compared to those in the CFRD group ($p = .003$) and CFND group ($p < .001$) even when stages completed were taken into account (see Figure 5.47).
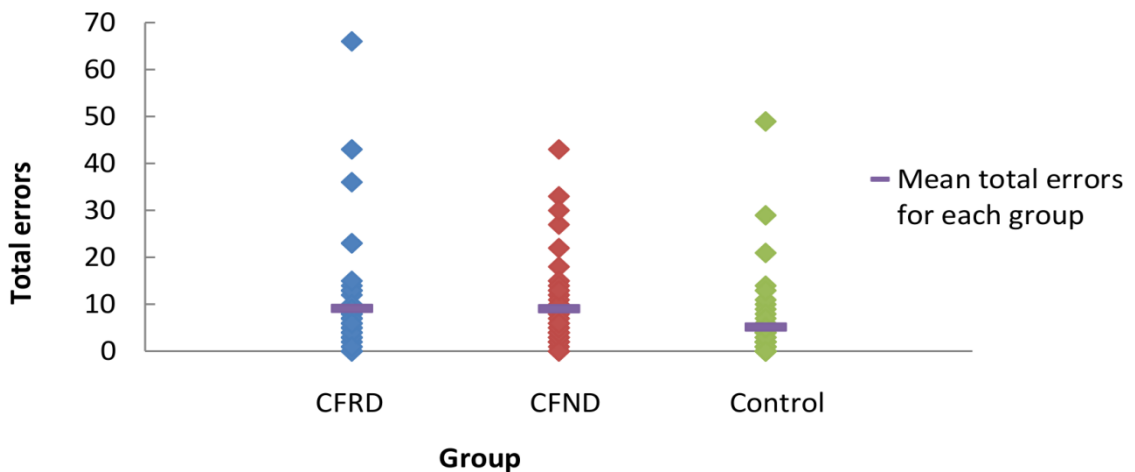
Figure 5.47 Study 1. Total number of errors produced on the PAL test

5.3.4.2.7 Total errors at n-patterns

12 data points were excluded as outliers. Age was a significant covariate, $F(1, 143) = 27.29$, $p < .0001$, which indicated that younger participants performed better than older participants. There was a significant main effect of group, $F(2, 143) = 7.09$, $p = .0012$ (AICC = -3003.2),

such that the control group made significantly less errors than the CFND group ($p = .0007$; see Figure 5.48). As expected, there was a significant main effect of level, $F(4, 564) = 82.34$, $p < .0001$, such that the control group made significantly less errors at locating 8 patterns than the CFND group ($p = .0003$). There was no significant group*level interaction $F(8, 564) = 2.22$, $p = .20$.
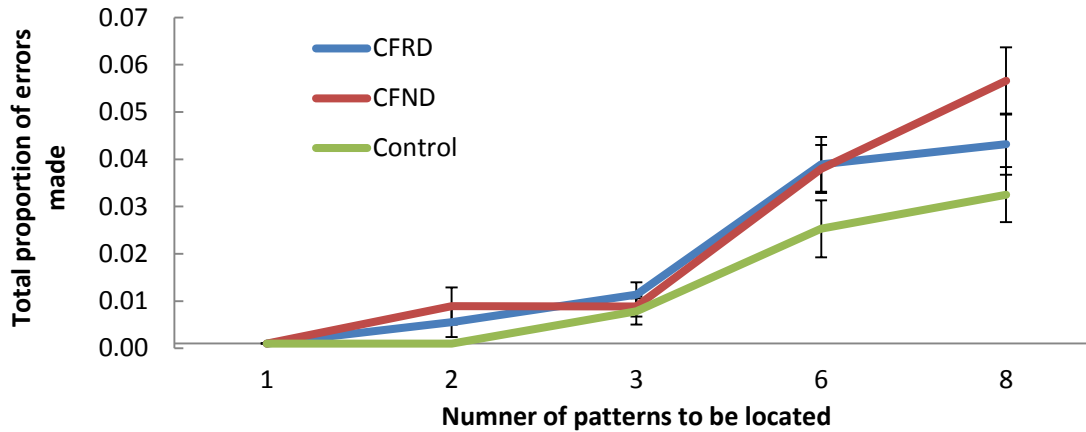
Figure 5.48 Study 1. Number of errors produced at each n-pattern (1,2,3,6,8; outliers removed) on the PAL test

5.3.4.3 **Verbal Recognition Memory (VRM)**

The cognitive test outcome measures are the same for immediate and delayed tests, but data were analysed separately since each involves different brain processes (Cowan, 2008). The outcome measures for the free recall test are the number of correctly recalled words, the number of novel words and the number of perseverations (number of times a participant repeated a word they had already successfully recalled from the word list). The outcomes measures for the recognition test are correct number of target words and number of false positives (see section 5.2.3.3.3; Table 5.4 for a definition of each outcome variable).

5.3.4.3.1 Immediate free recall

5.3.4.3.1.1 Number of correctly recalled words at immediate recall

The covariate for age showed a trend, $F(1, 143) = 2.87$, $p = .093$, $\eta_p^2 = .02$. Younger participants tended to recall more words than older participants. There was a significant main effect of group, $F(2, 143) = 8.94$, $p < .001$, $\eta_p^2 = .111$ ($R^2 = .123$) such that controls correctly recalled more words than those in the CFRD group ($p = .001$) and the CFND group ($p = .002$; see Figure 5.49).
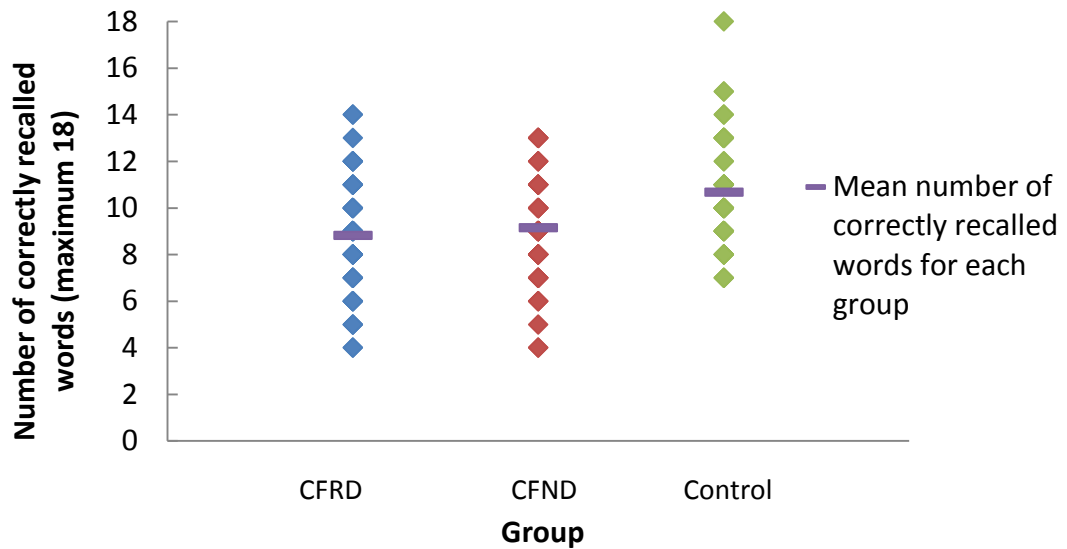
Figure 5.49 Study 1. Number of correctly recalled words at immediate free recall on the VRM Test

5.3.4.3.1.2 Number of novel words produced at immediate recall

Data were severely positively skewed and therefore an inverse transformation was applied. Data for three participants indicated that they were outliers and were removed from the analysis. Age was not a significant covariate, $F(1, 140) = 0.10$, $p = .76$, $\eta_p^2 = .001$ and therefore not a significant predictor of the number of novel words produced at immediate recall (covariates evaluated at 30.23 years). There was a significant main effect of group, $F(2, 140) = 5.80$, $p = .004$, $\eta_p^2 = .077$ ($R^2 = .77$) such that controls generated significantly less novel words at immediate recall than those in the CFRD group ($p = .003$; see Figure 5.50) reflecting controls superior performance.
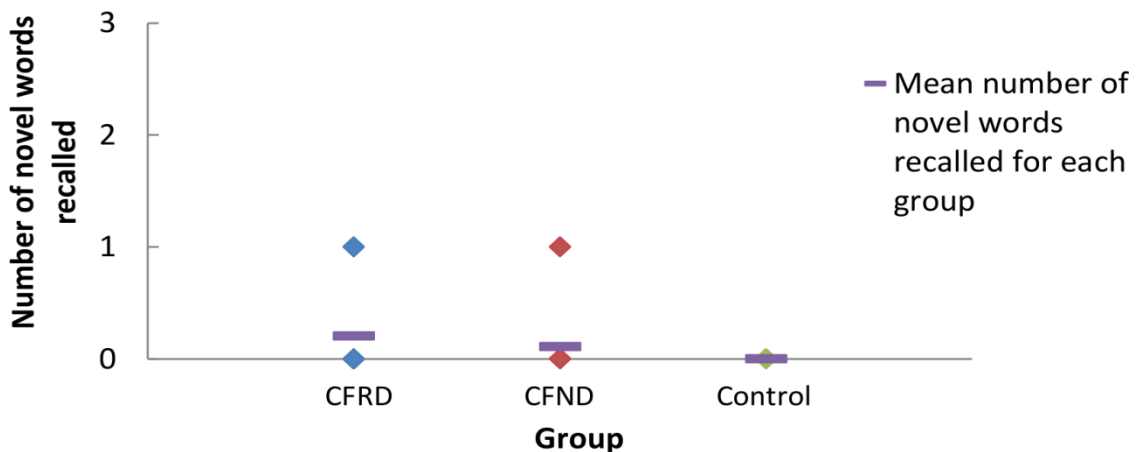
Figure 5.50 Study 1. Number of novel words produced at immediate free recall (excluding three outliers) on the VRM test

5.3.4.3.1.3   Number of perseverations produced at immediate recall

Data for one participant was removed from the analysis. Age was not a significant covariate, $F(1, 142) = 2.18$, $p = .14$, $\eta_p^2 = .015$. There was a significant main effect of group, $F(2, 142) = 6.55$, $p = .002$, $\eta_p^2 = .084$ ($R^2 = .99$) such that controls made significantly fewer words than those in the CFRD group ($p = .002$). There was also a trend for those in the control group to produce less perseverations than those in the CFND group ($p = .056$; see Figure 5.51).
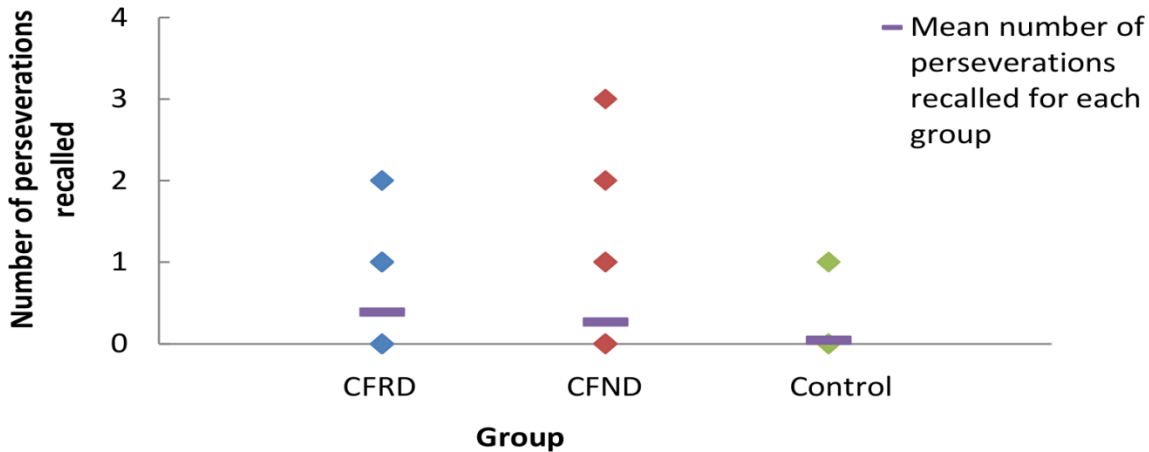
Figure 5.51 Study 1. Number of perseverations at immediate free recall (excluding one outlier) on the VRM test

5.3.4.3.2   Immediate recognition

5.3.4.3.2.1   Total number of correctly recognised target words (recognition task)

Data were reflected and inverse transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 143) = 2.04$, p $= .16$, $\eta_p^2 = .014$. There was no main effect of group, $F(2, 143) = 0.21$, $p = .81$, $\eta_p^2 = .003$ ($R^2 = .017$; see Figure 5.52).
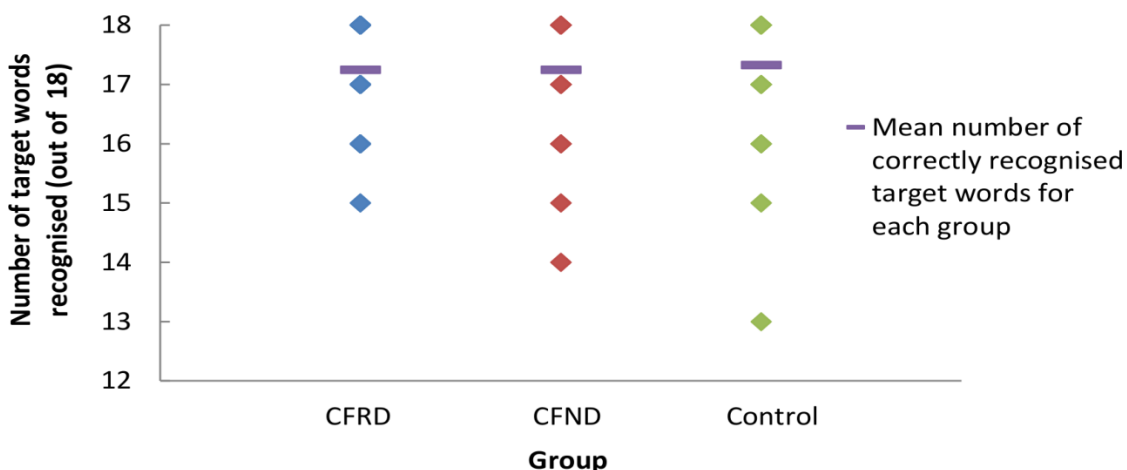
Figure 5.52 Study 1. Total number of correctly recognised target words on the immediate recognition test (excluding two outliers) on the VRM test

5.3.4.3.2.2   Total number of false positives (recognition task)

Data were substantially positively skewed and a logarithm transformation was applied. Data for three participants were removed from the analysis. Age was not a significant covariate, $F(1, 140) = 1.21$, $p = .27$, $\eta_p^2 = .009$. There was a no main effect of group, $F(2, 140) = 0.91$, $p = .41$, $\eta_p^2 = .013$ ($R^2 = .020$; see Figure 5.53).
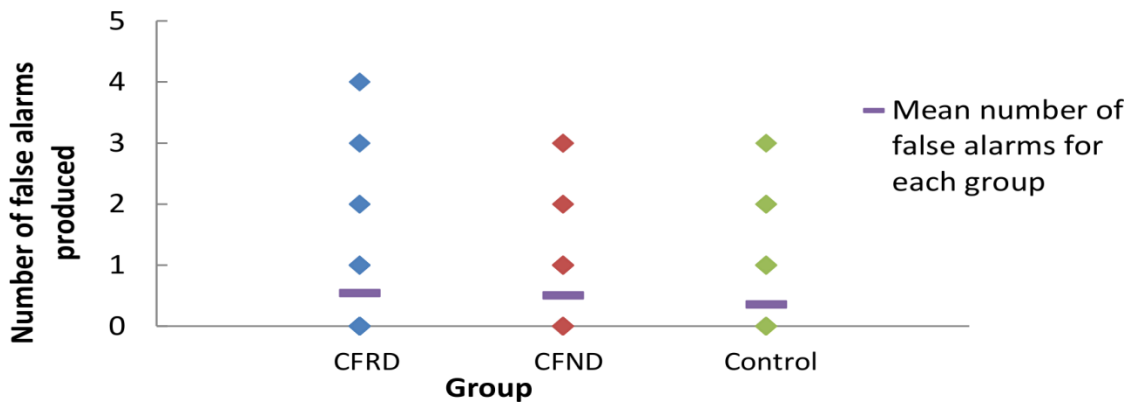
Figure 5.53 Study 1. Total number of false positives produced at immediate recognition on the VRM test

5.3.4.3.3   Delayed free recall

5.3.4.3.3.1   Total number of correctly recalled words at delayed recall

Age showed a trend when included as a covariate, $F(1, 143) = 2.93$, $p = .089$, $\eta_p^2 = .021$. Younger participants tended to recall more words than older participants. There was a significant main effect of group, $F(2, 143) = 9.81$, $p < .001$, $\eta_p^2 = .121$ ($R^2 = .128$) such that controls correctly recalled more words at delayed recall than those in the CFRD group ($p = .003$) and the CFND group ($p < .001$; see Figure 5.54).
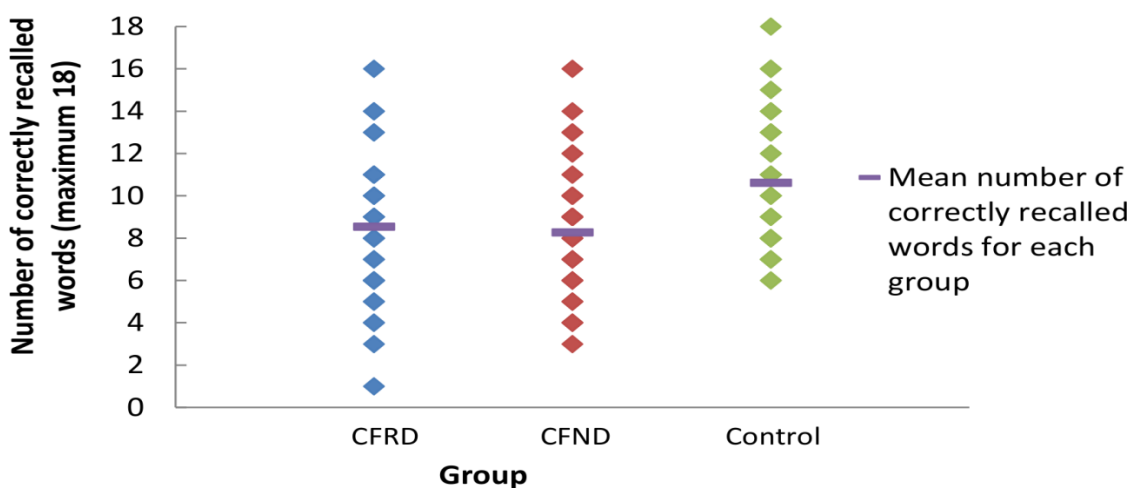
Figure 5.54 Study 1. Total number of correctly recalled words at delayed recall on the VRM test

5.3.4.3.3.2 Number of novel words produced at delayed recall

Data were severely positively skewed and therefore an inverse transformation was applied. Age was not a significant covariate, $F(1, 143) = 2.04$, $p = .16$, $\eta_p^2 = .014$. There was a significant main effect of group, $F(2, 143) = 8.14$, $p < .001$, $\eta_p^2 = .102$ ($R^2 = .111$) such that controls generated significantly less novel words at delayed recall than those in the CFRD group $(p = .001)$ and CFND group $(p = .004$; see Figure 5.55).
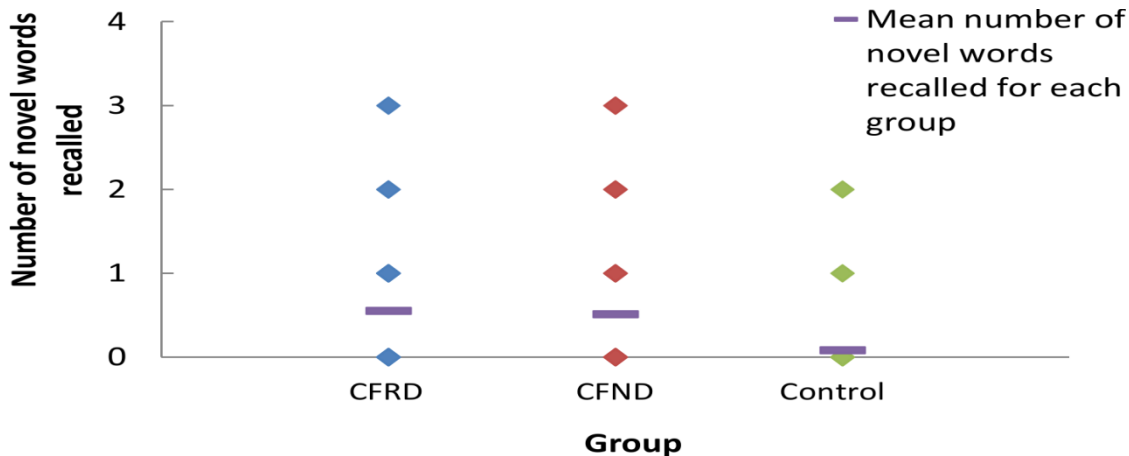
Figure 5.55 Study 1. Number of novel words produced at delayed free recall on the VRM test

5.3.4.3.3.3 Number of perseverations words produced at delayed recall

Data were severely positively skewed and therefore an inverse transformation was applied. Age was not a significant covariate, $F(1, 143) = 0.26$, $p = .61$, $\eta_p^2 = .002$. There was a significant main effect of group, $F(2, 143) = 6.68$, $p = .002$, $\eta_p^2 = .085$ ($R^2 = .088$) such that controls generated significantly less perseverations at delayed recall than those in the CFRD group $(p = .002)$ and CFND group $(p = .019$; see Figure 5.56).
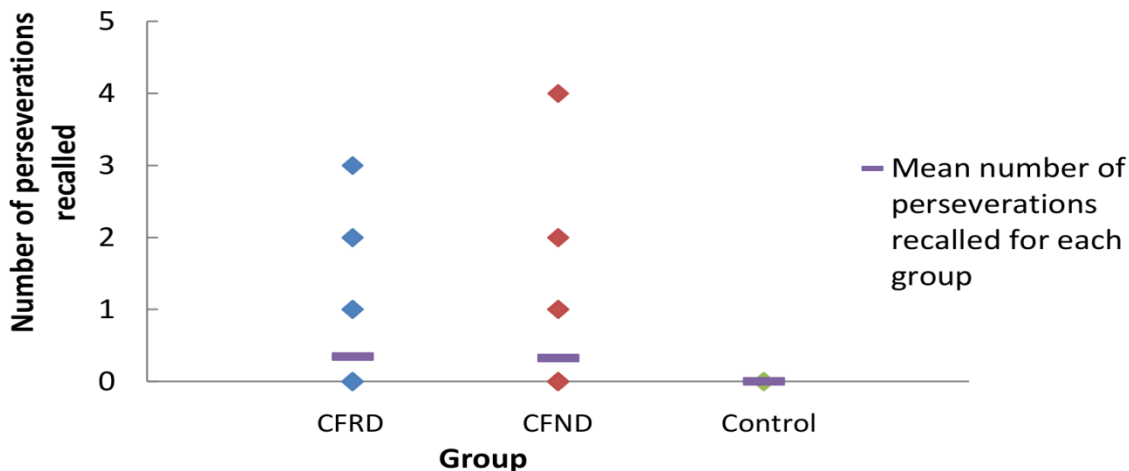
Figure 5.56 Study 1. Number of perseverations at delayed free recall on the VRM test

5.3.4.3.4 Delayed recognition

5.3.4.3.4.1 Total number of correctly recognised target words (recognition task)

Data were substantially negatively skewed and therefore data were reflected and a logarithm transformation applied. Data for one participant was removed from the analysis. Age showed a trend when included as a covariate, $F(1, 142) = 3.38$, p = .068, $\eta_p^2 = .023$. Younger participants correctly recognised more targets words than older participants. There was a significant main effect of group, $F(2, 142) = 3.97$, $p = .021$, $\eta_p^2 = .053$ ($R^2 = .070$). Post hoc analyses showed that the control group correctly recognised significantly more target words than those in the CFRD group ($p = .044$) and marginally significantly more target words than the CFRD group just failed to reach significance ($p = .055$; see Figure 5.57).
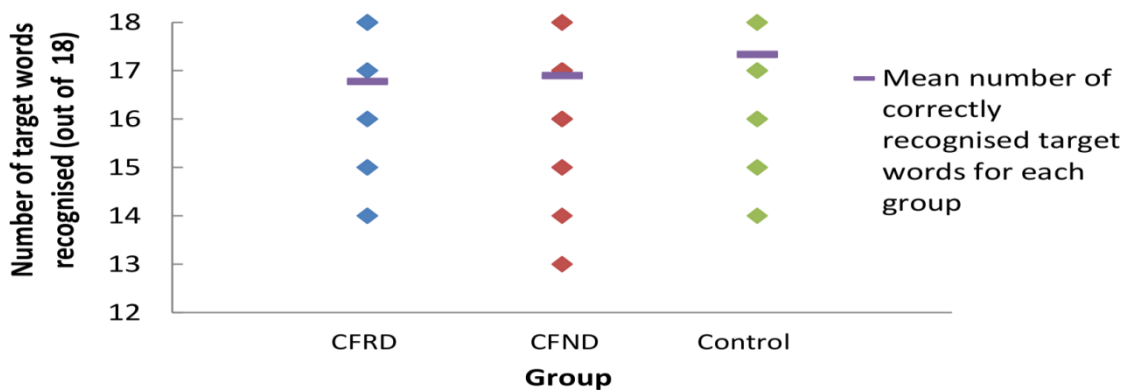
Figure 5.57 Study 1. Total number of correctly recognised target words on the delayed recognition test (excluding one outlier) on the VRM test

5.3.4.3.4.2 Total number of false positives (recognition task)

Age was not a significant covariate, $F(1, 143) = 0.74$, $p = .79$, $\eta_p^2 = .001$. There was no main effect of group, $F(2, 143) = 0.57$, $p = .57$, $\eta_p^2 = .008$ ($R^2 = .009$; see Figure 5.58).
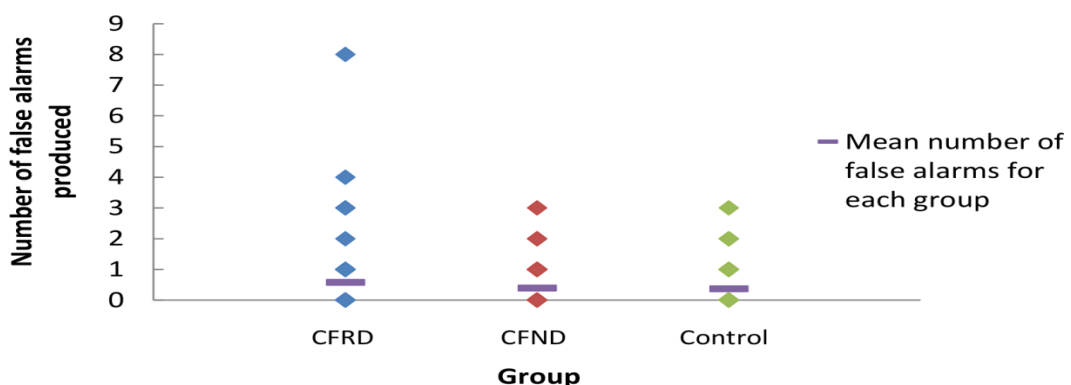
Figure 5.58 Study 1. Total number of false positives produced at delayed recognition on the VRM test

5.3.4.4 **Pattern Recognition Memory (PRM)**

The cognitive test outcome measures are the same for immediate and delayed tests. Data for immediate and delayed were analysed separately between the immediate and delayed tests because they involve different brain processes (Cowan, 2008). The outcome measures are the number of correctly recognised patterns and the reaction time to recognise the patterns (see section 5.2.3.3.4; Table 5.4 for a definition of each outcome variable).

5.3.4.4.1 Immediate pattern recognition

5.3.4.4.1.1 Number of correctly recognised patterns

Data were reflected and inverse transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 143) = 0.90$, $p = .35$, $\eta_p^2 = .006$. There was no significant main effect of group, $F(2, 143) = 1.16$, $p = .32$, $\eta_p^2 = .016$ ($R^2 = .019$; see Figure 5.59).
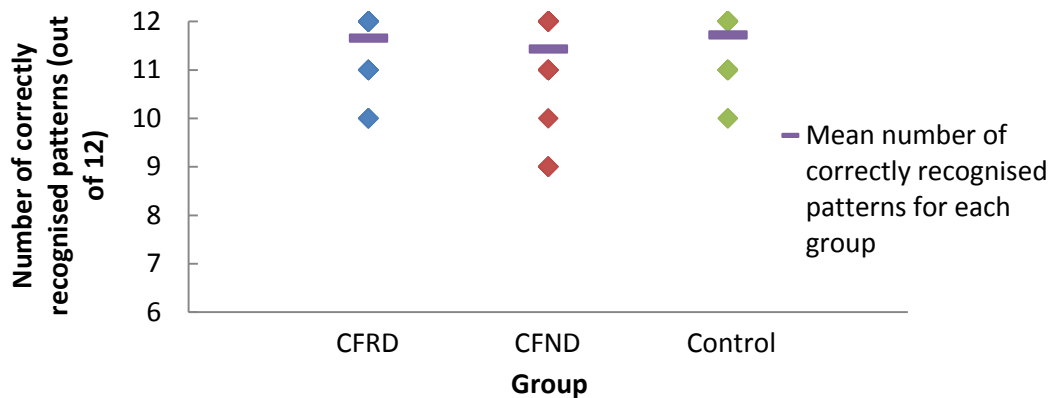
Figure 5.59 Study 1. Number of correctly recognised patterns at immediate recognition on the PRM test

5.3.4.4.1.2 Reaction time for correctly recognised patterns

Data were moderately positively skewed and therefore a square root transformation was applied. Data for one participant was removed from the analysis. Age was not a significant covariate, $F(1, 142) = 1.24$, $p = .27$, $\eta_p^2 = .009$. There was no significant main effect of group, $F(2, 142) = 2.04$, $p = .13$, $\eta_p^2 = .028$ ($R^2 = .036$; see Figure 5.60).
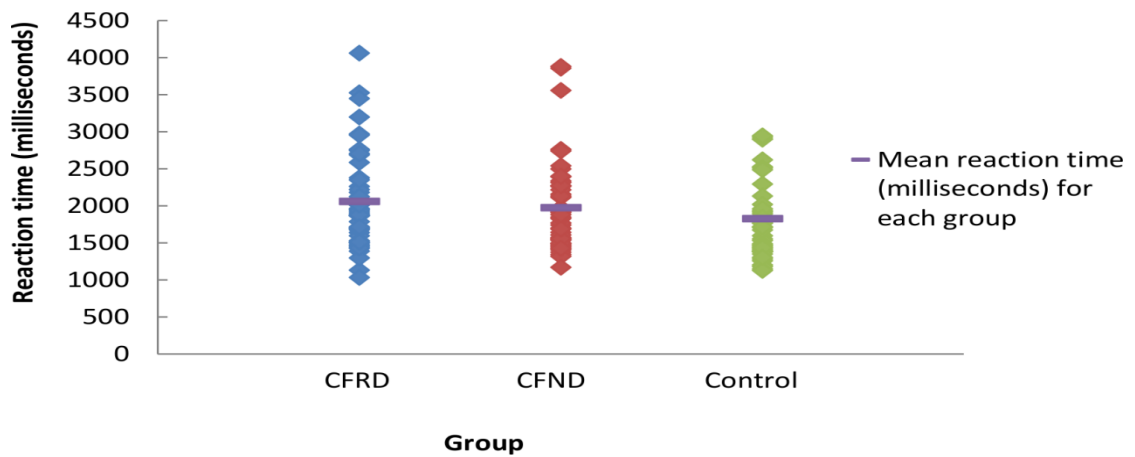
Figure 5.60 Study 1. Reaction time for correctly recognised patterns at immediate recognition on the PRM test

5.3.4.4.2 Delayed pattern recognition

5.3.4.4.2.1 Number of correctly recognised patterns

Data were moderately negatively skewed and therefore a reflected square root transformation was applied. Age was not a significant covariate, $F(1, 143) = 1.39$, $p = .24$, $\eta_p^2 = .01$. There was a significant main effect of group, $F(2, 143) = 3.26$, $p = .04$, $\eta_p^2 = .044$ ($R^2 = .052$). Post hoc tests showed that the control group correctly recognised significantly more patterns than those in the CFRD group ($p = .049$; see Figure 5.61) but not the CFRD group (ns).
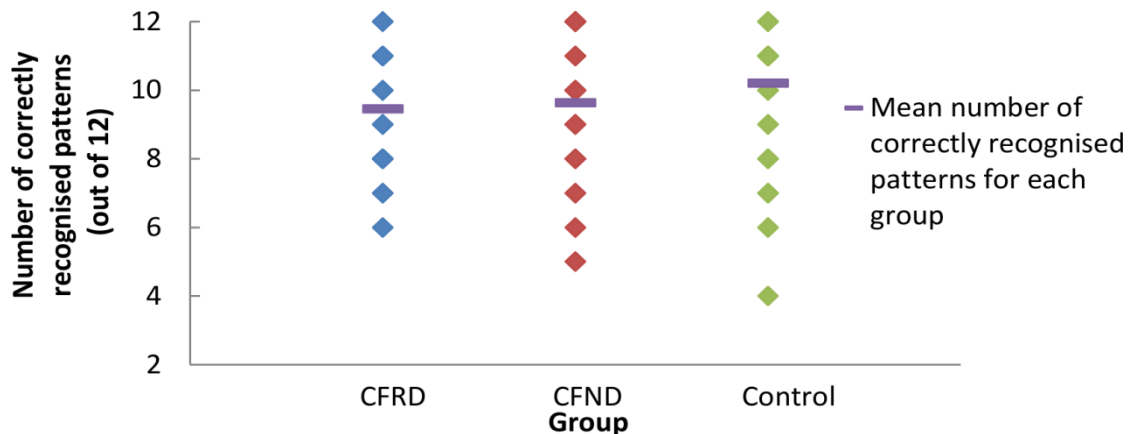
Figure 5.61 Study 1. Number of correctly recognised patterns at delayed recognition on the PRM test

5.3.4.4.2.2 Reaction time for correctly recognised patterns

Data were moderately positively skewed and therefore square root transformation was applied. Age was not a significant covariate, $F(1, 144) = 0.85$, $p = .36$, $\eta_p^2 = .006$. There was a significant main effect of group, $F(2, 144) = 3.76$, $p = .026$, $\eta_p^2 = .05$ ($R^2 = .058$), such that

the control group were significantly faster at identifying the correct pattern from the two-choice forced discrimination paradigm compared to the CFRD group (p = .021; see Figure 5.62) but not CFND (ns).
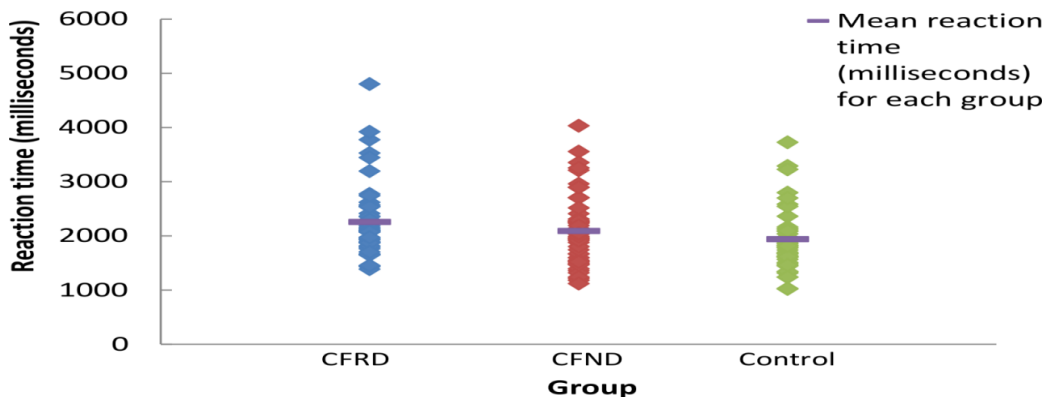
Figure 5.62 Study 1. Reaction time for correctly recognised patterns at delayed recognition on the PRM test

5.3.4.5 Rapid Visual Processing (RVP)

There are a total of 36 target sequences to detect (see section 5.2.5.3.5) on the four minute task (9 per minute). The outcome measures for the RVP tests are: total hits, total hits at each minute, total false alarms, total false alarms at each minute, reaction time for hits, reaction time for hits at each minute, A' prime, and B' prime (see section 5.2.3.3.5, and Table 5.4 for a definition of each outcome variable).

5.3.4.5.1 Total hits (correct detections of target sequences)

Data were reflected and square root transformed due to moderate negative skewness. Age was not a significant covariate, $F(1, 143) = 0.08$, p = .78, $\eta_p^2 = .001$. There was a main effect of group, $F(2, 143) = 29.56$, $p < .001$, $\eta_p^2 = .293$ ($R^2 = .296$), such that the control group made significantly more correct detections of target sequences compared to those in the CFRD ($p < .001$) and CFND group ($p < .001$; see Figure 5.63). The majority of the control group detected at least 50% of target sequences, whereas performance in the CFRD group varied from detecting nearly 100% of target sequences to less than 12%.
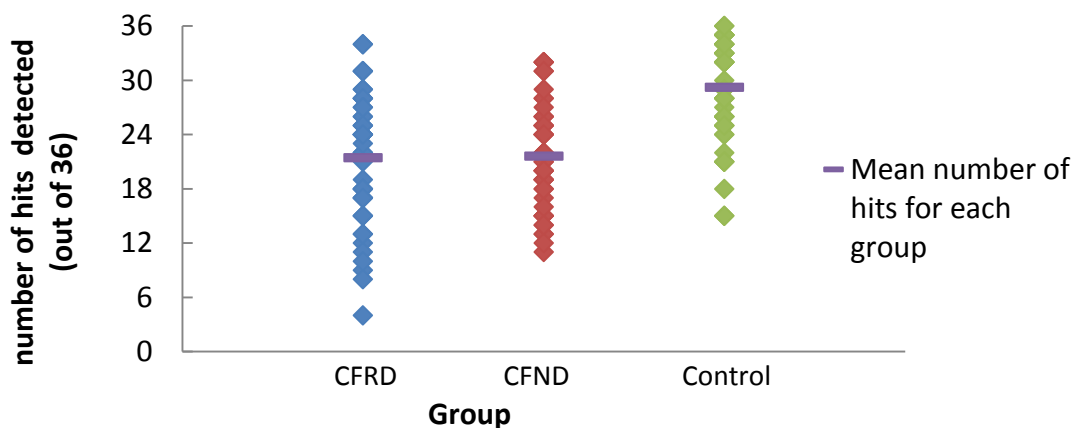
Figure 5.63 Study 1. Total hits (correct detections) on the RVP test

5.3.4.5.2 Total hits at each minute

Age was not a significant covariate, $F(1, 143) = 0.23$, $p = .63$. There was a significant main effect of group, $F(2, 143) = 24.83$, $p < .0001$ (AICC = 2260.8), such that the control group detected significantly more target sequences than the CFND ($p < .0001$) and CFRD group ($p < .0007$; see Figure 5.64). As expected, there was a significant main effect of level, $F(3, 432) = 2.94$, $p = .03$, but not significant group*level interaction $F(6, 432) = 0.27$, $p = .95$. The control group corrected detected more target sequences than the CFND group at minute 1 ($p < .0001$), minute 2 ($p = .0005$), minute 3 ($p = .0004$) and minute 4 ($p = .0005$), and more than the CFRD group at minute 1 ($p < .0001$), minute 2 ($p < .0001$), minute 3 ($p < .0001$) and minute 4 ($p = .0005$).
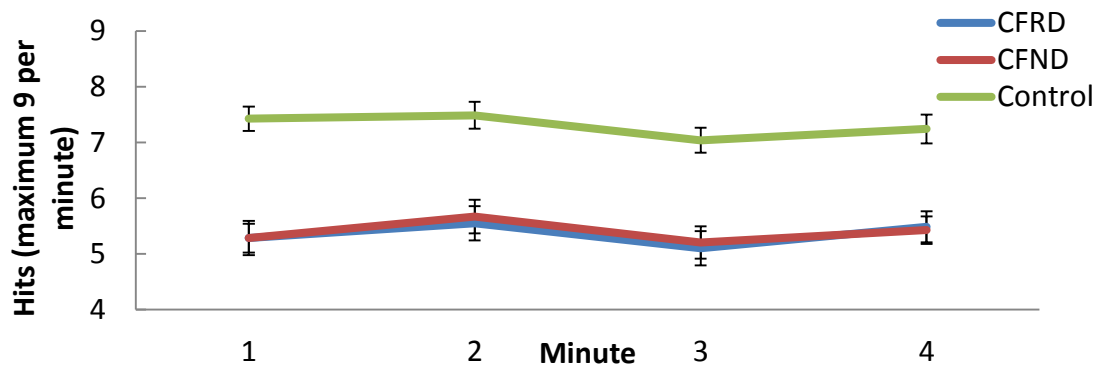
Figure 5.64 Study 1. Mean (+/-SE) number of hits at each minute of the RVP test

5.3.4.5.3 Total false alarms

Data were reflected and square root transformed due to moderate negative skewness. Data for one participant included data points was excluded. Age was not a significant covariate, $F(1, 142) = 1.16$, $p = .28$, $\eta_p^2 = .008$. There was no significant main effect of group, $F(2, 142) = 2.12$, $p = .12$, $\eta_p^2 = .029$ ($R^2 = .032$; see Figure 5.65).
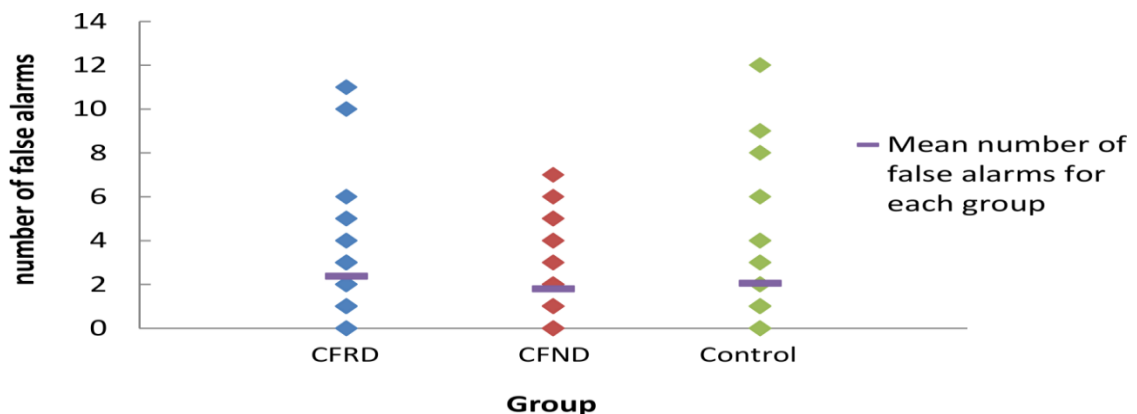
Figure 5.65 Study 1. Total number of false alarms produced on the RVP test (excluding one outlier)

5.3.4.5.4 Mean reaction time for hits

Data were square root transformed due to moderate positive skewness. Age was a significant covariate, $F(1, 140) = 4.33$, $p = .039$, $\eta_p^2 = .030$. Younger participants responded faster to detecting target sequences than older participants. There was a no main effect of group, $F(2, 140) = 0.97$, $p = .38$, $\eta_p^2 = .014$ ($R^2 = .037$). Figure 5.66 shows there was more variation in reaction time when correctly responding to target sequences in the CFRD and CFND groups than the controls.
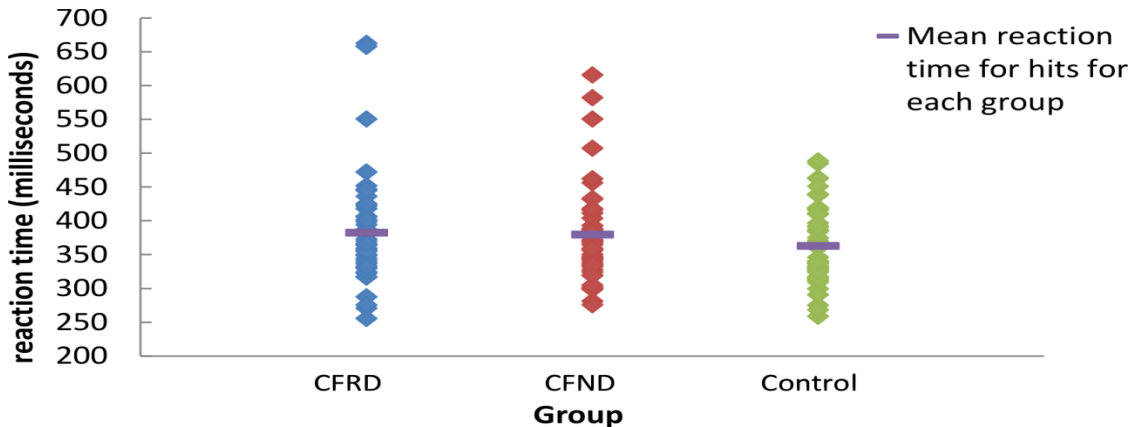
Figure 5.66 Study 1. Mean reaction time for hits on the RVP test

5.3.4.5.5 Reaction time for hits at each minute

12 data points were excluded as outliers. Age was a significant covariate, $F(1, 143) = 4.63$, $p = .03$, which indicated that younger participants responded faster than older participants. There was no significant main effect of group, $F(2, 143) = 1.09$, $p = .34$ (AICC = 6464.3). As expected, there was a significant main effect of level, $F(3, 420) = 7.46$, $p < .0001$, such that responding was slower to target sequences over time (see Figure 5.67), and there was a significant group*level interaction $F(6, 420) = 2.15$, $p = .047$. The post hoc tests showed no significant differences between groups.
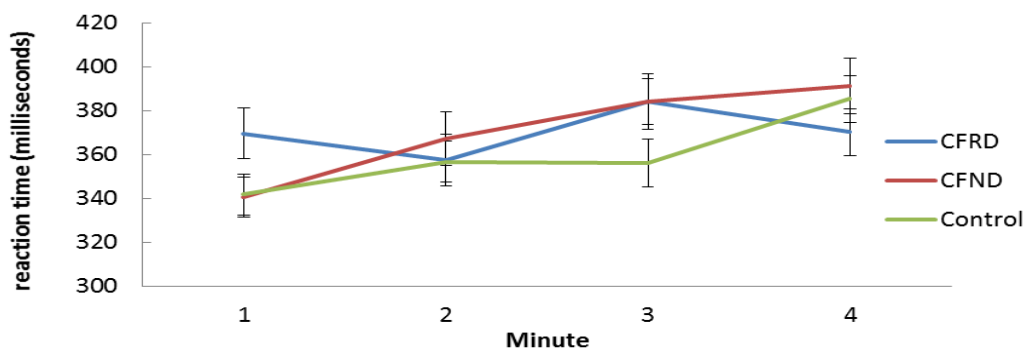
Figure 5.67 Study 1. Mean (+/-SE) reaction time for hits at each minute of the RVP test

5.3.4.5.6 A' Prime

Data were reflected and square root transformed due to moderate negative skewness. Age was not a significant covariate, $F(1, 143) = 0.35$, $p = .55$, $\eta_p^2 = .002$. There was a significant main effect of group, $F(2, 143) = 23.97$, $p < .001$, $\eta_p^2 = .251$ ($R^2 = .256$), such that the control group had a significantly better sensitivity to detecting target sequences compared to those in the CFRD ($p < .001$) and CFND group ($p < .001$; see Figure 5.68).
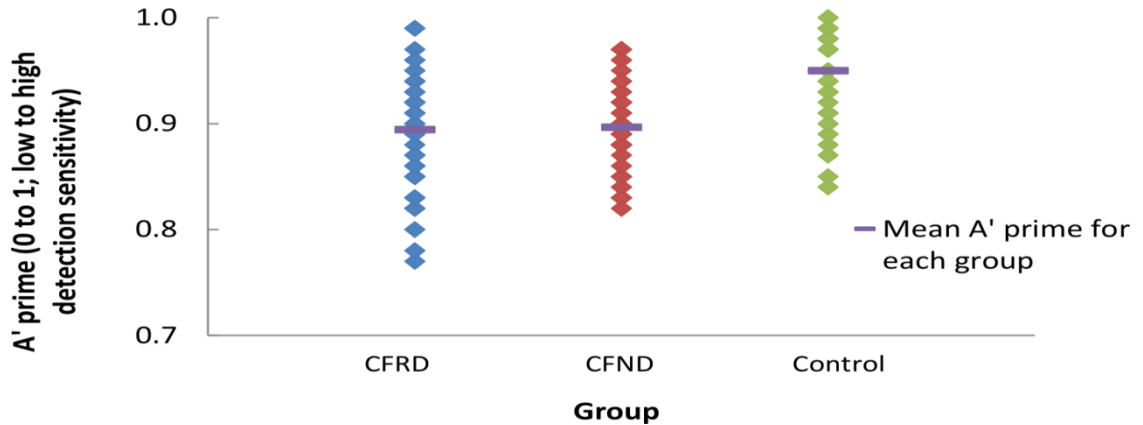
Figure 5.68 Study 1. A' prime (Sensitivity to the target, regardless of response tendency) on the RVP test

5.3.4.5.7 B' Prime

Data were reflected and an inverse transformation applied due to severe negative skewness. There was a significant main effect of group, $F(2, 143) = 7.03$, $p = .001$, $\eta_p^2 = .090$, ($R^2 = .097$), such that the control group were significantly more biased (i.e. made more guesses) compared to those in the CFND ($p = .001$) and there was a trend for the control group to be more biased than the CFRD group ($p = .083$; see Figure 5.69).
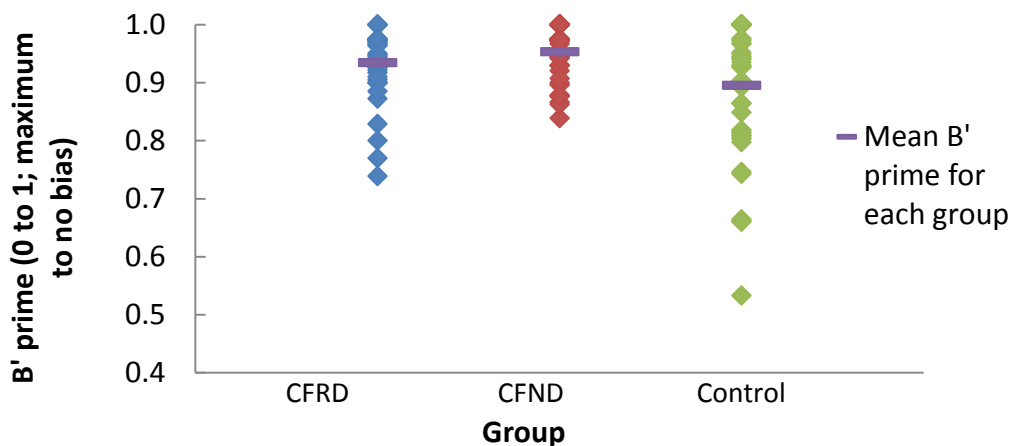
Figure 5.69 Study 1. B' prime (tendency to respond regardless of whether the target sequence is present) on the RVP test

5.3.4.6 **Spatial span (SSP)**

The outcome measures for SSP are span length, number of attempts (overall and per level), reaction time (mean time to first and last response), and errors (total and usage; see section 5.2.3.3.6, and Table 5.4 for a definition of each outcome variable). As the degree of test completion varies as a function of individual performance (i.e. test difficulty increases with each span length (2-9) and the test terminates if a sequence is not successfully recalled at 'n' span length after 3 attempts), span length was included as a covariate in the analyses for all subsequent SSP outcome measures.

5.3.4.6.1 Span length (longest number sequence successfully recalled)

Data were reflected and square root transformed due to moderate negative skewness. Age showed a trend when included as covariate, $F(1, 143) = 3.21$, $p = .076$, $\eta_p^2 = .022$. Younger participants located more patterns on the first trial of each stage than older participants. There was a significant main effect of group, $F(2, 143) = 5.98$, $p = .003$, $\eta_p^2 = .077$ ($R^2 = .094$), such that the control group reached a higher span length compared to those in the CFRD ($p = .005$) and CFND group ($p = .028$; see Figure 6.70). The lowest span length successfully recalled was 3 in the CFRD group.
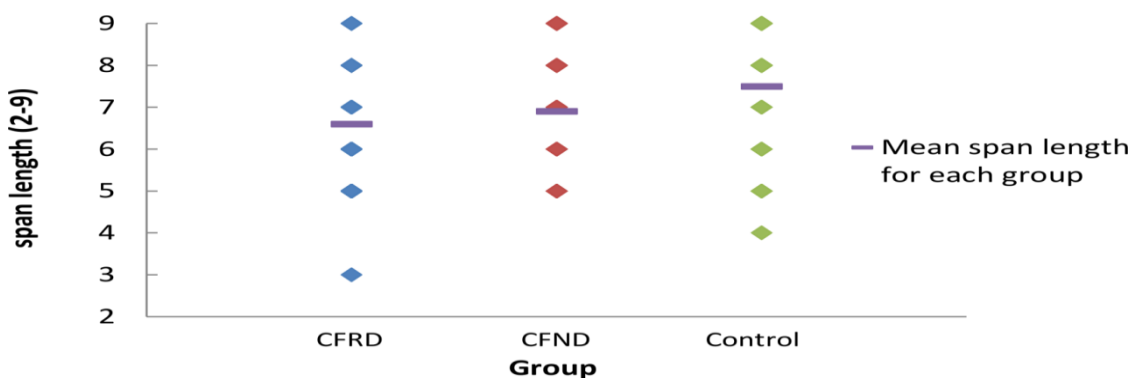
Figure 5.70 Study 1. Span length (longest number sequence successfully recalled; 2-9) on the SSP test

5.3.4.6.2 Total number of attempts

Age was not a significant covariate, $F(1, 142) = 0.24$, $p = .63$, $\eta_p^2 = .002$. Span level was a significant covariate, $F(1, 142) = 128.147$, $p < .001$, $\eta_p^2 = .474$. More attempts were required on the higher span levels compared to the lower levels. There was no main effect of group, $F(2, 142) = 0.21$, $p = .81$, $\eta_p^2 = .003$ ($R^2 = .489$; see Figure 5.71). The higher number of attempts in the control group is a function of better overall performance on this test i.e. they reached higher span levels, and therefore, as task difficulty increased, so did the number of attempts. However, as Figure 5.72 shows, people in the control group needed less attempts at the higher levels.
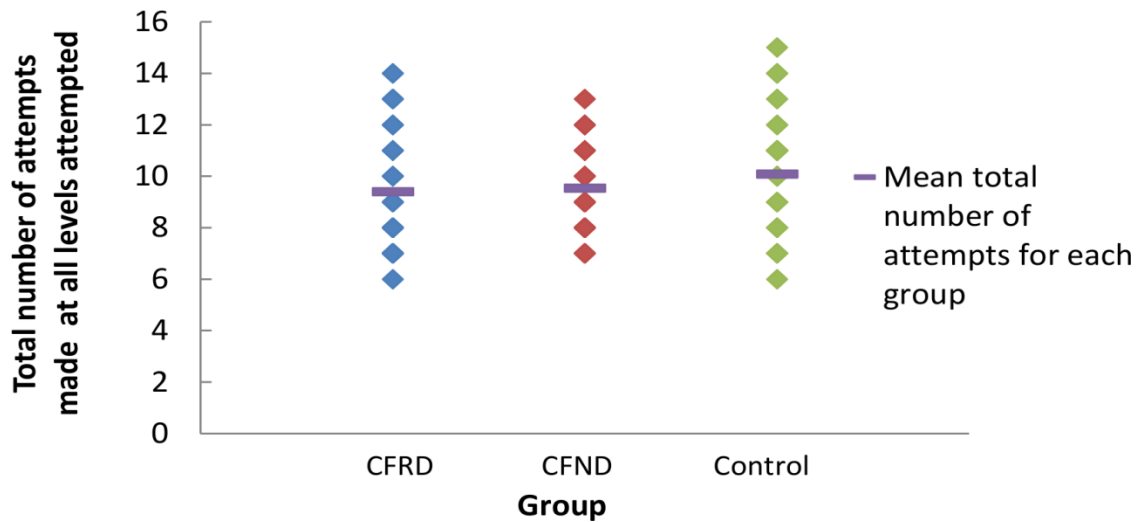
Figure 5.71 Study 1. Total number of attempts made at all levels reached on the SSP test
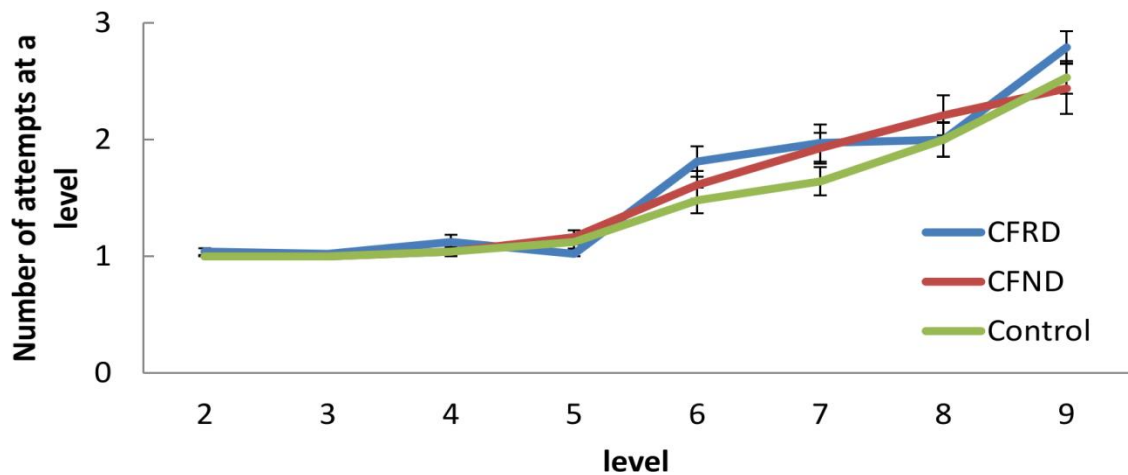
Figure 5.72 Study 1. Mean (+/- SE) number of attempts made at each level on the SSP test

5.3.4.6.3 Reaction time outcome measures on the SSP test

5.3.4.6.3.1 Mean time to first response

Age was not a significant covariate, $F(1, 142) = 0.49$, $p = .48$, $\eta_p^2 = .003$ and span level was not a significant covariate, $F(1, 142) = 0.99$, $p = .32$, $\eta_p^2 = .007$. There was a significant main effect of group, $F(2, 142) = 4.42$, $p = .014$, $\eta_p^2 = .059$ ($R^2 = .063$), such that there was a trend for the control group to respond faster to initiate recalling a sequence compared to the CFRD group ($p = .067$; see Figure 5.73). All the control group made their response within 4 seconds of the presentation finishing, while some participants in the CFRD group took at least 4 seconds before making their first response.
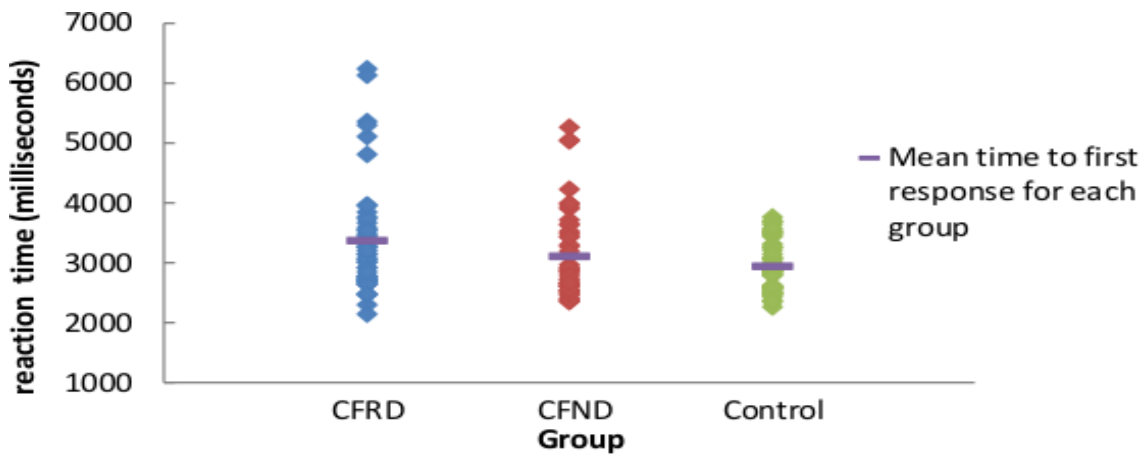
Figure 5.73 Study 1. Mean time to first response (milliseconds) on the SSP test

5.3.4.6.3.2   Mean time to last response

Data for four participants were excluded as outliers. Age was not a significant covariate, $F(1, 138) = 1.55$, $p = .22$, $\eta_p^2 = .011$. Span level was a significant covariate, $F(1, 138) = 16.55$, $p < .001$, $\eta_p^2 = .107$. The mean time to complete recalling a sequence took longer with increasing span length. There was no significant main effect of group, $F(2, 138) = 0.10$, $p = .90$, $\eta_p^2 = .001$ ($R^2 = .136$; see Figure 5.74).
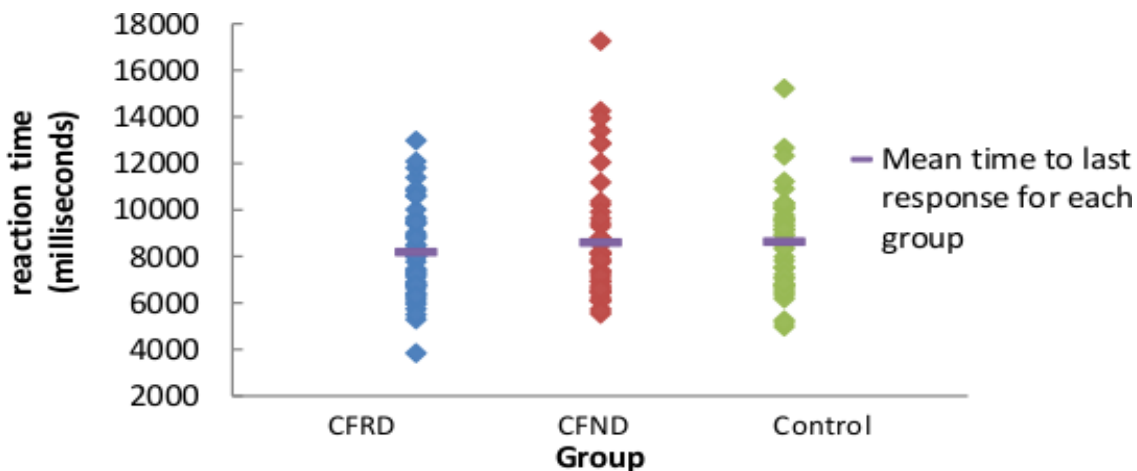
Figure 5.74 Study 1. Mean time to last response (milliseconds) on the SSP test (excluding four outliers)

5.3.4.6.4   Errors

5.3.4.6.4.1   Total errors

Data were square root transformed due to moderate positive skewness. Data for four participants was excluded. Age was not a significant covariate, $F(1,139)=1.39$, $p=.24$, $\eta_p^2=.010$, but span length was, $F(1, 138) = 9.87$, $p = .002$, $\eta_p^2 = .067$. There was no

significant main effect of group, $F(2, 138) = 0.98$, $p = .38$, $\eta_p^2 = .014$ ($R^2 = .072$; see Figure 5.75).
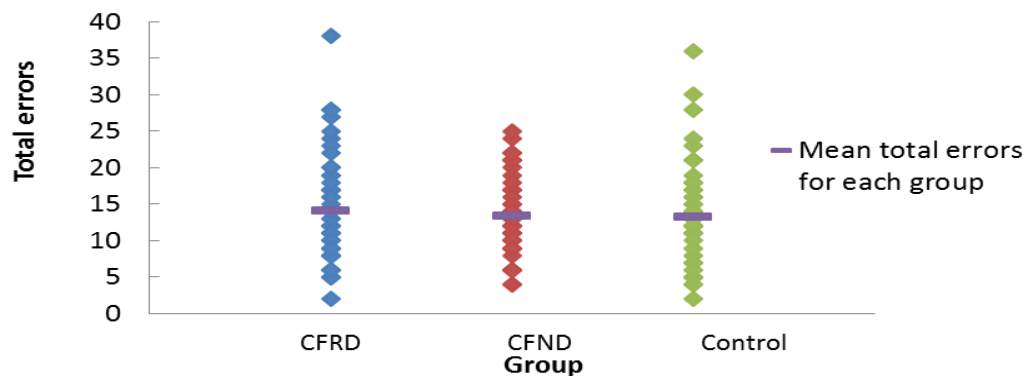
Figure 5.75 Study 1. Total number of errors produced whilst recalling sequences on the SSP test (excluding four outliers)

5.3.4.6.4.2 Total usage errors

Data were square root transformed due to moderate positive skewness. Data for one participant was removed from the analysis. Age was not a significant covariate, $F(1, 141) = 0.64$, $p = .43$, $\eta_p^2 = .005$, but span length was, $F(1, 141) = 43.79$, $p < .001$, $\eta_p^2 = .237$. There was a significant main effect of group, $F(2, 141) = 3.95$, $p = .02$, $\eta_p^2 = .053$ ($R^2 = .311$), such that the control group made significantly fewer errors selecting a box which was not part of the sequence compared to those in the CFND group ($p = .017$; see Figure 5.76).
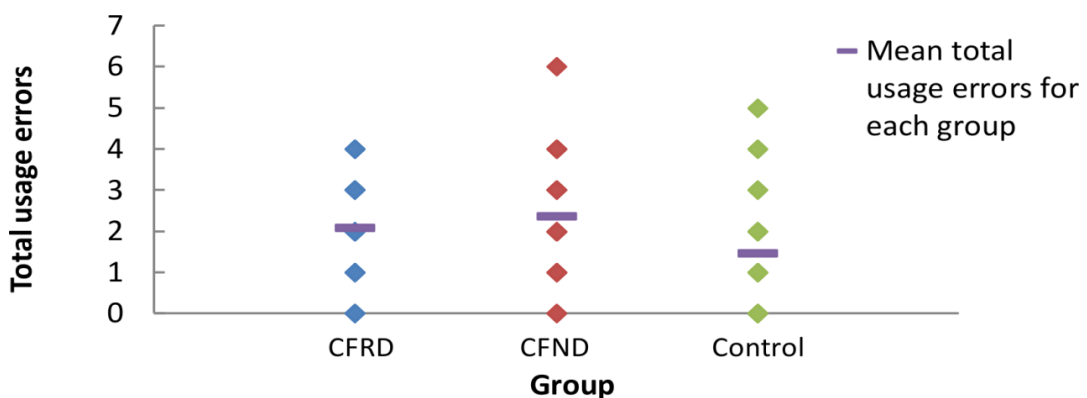
Figure 5.76 Study 1. Total number of usage errors produced on the SSP test (excluding one outlier)

5.3.4.7 Attention switching task (AST)

A total of 160 responses were required per test administration. The outcome measures for AST are accuracy (correct trials), reaction time for correct trials, errors (omission and

commission), congruency cost, and switch cost (see section 5.2.3.3.7, and Table 5.4 for a definition of each outcome variable). As there were an unequal number of switched and non-switched trials, reaction time for switched and non-switched trials and switch cost should be treated with some degree of caution.

5.3.4.7.1 Total correct trials

5.3.4.7.1.1 Total correct trials (overall accuracy)

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 143) = 0.18$, $p = .68$, $\eta_p^2 = .001$. There was no significant main effect of group, $F(2, 143) = 4.03$, $p = .02$, $\eta_p^2 = .053$ ($R^2 = .054$) such that the control group correctly responded to significantly more trials than the CFND group ($p = .016$ see Figure 5.77).
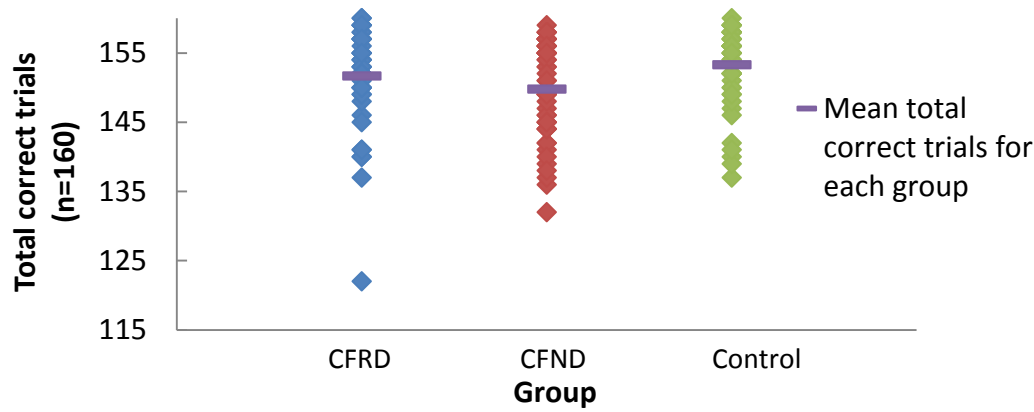
Figure 5.77 Study 1. Total number of correct trials on the AST

5.3.4.7.1.2 Mean reaction time for total correct trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 143) = 0.81$, $p = .37$, $\eta_p^2 = .006$. There was a significant main effect of group, $F(2, 143) = 9.64$, $p < .001$, $\eta_p^2 = .119$ ($R^2 = .125$). Post hoc tests showed the control group were significantly faster to respond to correct trials compared to the CFRD group ($p < .001$). There was also a trend for the control group to respond faster to trials than the CFND group ($p = .065$; see Figure 5.78).
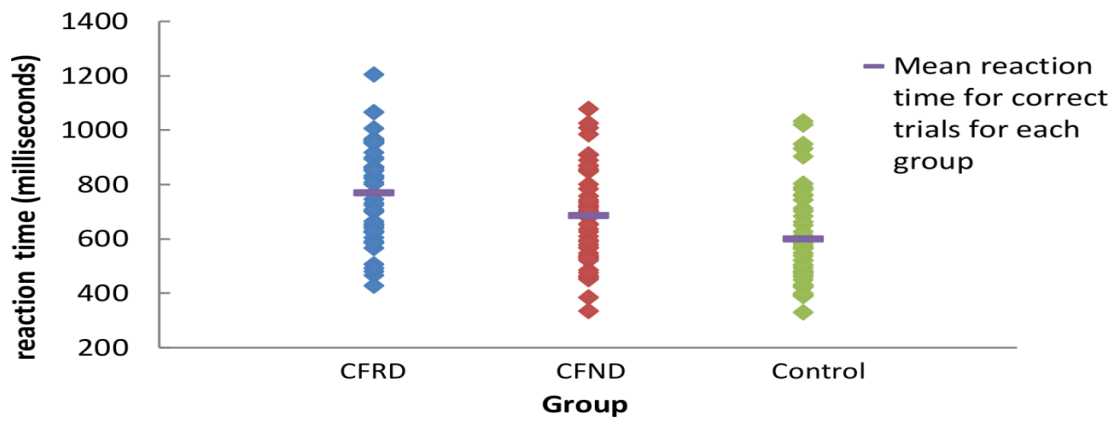
Figure 5.78 Study 1. Reaction time for correct trials on the AST

5.3.4.7.2 Direction trials

5.3.4.7.2.1 Total correct trials with direction as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 143) = 0.54$, $p = .46$, $\eta_p^2 = .004$. There was a weak trend for a significant main effect of group, $F(2, 144) = 2.44$, $p = .091$, $\eta_p^2 = .033$ ($R^2 = .033$) but the post hoc tests revealed no significant differences between groups (see Figure 5.79).
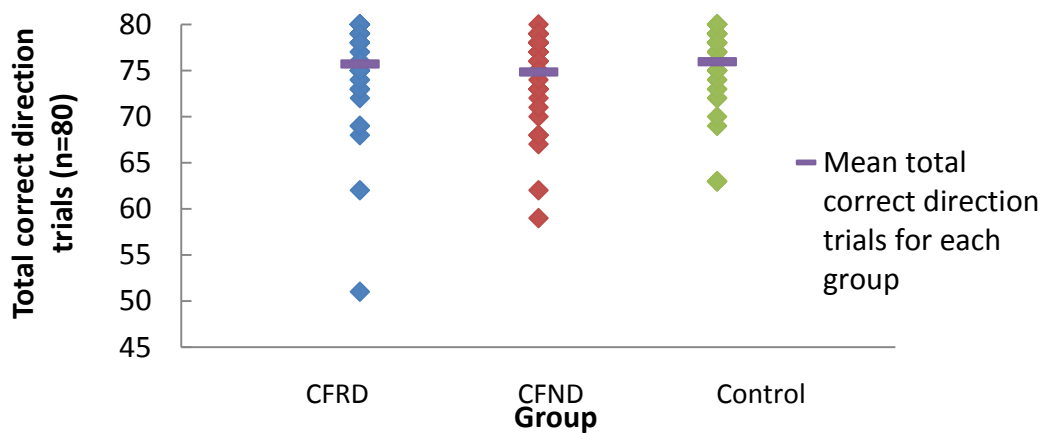
Figure 5.79 Study 1. Number of correct direction trials on the AST

5.3.4.7.2.2 Reaction time for correct trials with direction as the rule

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 143) = 0.80$, $p = .37$, $\eta_p^2 = .006$. There was a significant main effect of group, $F(2, 143) = 7.96$, $p = .001$, $\eta_p^2 = .100$ ($R^2 = .109$), such that the control group responded significantly faster to correct direction trials compared to the CFRD group ($p < .001$; see Figure 5.80). There was a trend for the CFND group to respond faster to correct direction trials compared to the CFRD group ($p = .07$).
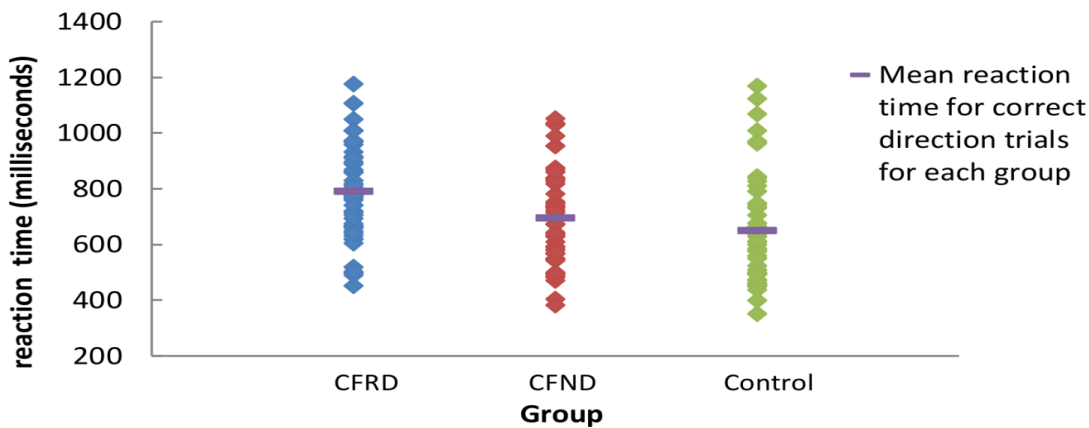
Figure 5.80 Study 1. Reaction time for correct direction trials on the AST

5.3.4.7.3 Side trials

5.3.4.7.3.1 Total correct trials with side as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 143) = .000$, $p = .995$, $\eta_p^2 < .001$. There was a significant main effect of group, $F(2, 143) = 7.34$, $p = .001$, $\eta_p^2 .093$ ($R^2 = .95$; see Figure 5.81). Post hoc tests showed that the control group correctly responded to significantly more trials with side as the rule than the CFND group ($p < .001$) and CFRD group ($p = .036$). On average, all three groups correctly responded to 94% of side trials. Participants also responded correctly to more side trials than direction trials (see section 5.3.4.7.2.1).
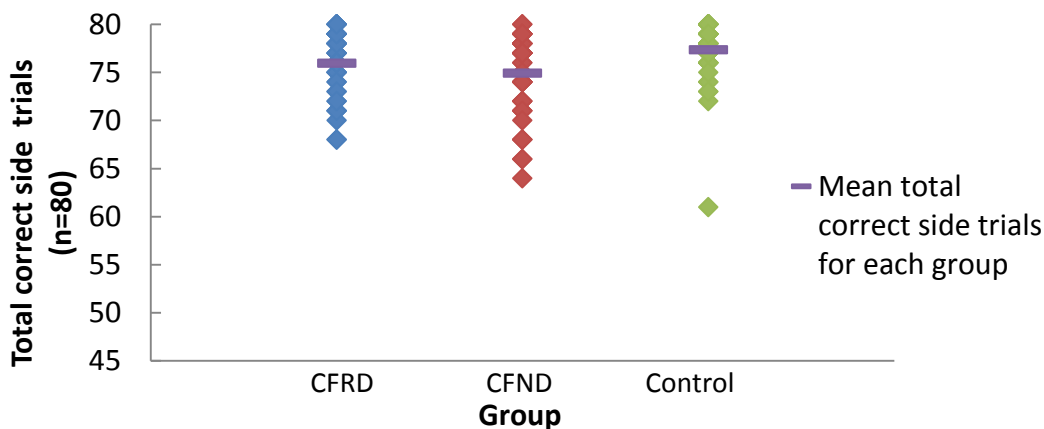
Figure 5.81 Study 1. Number of correct side trials on the AST

5.3.4.7.3.2 Reaction time for correct trials with side as the rule

Data for one participant was excluded from the analysis. Age was not a significant covariate, $F(1, 142) = .001$, $p = .97$, $\eta_p^2 < .001$. There was a significant main effect of group, $F(2, 142) = 12.82$, $p < .001$, $\eta_p^2 = .153$ ($R^2 = .153$), such that the control group responded significantly faster to correct side trials compared to the CFRD group ($p < .001$). There was also a trend for the control group to respond faster than the CFND group ($p = .078$; see Figure 5.82).
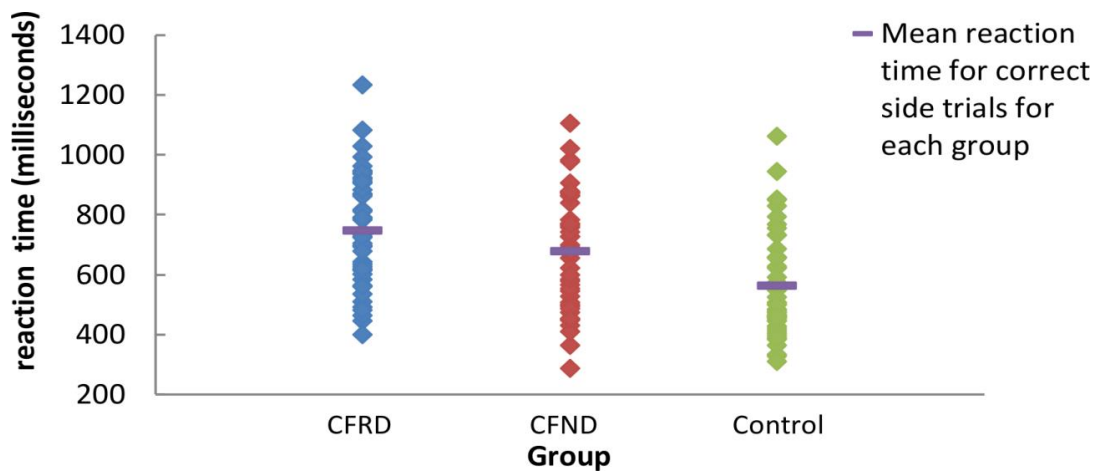
Figure 5.82 Study 1. Reaction time for correct side trials on the AST (excluding one outlier)

5.3.4.7.4 Congruent trials

5.3.4.7.4.1 Total correct congruent trials

Data were reflected and inversely transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 143) = 0.38$, $p = .54$, $\eta_p^2 = .003$. There was a significant main effect of group, $F(2, 143) = 3.16$, $p = .046$, $\eta_p^2 = .042$ ($R^2 = .043$). Post hoc analyses showed that the control group correctly responded to significantly more congruent trials compared to the CFND group ($p = .044$; see Figure 5.83).
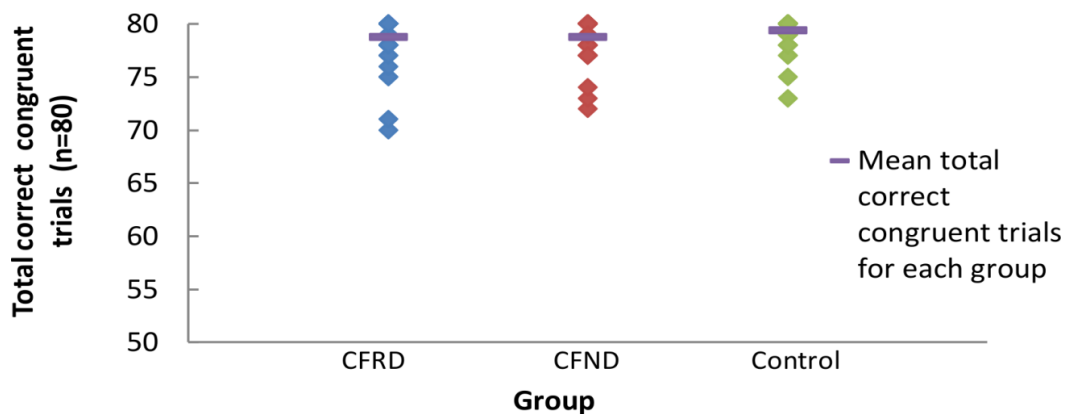
Figure 5.83 Study 1. Number of correct congruent trials on the AST

5.3.4.7.4.2 Reaction time for correct congruent trials

Data for one participant was excluded as an outlier. Age was not a significant covariate, $F(1, 142) = 0.004$, $p = .95$, $\eta_p^2 < .001$. There was a significant main effect of group, $F(2, 142) = 11.13$, $p < .001$, $\eta_p^2 = .135$ ($R^2 = .136$), such that the control group responded significantly faster to correct congruent trials compared to the CFRD group ($p < .001$; see Figure 5.84). There was also a trend for the control group to respond faster to correct congruent trials relative to the CFND group ($p = .066$), and a trend for the CFND to respond faster than the CFRD group ($p = .067$).
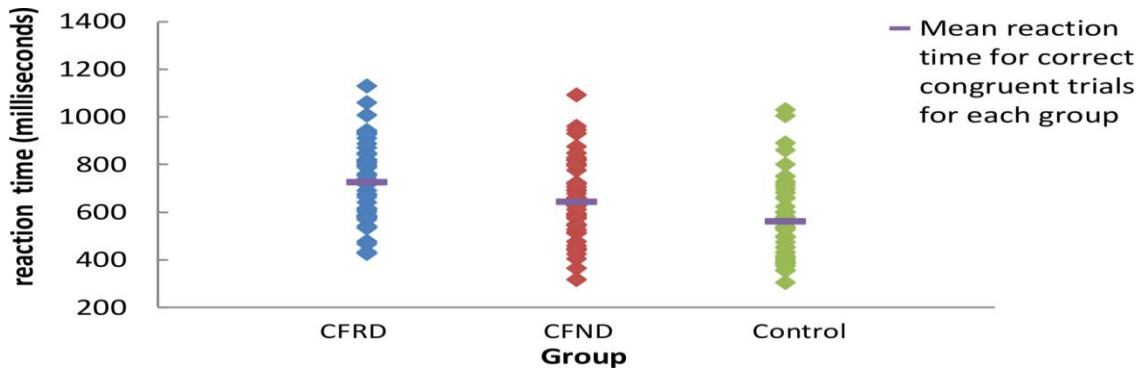
Figure 5.84 Study 1. Reaction time for correct congruent trials on the AST (excluding one outlier)

5.3.4.7.5 Incongruent trials

5.3.4.7.5.1 Total correct incongruent trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1,143)=.91$, $p=.34$ $\eta_p^2=.006$. There was a significant main effect of group, $F(2,143)=9.24$, $p< .001$, $\eta_p^2=.114$ ($R^2 = .121$; see Figure 5.85), such that the control group responded significantly faster than CFRD ($p <.001$) and there was a tendency for the CFND group to respond faster than the CFRD group ($p= .055$). Participants correctly responded to more congruent trials than incongruent trials (see section 5.3.4.7.4.1).
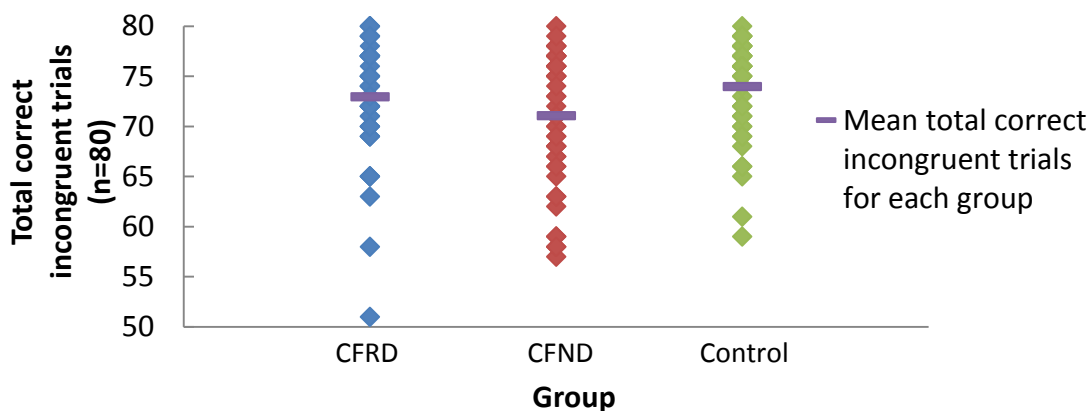
Figure 5.85 Study 1. Number of correct incongruent trials on the AST

5.3.4.7.5.2 Reaction time for correct incongruent trials

Data for one participant was excluded. Age was not a significant covariate, $F(1, 142) = 0.007$, $p = .93$, $\eta_p^2 < .001$. There was a significant main effect of group, $F(2, 142) = 3.74$, $p = .026$, $\eta_p^2 = .050$ ($R^2 = .054$), such that the control group responded significantly faster to correct incongruent trials compared to the CFND group ($p = .030$; see Figure 5.86).
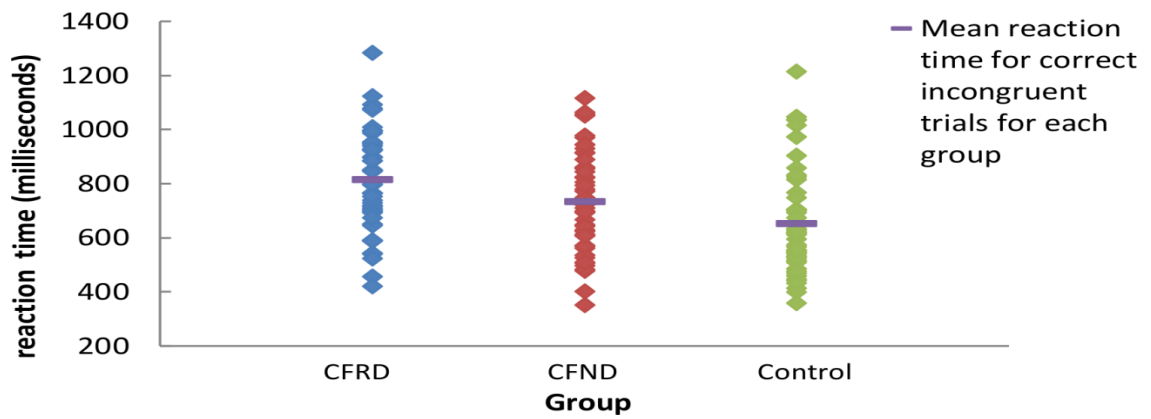
Figure 5.86 Study 1. Mean reaction time for correct incongruent trials on the AST

5.3.4.7.6 Switched trials

5.3.4.7.6.1 Proportion of correct switched trials

Data were reflected and inversely transformed due to severe negative skewness. Data for one participant was excluded as an outlier. Age was not a significant covariate and did not improve model fit so was removed from the model. There was a significant main effect of group, Wadj$F$(2, 94.69) = 5.37, p = .006, η_p^2 = .074 (R^2 = .074). Post hoc analyses showed that the control group correctly responded to significantly more switched trials than the CFND group (p = .003; see Figure 5.87). On average, all three groups correctly responded to 93% of switched trials.
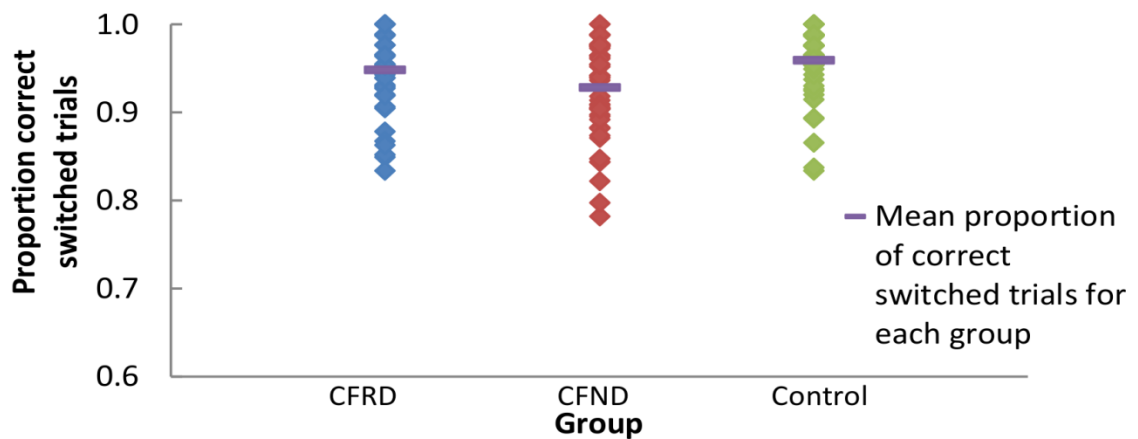
Figure 5.87 Study 1. Number of correct switched trials on the AST (excluding one outlier)

5.3.4.7.6.2 Reaction time for correct switched trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, F(1, 143) = 0.09, p = .77, η_p^2 = .001. There was a significant main effect of group, F(2, 143) = 10.33, p < .001, η_p^2 = .126 (R^2 = .128), such that the control group were significantly faster to respond to correct switched trials compared to the CFRD

group ($p < .001$). There was a trend for the control group to respond faster than the CFND group ($p = .072$; see Figure 5.88). There was also a trend for the CFND group to respond faster to correctly responded to switched trials relative to the CFRD group ($p = .099$).
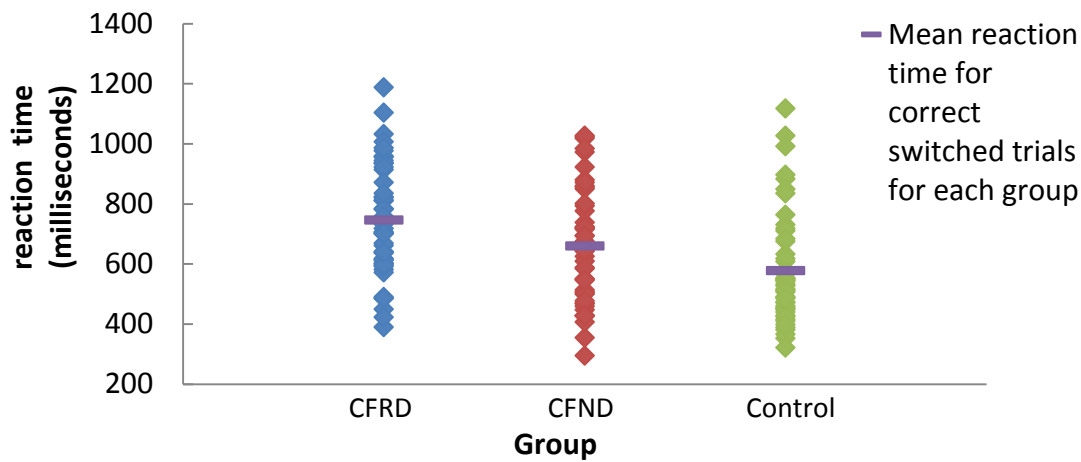
Figure 5.88 Study 1. Reaction time for correct switched trials on the AST

5.3.4.7.7 Non switched trials

5.3.4.7.7.1 Proportion of correct non switched trials

Data were reflected and an inverse transformation applied due to severe negative skewness. Data for one participant was excluded as an outlier. Age was not a significant covariate and did not improve model fit and therefore was removed. There was no significant main effect of group, $F(2, 143) = 1.60$, $p = .21$, $\eta_p^2 = .022$ ($R^2 = .022$; see Figure 5.89). On average, participants in each group responded to 94% of non switched trials. Participants were slightly better at responding to non switched trials.
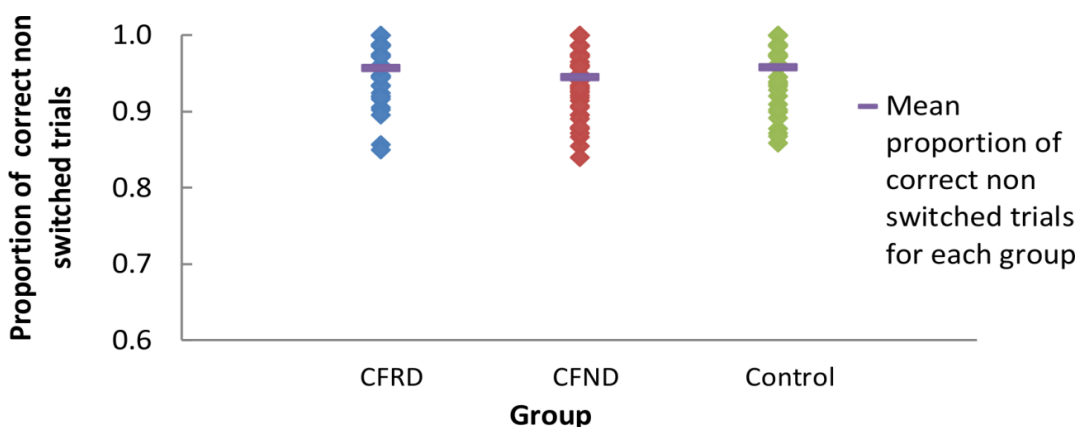
Figure 5.89 Study 1. Number of correct non-switched trials on the AST (excluding one outlier)

5.3.4.7.7.2   Reaction time for correct non switched trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 143) = 2.29$, $p = .13$, $\eta_p^2 = .016$. There was a significant main effect of group, $F(2, 143) = 8.06$, $p < .001$, $\eta_p^2 = .101$ ($R^2 = .117$), such that the control group were significantly faster to respond to correct non switched trials compared to the CFRD group ($p < .001$). There was a trend for the control group to respond faster than the CFND group ($p = .068$; see Figure 5.90).
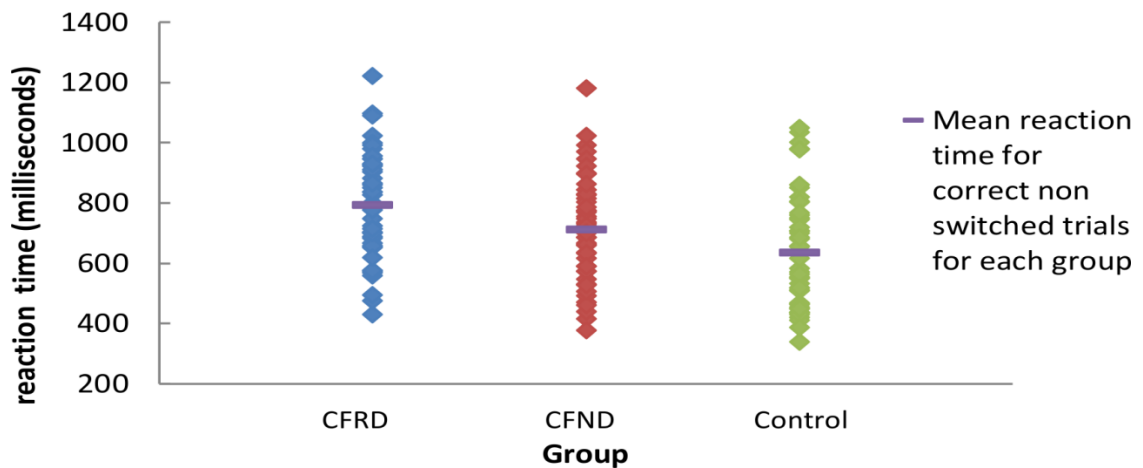
Figure 5.90 Study 1. Reaction time for correct non switched trials on the AST (excluding one outlier)

5.3.4.7.8   Omission errors

Data were inverse transformed due to severe positive skewness. Age was a not a significant covariate, $F(1, 143) = 2.39$, $p = .12$, $\eta_p^2 = .01$. The main effect of group showed a trend, $F(2, 143) = 2.57$, $p = .08$, $\eta_p^2 = .035$ ($R^2 = .048$; see Figure 5.91). Post hoc tests showed that there were no differences between groups.
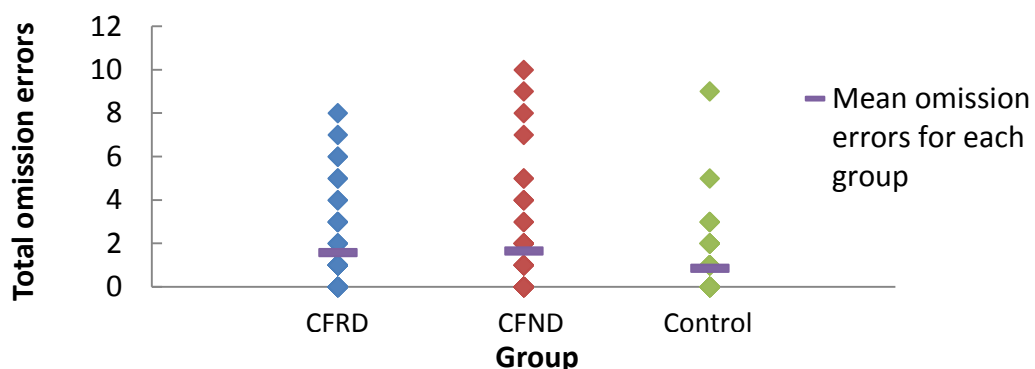
Figure 5.91 Study 1. Total number of omission errors produced on the AST

5.3.4.7.9 Commission errors

There were too few data points to perform analysis for commission errors. This showed that participants did not, on the whole, respond too soon, either prior to the end of the pre-empt window or prior to the stimulus being shown.

5.3.4.7.10 Congruency cost

Age was not a significant covariate, $F(1, 142) = 0.014$, $p = .91$, $\eta_p^2 < .001$. There was no significant main effect of group, $F(2, 143) = 0.74$, $p = .48$, $\eta_p^2 = .010$ ($R^2 = .012$). Figure 5.92 shows that on average, participants in all three groups responded faster to congruent trials.
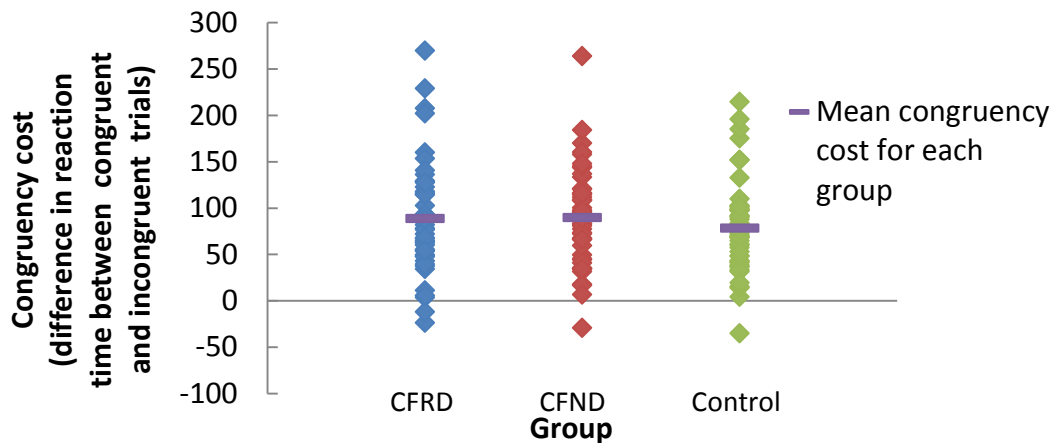
Figure 5.92 Study 1. Congruency cost for correct trials (subtraction of congruent from incongruent reaction times for correct trials) on the AST

5.3.4.7.11 Switch cost

Data were reflected and a square root transformation applied due to moderate negative skewness. Age was a significant covariate, $F(1, 143) = 8.00$, $p = .005$, $\eta_p^2 = .053$. There was no significant main effect of group, $F(2, 143) = 1.36$, $p = .26$, $\eta_p^2 = .019$ ($R^2 = .068$; see Figure 5.93). On average, participants in all three groups were faster at responding to non switched trials than switched trials.
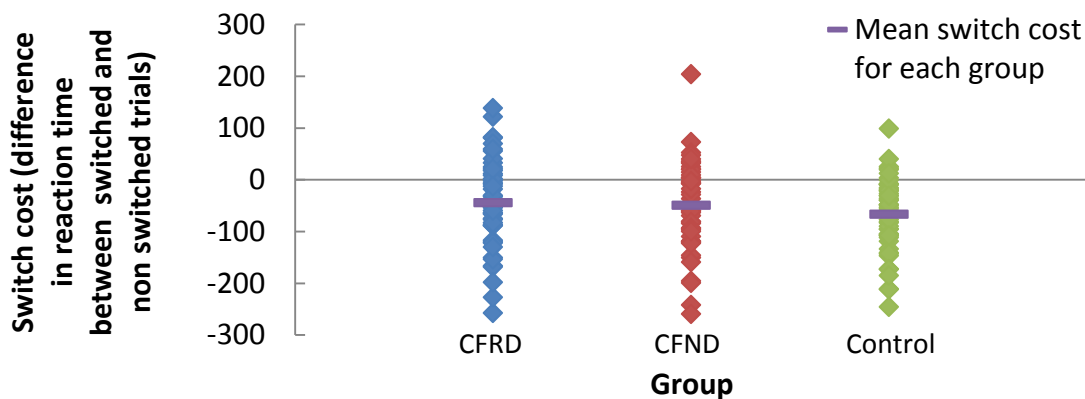
Figure 5.93 Study 1. Switch cost for correct trials (subtraction of switched from non switched reaction times) on the AST

5.3.5 Cognitive test evaluation questionnaire (CTEQ)

Two people with CFND did not complete the CTEQ during the testing session due to time constraints. As there was a significant difference in age between the three groups, and age was a significant covariate on some of the cognitive tests, age was included in the analysis of the CTEQ. Table 5.7 shows the scores for CFRD, CFND and control group.

Table 5.7 Study 1. Subjective experience of completing the cognitive test battery in people with CFRD, CFND and controls

	CFRD group n=49	CFND Group n=47	Healthy Control group n=49	F (2,141)	*p* value	η_p^2
	Mean (SE)	Mean (SE)	Mean (SE)			
Time pressure[52]	34.62 (3.66)	31.02 (3.78)	40.85 (3.64)	1.80	.17	.025
Test difficulty[52]	47.32 (3.19)	49.60 (3.30)	49.63 (3.17)	0.17	.84	.003
Ability to concentrate[52]	81.89 (2.42)	80.20 (2.50)	82.14 (2.40)	0.98	.38	.002
Effort[52]	84.93 (1.95)	85.08 (2.02)	88.19 (1.94)	1.40	.25	.010
Performance[53]	58.78 (2.64)	54.41 (2.73)	62.28 (2.62)	3.40	.04	.028
Frustration[52]	41.41 (3.71)	42.17 (3.83)	36.64 (3.69)	0.65	.52	.003

There was no difference in cognitive test difficulty, perceived time pressure, ability to concentrate, effort, and frustration experienced in completing the cognitive tests between the CFRD, CFND and control groups. Age was a significant covariate for perceived performance. Younger participants rated their performance as better than older participants. The control group's ratings of how well they thought they had performed were significantly higher than those of the CFND group (*p*=.031). Figure 5.94 and Figure 5.95 show the distribution of ratings of which was the hardest and easiest test respectively. The CFRD and CFND groups were more likely to rate the RVP as the hardest while the controls rated the SSP the hardest. Ratings of which tests participants found easiest were most widely distributed across tests. The PRM test was rated as easiest by more of the CFND and control groups, while the VRM was rated as easiest by more of the CFRD group.

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[52] age was not a significant covariate
[53] age was a significant covariate, $F(2,141)=4.064, p=.046, \eta_p^2=.028$
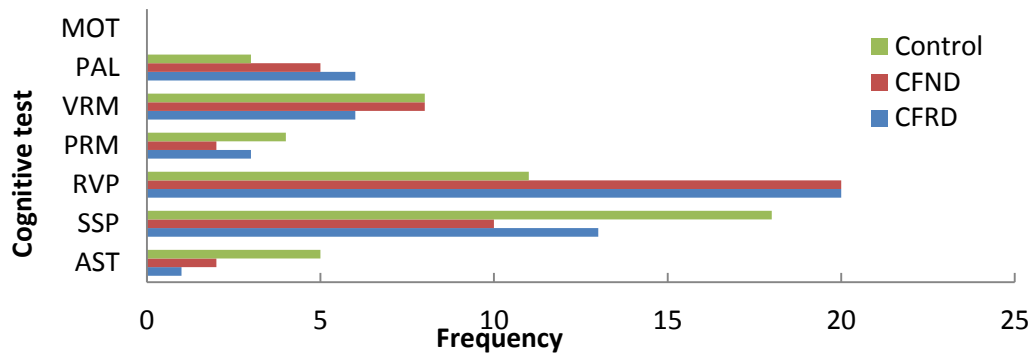
Figure 5.94 Study 1. Distribution of which was the hardest test from the cognitive battery for each experimental group (CFRD, CFND and healthy control)
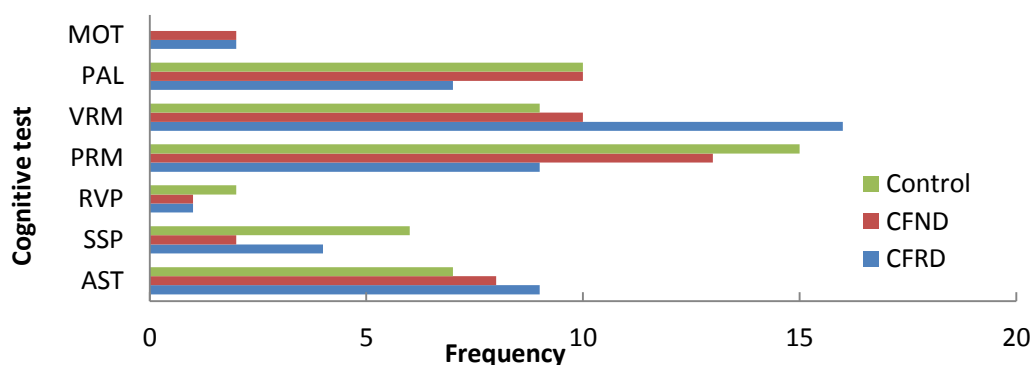
Figure 5.95 Study 1. Distribution of which was the easiest test from the cognitive battery for each experimental group (CFRD, CFND and healthy control)

5.4 Summary of findings

5.4.1 Participant characteristics

- The three groups were matched on gender and education level achieved, but not age. Age differed significantly with CFND being younger than CFRD and controls.

- There were no significant differences between groups for the time of day testing was completed, SES (Townsend score), BMI, CO (COppm and %COHb), anxiety score on the HADS or the number of subjective minor daily cognitive errors.

- More participants in the control group were in full time employment compared to the two groups of people with CF. People with CFRD showed the highest frequency of unemployment.

- Participants in the control group weighed significantly more than people with CFND, and there was a trend for a lower BMI in the CFND group.

- Blood glucose levels were significantly higher in the CFRD group relative to the CFND and control group.

- The control group subjectively rated their health as significantly better and scored significantly lower on the depression aspect of the HADS than those in the CFRD and CFND groups.

- There were no significant differences between the groups with CF for clinical characteristics except that people with CFRD had an average higher HbA1c, SBP and DBP readings, and a trend towards a faster pulse rate.

5.4.2 Findings from the cognitive tests (Aim 1)

A detailed summary of the outcomes for each tests is presented in Table 5.8. Taken together, the cognitive assessments indicated that:

- People with CFRD performed worse than controls on visual memory and new pattern and/or location learning (PAL, PRM), verbal memory (VRM), attention and processing speed (RVP, AST), spatial working memory (SSP) and cognitive flexibility (AST).
- People with CFND performed worse than controls on visual memory and new pattern and/or location learning (PAL), verbal memory (VRM), attention and processing speed (RVP), spatial working memory (SSP) and cognitive flexibility (AST).
- People with CFRD had poorer performance than those with CFND on cognitive flexibility (AST; processing speed).
- Impairment was not evident for motor function (MOT).

Table 5.8 Study 1. Summary of cognitive test outcomes for Aim 1: the effect of CFRD relative to CFND and controls, and CFND relative to controls ('+' better performance, '-' worse performance, '0' no difference)

Test	Outcome measure	Age covariate	The effect of CFRD relative to controls	The effect of CFND relative to controls	Differences between CFRD and CFND
MOT	Mean error	No	0	0	0
	Reaction time	n/a	0	0	0
PAL	Stages completed	Yes	0	0	0
	Stages completed on first trial	Yes[54]	-	-	0
	First trial memory score	Yes[55]	-	-	0
	Total trials	Yes[56]	-	-	0
	Total errors at n patterns	Yes	-	-	0
	Total errors	Yes[56]	-	-	0
	Total errors at n patterns	Yes	-	-	0
VRM	Immediate free recall	Trend	-	-	0
	Immediate novel words	No	-	0	0
	Immediate perseverations	No	-	- (trend)	0
	Immediate target recognition	No	0	0	0
	Immediate false alarm recognition	No	0	0	0
	Delayed free recall	Trend	-	-	0
	Delayed novel words	No	-	-	0
	Delayed perseverations	No	-	-	0

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[54] 'Stages completed' was also added in the model as a covariate, but was not a significant predictor of stages completed on the first trial.

[55] 'Stages completed' was also added in the model as a covariate. There was a trend for stages completed to be a significant predictor of first trial memory score.

[56] 'Stages completed' was also added in the model as a covariate. Stages completed to be a significant predictor for total trials and total errors.

Test	Outcome measure	Age covariate	The effect of CFRD relative to controls	The effect of CFND relative to controls	Differences between CFRD and CFND
VRM *continued*	Delayed target recognition	Trend	-	- (trend)	0
	Delayed false alarm recognition	No	0	0	0
PRM	Immediate number correct	No	0	0	0
	Immediate reaction time	No	0	0	0
	Delayed Number correct	No	-	0	0
	Delayed reaction time	No	-	0	0
RVP	Total hits	No	-	-	0
	Total hits at each minute	No	-	-	-
	False Alarms	No	0	0	0
	Mean reaction time for hits	Yes	0	0	0
	Reaction time: minute by minute	Yes	0	0	0
	A' Prime	No	-	-	0
	B' Prime	No	+ (trend)	+	0
SSP	Span length	Trend	-	-	0
	Total number of attempts	No[57]	0	0	0
	Mean time to first response	No[58]	- (trend)	-	-
	Mean time to last response	Yes[57]	0	0	0
	Total errors	No[57]	0	0	0
	Total usage errors	No[32]	0	-	0

[57] Span length was also included in the model as a covariate and was a significant predictor for total number of attempts, mean time to last response and errors (total and usage)
[58] Span length was also included in the model as a covariate but was not a significant predictor for, mean time to first response

Test	Outcome measure	Age covariate	The effect of CFRD relative to controls	The effect of CFND relative to controls	Differences between CFRD and CFND
AST	Total correct trials	Yes	0	-	0
	Mean reaction time for correct trials	No	-	- (trend)	0
	Correct direction trials	No	0	0	0
	Mean reaction time for direction trials	No	-	0	- (trend)
	Correct side trials	No	-	-	0
	Mean reaction time for side trials	No	-	- (trend)	0
	Correct congruent trials	No	0	-	0
	Mean reaction time for congruent trials	No	-	- (trend)	- (trend)
	Correct incongruent trials	No	0	-	0
	Mean reaction time for incongruent trials	No	-	0	- (trend)
	Correct switched trials	n/a	0	-	0
	Mean reaction time for switched trials	No	-	- (trend)	- (trend)
	Correct non-switched trials	n/a	0	0	0
	Mean reaction time for non-switched trials	No	-	- (trend)	0
	Omission errors	No	0	0	0
	Commission errors	No	0	0	0
	Congruency cost	No	0	0	0
	Switch cost	Yes	0	0	0

5.4.3 Findings from the subjective ratings questionnaires (Aim 2 and 3)

- Overall sleep quality did not differ between the groups in terms of ratings for the previous week and night before the test session. People with CFRD tended to report more periods of wakefulness, feeling less alert on waking and feeling less alert one hour after waking compared to people with CFND and controls.

- Age influenced how easy and quickly it was to get to sleep, how easy and how long it took to wake up and how alert people felt one hour after waking, with older participants rating these parameters as better than young participants.

- There was a tendency for participants to report feeling more stressed during the past month compared to the past week. There was a trend for those in the CFRD group to report greater stress than those in the control group.

- People with CFRD reported feeling less contented, mentally alert and energetic, sleepier and having a lower ability to concentrate than the control group at the time of testing. Age predicted how sleepy participant were, with older participants feeling less sleepy.

- CFRD and CFND differed in their self reported ability to concentrate with CFRD rating their state as worse.

- People with CFND rated their performance as poorer than the control group, and younger participants rated they had performed better than older participants. There were no differences between the three groups on other cognitive workload measures.

- The CFRD and CFND groups were more likely to rate the RVP as the hardest while the controls rated the SSP the hardest.

- Ratings of which tests participants found easiest were most widely distributed across tests. The PRM test was rated as easiest by more of the CFND and control groups, while the VRM was rated as easiest by more of the CFRD group.

5.5 Discussion

The first aim of the study was to objectively investigate cognitive function in adults with insulin treated CFRD, compared to adults with CFND and healthy adult controls. It was hypothesised that people with CFRD may share the same cognitive impairments observed in people with T1DM and T2DM respectively given their common clinical characteristics. The second aim of this study was to investigate whether people with CF (CFRD and CFND) report subjective cognitive impairments compared to a healthy control group. The third aim was to investigate whether there were any differences in participant characteristics, previously demonstrated to be associated with cognitive functioning, and subjective evaluations of sleep, stress, mood and mental alertness between the people with CF, with and without diabetes, and healthy controls.

5.5.1 Aim 1: To investigate cognitive function in adults with insulin treated CFRD, compared to adults with CF who do not have diabetes (CF non-diabetics; CFND) and healthy adult controls

The three groups were matched on gender and education level achieved, but not age which varied in relation to disease duration. People with CFRD were older than those with CFND. Age

was therefore included as a covariate in the cognitive data and subjective data analyses to try to control for this.

The present study found there were clear differences in cognitive function in the two patient groups compared with controls in the domains of memory, attention and processing speed, working memory and cognitive flexibility (see section 5.4.2). These differences point to impairment in CF which is worse in CFRD than CFND in terms of cognitive flexibility (processing speed).

The cognitive impairments seen in people with insulin treated CFRD are akin to those consistently observed in people with T1DM and T2DM respectively (Awad et al., 2004; Brands et al., 2005; Palta et al., 2014). People with CFRD showed poor cognitive flexibility which is consistent with the impairment seen in people with T1DM. On the AST, there was no difference in accuracy, but people with CFRD required longer to achieve the same accuracy of performance suggesting a cognitive flexibility/ speed-accuracy trade-off. The deficits apparent in verbal memory and executive function are consistent with impairments seen in people with T2DM. Fewer correct responses and more errors were produced for immediate and delayed free recall verbal memory. There was no difference on the immediate recognition task which suggests that poor free recall performance is not due to a failure to encode the words. The worse delayed recognition performance in people with CFRD suggests evidence of impaired long term verbal memory. Visual memory and learning was shown to be impaired as completion of all stages on the PAL test varied by group. More errors were produced and therefore more trials were needed to produce the same visual memory performance as the control group. However, impairment was worse in CFND than CFRD, and will subsequently be discussed in more detail. Likewise, spatial working memory was shown to be impaired as completion of the higher span lengths on the SSP test was dependent on participant ability. People with CFRD reached a lower span length. There was a tendency for them to take more time to respond when recalling these lower span sequences. This suggests that people with CFRD require more thinking time to successfully recall sequences, or they were more cautious in their responding. The finding that people with CFRD require more thinking time was also apparent for delayed visual memory with people producing fewer correct responses and taking longer to do so. In conjunction with verbal memory performance, this suggests there is impairment in long term memory. People with CFRD also commonly exhibited a slowing in processing speed observed in both T1DM and T2DM. Although there was no difference in reaction time to detecting hits on the RVP, people with CFRD detected substantially fewer hits than the control group across all four minutes of the test reflecting diminished processing speed and sustained attention. As people with CFRD were less biased in responding (indicated by B' prime) on the RVP test, this also reflects a cautious responding style compared to healthy controls.

Microvascular and macrovascular complications have been shown to be associated with cognitive impairment in T1DM and T2DM (see Chapter 3, section 3.2.3.4 and 3.2.3.5). People with CFRD had, on average, a diabetes duration of 10 years. Therefore, those people who have had CFRD for at least 5 years will have started to have screening tests for microvascular complications as part of their annual CFRD review. However, none of the patients with CFRD

who had undergone screening had a diagnosis of microvascular complications. Furthermore, no person with CFRD had a diagnosis of macrovascular disease which supports that macrovascular complications have not been reported in people with CFRD (Perano et al., 2014). Therefore, any cognitive impairment in the CFRD group is independent of micro- and macro-vascular disease. Inclusion of both a T1DM and T2DM group in the study design would have allowed comparison between the three diabetic groups. However, given the wealth of research into cognitive function in T1DM and T2DM, the focus of this exploratory study was in relation to people with CF with and without CFRD, and their performance in comparison to healthy controls.

Impairment in processing speed is consistent with previous studies of diabetes which used CANTAB. Ba-Tin et al. (2011) found that performance was impaired on the RVP in both diabetics, with and without diabetic complications, compared to healthy controls, after controlling for age. However, there was no difference between groups on the PAL test, and the effect on the PRM test was lost after controlling for age. Data presented in the paper were log transformed so a comparison of performance between studies is not possible. Ba-Tin also failed to report details of the test modes, or the specific outcome measure for all but one test. This suggests that the conclusions drawn may be based on one outcome measure for each test. Lasselin et al. (2012) found no difference on the immediate or delayed PRM test for percentage of correct responses (equivalent to number of correct responses in this present study) and mean reaction time between healthy controls and people with insulin treated T1DM, insulin treated T2DM and insulin free T2DM. This suggests that the impaired delayed visual memory observed in people with CFRD may be independent of receiving insulin therapy.

People with CFND were significantly younger than both people with CFRD. Younger age was a predictor of better performance on the PAL test. Performance was not impaired for people with CFND relative to controls on the PRM task (either immediate or delayed) which suggests that the deficit in performance seen on the PAL test in people with CFND is due to impairment in learning the subsequent new locations of patterns. Impaired visual spatial memory have been shown in people with IGT and T2DM (Awad et al., 2004; Lamport, Lawton, Mansfield, Moulin, & Dye, 2014) and suggested to be as a result of damage to the hippocampus (Collie et al., 2002; Convit, Wolf, Tarshish, & de Leon, 2003). Table 5.6 shows that, despite having received a NGT OGTT result within the past 12 months, people with CFND have previously received, on average, 1.2 impaired OGTT results over a 9 year period. It may be that at the time of testing some people with CFND were experiencing IGT with normal glucose profile, which is supported by some people with CFND having a high blood glucose reading, mirroring values seen in people with CFRD. Therefore, the deficit in learning the new locations of patterns in people with CFND may be related to previous periods or presence of IGT.

The better performance in those with CFRD may be explained by some people noting they had employed strategies in locating the patterns on the PAL test, possibly to compensate for this deficit. CFRD is associated with older age and additional treatment. The use of memory aids and association strategies have been shown to be used by older adults to support everyday memory and medication adherence (Boron et al., 2013). Furthermore, Boron et al. also found a positive association between the number of strategies used and the number of medications,

education level, and efficacy and anxiety regarding remembering to take treatment. Therefore, people with CFRD, particularly those who had achieved a higher education level, may try to employ a greater number of association strategies in everyday life in an attempt to adhere to treatment. People with CFRD may have benefitted from utilising these association strategies on the PAL test compared to people with CFND. The use of memory or association strategies did not transfer for delayed visual memory, or spatial working memory. This may be because the pace of stimuli presentation was slower on the PAL test compared to SSP (i.e. allowed a longer encoding time), and patterns are more distinct in appearance compared to coloured boxes, which allow people to use names to describe and help remember them spatially. However, after a 30 minute delay, the distractor on the PRM is too similar to the description which was used to remember the originally presented pattern.

Previous research has also shown that people with CF experience impairments in memory, executive function and processing speed (see Chapter 2) which may explain the evident impairments observed in the CFND on the same domains as in CFRD, albeit to a lesser degree. This confirms the sensitivity of the CANTAB system in detecting subtle changes in cognitive function (Joyce, Blumenthal, & Wessely, 1996; Lasselin et al., 2012; Sahakian & Owen, 1992). Cognitive flexibility was the only domain which showed significant differences when comparing people with CFRD to CFND in this study. This difference can be explained by a speed-accuracy trade off. People with CFRD responded slower than people with CFND, but this was compensated by the better accuracy rate.

5.5.1.1 Subjective evaluation of cognitive performance

There were no differences between the three groups on the cognitive workload measures except for perceived performance (see section 5.4.2). Younger age was predictive of rating how well participants thought they had performed on the tests, and people with CFND thought they had performed not as well as the control group. This rating may be largely based on the subjective rating of performance on tests in which the CFND group showed the largest deficit in performance compared to the controls (i.e. visual memory and new learning, and attention and processing speed).

RVP requires a high level of sustained attention and was rated as the hardest test in the cognitive battery by both groups of people with CF. People with CF often reported in the debriefing questionnaire that this test was hard due to the pace of the stimuli being presented. As people with CF reported it was significantly harder for them to concentrate compared to controls, this supports their rating in this test was the hardest. The control group were more likely to rate the domain of spatial working memory as the hardest which may be reflective of controls reaching the higher span lengths than people with CF on the SSP test. There was more variation in which tests participants found easiest. The PRM test was more likely to be rated as easiest by the CFND and control groups, while the VRM test was more likely rated as easiest in the CFRD group. The fact PRM was not selected as the easiest test by people with CFRD may reflect difficulty in the delayed part in the test. As more novel words and perseverations of words were made by the CFRD group, this may have contributed to their thinking they had performed better on the VRM test due to the amount of words they recalled.

5.5.2 Aim 2: To investigate whether people with CF, regardless of glucose tolerance (i.e. CFRD or CFND) report subjective cognitive impairments compared to a healthy control group.

There was no difference in the subjective reporting of daily minor cognitive daily errors which have occurred in the past 6 months between the three groups. This highlights a lack of association between objectively and subjectively reported memory impairment. Epker and Maddrey (1999) observed that people with CF reported symptomology which suggested they experience cognitive impairment. However, the results of this study demonstrate that in patients with CF, symptomology did not differ significantly to healthy controls. This highlights the importance of including a healthy control group when assessing cognitive function.

Hertzog Pearman (2013), in a review of the literature, concluded that there is a weak correlation between subjective memory complaints and objective memory performance, and propose that research should stop reporting this lack of association. They argue that subjective cognitive impairments are more strongly associated with emotional instability, depressive symptomology and negative affect than objective performance. Although the present study found that people with CF reported significantly more depressive symptomology than the control groups, this was not mirrored in higher ratings of subjective cognitive impairments. However, this may be due to the different time scales in which participants reported their answers; the HADS asked participants to report their mood over the past week, while the CFQ asked participants to report the occurrences of cognitive errors over the previous 6 months.

5.5.3 Aim 3: To investigate whether there were any differences in participant characteristics (which have been shown to be associated with cognitive functioning), and subjective evaluations of sleep, stress, mood and mental alertness between the people with CF (CFRD and CFND) and healthy controls

As mentioned in section 5.5.1, groups were matched on gender, education and age varied as a function of disease. There was no difference in educational attainment between the three groups, but people with CFRD are more likely to be awarded with Diplomas, Degrees and Masters than CFND. People with CFND were younger and therefore may not yet have had the opportunity to complete higher education level qualifications. Additionally, or alternatively, people in the CFND may have experienced practical, physical or emotional barriers to educational attainment because of CF (Chapter 1, section 1.6.4, Table 1.4). There were no differences in SES scores between the groups, and therefore any differences in cognitive scores cannot be explained by lower SES in groups with CF, and the higher rate of unemployment in people with CFRD is thought to be due to worse disease severity (see Chapter 1, Table 1.5).

People with CFRD were significantly older at the age of CF diagnosis which may reflect the method of screening for CF and how it has changed over recent decades. People with CFND in this study were relatively young and had received a diagnosis at an earlier age which has reported to have a positive impact on cognition in CF (Koscik et al., 2005) and may explain the degree of cognitive impairment seen in people with CFRD.

Severe levels of depression have been associated with cognitive impairment in the domains of episodic memory, executive function and processing speed (McDermott & Ebmeier, 2009; O. J. Robinson et al., 2013). Although people with CF were found to have significantly higher depression scores than controls, no participant in this study scored in the severe depression range. Nevertheless, people with CF did score in the moderate depression range, which may explain some of variance in cognitive impairment seen in the two patient groups. As expected, ratings of health and feeling well were lower in people with CF as a function of disease. However, some patients rated their health status as very /healthy which may be reflective of an optimistic coping style (Chapter 1, section 1.6.3).

As expected, blood glucose levels were higher in people with CFRD compared to people with CFND and controls. Likewise, people with CFRD also had higher HbA1c readings than people with CFND. This is a function of disease and therefore was not controlled for in the analysis. The large variation in blood glucose levels in the CFRD group and to some extent the CFND reflects poor glycaemic control and fluctuations in insulin sensitivity people with CF experience. A number of participants were excluded from taking part in the study as their blood glucose levels did not fall below 12mmol/L, although this was partly through choice. This excluded patients who consistently have readings >20mmol/L and who may show a greater degree of cognitive impairment due to chronic hyperglycaemia. Research has shown cognitive impairment to be apparent in people with T1DM when blood glucose levels are >15mmol/L and therefore 12mmol/L reflected a good cut off to include as many participants in the study as possible.

Despite having NGT at the time of testing, some people with CFND have had IGT OGTT results in the past (see Table 5.6) and the lower weight in some people with CFND might be indicative of the decline in nutritional status and the start of the pre diabetic period (Chapter 1, section 1.5.4.2). This decline in weight is contrary to the usual weight gain seen in people with T2DM in the diabetic period. In CF, OGTTs are performed every 12 months in people with NGT at a time of clinical stability. However, some people with CFND in the study may have been tested near the time the OGTT was due, and have a glucose tolerance more reflective of IGT than NGT.

There were no differences on lung function or oxygen saturation measures between people with CFRD and CFND. Therefore the overall worse performance in people with CFRD cannot be explained by worse lung disease severity. Working memory was found to be consistently affected in studies which have previously investigated hypoxia and hypoxaemia as a mechanism for cognitive dysfunction in CF (see Chapter 2, section 2.2.1.3; Matt Maddrey et al., 1997, 1998, Epker and Matt Maddrey 1999; Netson, Carey, Moffett, Baer, and Haut, 2008). However, these studies do not reported whether people were receiving oxygen therapy or if oxygen saturation levels were above 90% at the time of testing. People with CF in the present study had all oxygen saturation levels 91% or above and were not receiving overnight or continuous oxygen. Therefore, the worse spatial working memory cannot not be explained by patients experiencing hypoxia at the time of testing.

Research has shown PEs are associated with worse cognitive performance, and alleviation of the PE improves working memory and vigilance on processing speed tasks (Dobbin et al., 2005a). Therefore, some degree of cognitive impairment seen in both groups of people with CF

on spatial working memory and diminished processing speed (particularly the RVP test which required visual sustained attention) may be associated with suffering from a PE. However, as the number of people suffering from a PE was not significantly different between groups, this was not investigated as a predictor of cognitive impairment in this study.

Features of the metabolic syndrome have been associated with cognitive impairment (Chapter 3, section 3.3.3). However, these features are not common in CF (Moran et al., 2010). Chapter 3 (section 3.3.3.1.2) showed that being overweight and obesity in younger and older adults is associated with impaired executive function (Gunstad et al., 2007). BMI was not significantly different between the groups, and overall within the normal range, and therefore was not included as a predictor of cognitive function in the analysis. The heaviest weight recorded was in the CFRD group (104.6kg) which reflects the rise of obesity in CF (Chapter 1, section 1.5.1). Research investigating cognitive function in CF may need to factor in obesity as a mechanism for cognitive impairment in the future.

SBP has been shown to be a risk factor for cognitive impairment in people with the metabolic syndrome, particularly in young and middle aged adults (Hassing et al., 2004), and in people with T2DM (see Chapter 3, section 3.3.3.1.1). People with CFRD in this study had higher SBP and DBP values than people with CFND, but there was more variation in the readings in the CFND group. Although hypertension is not common in CF, on average, both groups had readings in the prehypertension range. The recent systematic review by Meusel et al. (2014) found that hypertension in T2DM is associated with executive function and processing speed impairments whilst memory seem to be spared. Therefore, prehypertension in both groups of people with CF may explain some of the variance in cognitive impairment in executive function and processing speed.

Inflammation has been shown to be associated with cognitive impairment in people with metabolic syndrome and T2D (see Chapter 3, section 3.2.3.1.4). High CRP have been shown to be associated with worse visual spatial memory and is often elevated in CF (Marioni et al., 2010; Noble et al., 2010). However in this study there was no significant differences between CFRD and CFND.

People with CFRD reported worse sleep quality than CFND and controls. Sleep quality has previously been shown to influence cognitive function in CF (see Chapter 2, section 2.3.4). Dancey et al. (2002) suggested that people with CF compensate for chronic sleep loss by slowing their responding rate in order to maintain accuracy which explains the performance of people with CFRD on the task of cognitive flexibility (AST). Likewise, although all participants reported feeling more stressed during the past month compared to the past week, there was a trend for those in the CFRD group to be more stressed than those in the control group which may also have contributed to cognitive impairment in CFRD.

There was a tendency for people with CFRD to have less ability to concentrate than people with CFND just before starting the cognitive tests. This may explain the increased thinking time on domains of visual delayed memory and spatial working memory, and (as previously mentioned in section 5.5.1.1l) slowing in processing speed on the task of cognitive flexibility in people with CFRD.

5.6 **Conclusion**

Age was significantly different between the groups and therefore the most important variable to control for in the analysis. People with CFRD showed cognitive impairment in the domains of visual memory and new learning, immediate and delayed verbal memory, attention and processing speed, spatial working memory and cognitive flexibility compared to healthy controls. The cognitive impairments seen in insulin treated people with CFRD are akin to those observed in people with T1DM and T2DM respectively. People with CFRD had an average diabetes duration of 10 years, and the cognitive impairment observed in the CFRD group is independent of micro- and macro- vascular disease. Previous research has shown that people with CF (without CFRD) experience impairments in memory, executive function and processing speed which explains why the CFND group also exhibit impairments in the majority of domains affected by CFRD, but to a lesser degree. This highlights the sensitivity of the CANTAB system in detecting subtle changes in cognitive function. There is no association between subjective and objective cognitive performance. People with CFRD generally report worse sleep quality, perceived stress and mood which may have contributed to the pattern of impairment seen in this group.

Chapter 6

Changes in cognitive function in people with CFRD during a 1-3 year period: a follow up study (Study 2)

6.1 Introduction

The study reported in Chapter 5 showed clear differences in cognitive function in people with CFRD and CFND compared with healthy controls in the domains of memory, attention and processing speed, working memory and cognitive flexibility (see Chapter 5, section 5.4.2). Furthermore, there was a trajectory of cognitive impairment in CF, with significantly worse cognitive function in CFRD than CFND in terms of cognitive flexibility (processing speed) and the majority of other domains but to a lesser extent. In addition the results of this study suggest that factors associated with the metabolic syndrome (hypertension and inflammation), depression, glycaemic control (blood glucose level during testing and HbA1c), sleep quality, stress and mood may have contributed to the degree of impairment seen in people with CF.

Chronic hyperglycaemia and duration of diabetes have been proposed to contribute to the development of cognitive impairment in people with T1DM and T2DM (see Chapter 3, section 3.2.3.3). Furthermore, prolonged poor glycaemic control has been shown to also increase the risk of diabetic complications (West et al., 2014). Therefore, it is plausible that over time, people with CFRD may experience a greater degree of cognitive impairment compared to people with CFND, due to longer diabetes duration, poor glycaemic control and the development of microvascular complications. Factors previously shown to be associated with cognitive function such as lung disease severity, depression, sleep quality, and mood may have also changed over time as a function of disease and influence the degree of cognitive impairment.

During Study 1, some people with CFRD verbally communicated feeling that they could have performed better on the cognitive tests than they thought they had done. Although every effort was made to reduce the anxiety provoking aspect of completing the cognitive tests (see Chapter 5, section 5.2.3.1) and time was spent building a rapport with the participants during the recruitment and screening procedure, some patients expressed anxiety that they felt their memory was not as good as it used to be. This anxiety and worry about having a decline in memory function, in conjunction with the novelty of performing the cognitive tests may have influenced their objective performance. Therefore, the first aim of this study was to investigate whether cognitive function had changed in people with CFRD during a 1-3 year period. The second aim was to investigate whether the number of subjective cognitive daily errors had remained stable over this period of time. The third aim was to investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period. It was hypothesised that changes in glycaemic

control, severity of lung function disease and mood would influence the profile of cognitive function in people with CFRD.

6.2 Method

6.2.1 Design

A repeated measures design with two levels of time of testing; i) baseline and ii) follow up (24±12 months later).

6.2.2 Participants

The 49 PI people with CFRD who participated in Study 1 (Chapter 5) were eligible to take part in follow-up testing providing they still met the inclusion criteria outlined in Study 1 (see Chapter 5, section 5.2.2.1) at follow-up. Participants were not approached if they met any of the exclusion criteria outlined in study 1 at follow-up (see Chapter 5, section 5.2.2.2).

6.2.3 Cognitive Tests

The same CANTAB cognitive test battery employed in Study 1 was used for follow-up testing. Details of these tests and outcome measures are described in Chapter 5 (section 5.2.3). However, due to practise effects, parallel versions of the tests[59] were used where possible. As only one version of MOT is available within CANTAB, the same version had to be used at both baseline and follow-up. Parallel forms of the VRM[60], PRM and SSP tests were, however, available and utilised. As stimuli on the PAL, RVP and AST test are administered in pseudo random order, and as no equivalent alternative form of these tests are available, the same version of each of these tests was used at both baseline and follow-up.

6.2.4 Questionnaires

The following self report measures were administered. Details of questionnaires used at baseline (Study 1), can be found in Chapter 5.

- The Leeds Sleep Evaluation Questionnaire (LSEQ) - modified (previous night and last week; see section 5.2.4.1)
- The Perceived Stress Scale (PSS-10) –modified (previous week and month; see section 5.2.4.2)
- Hospital Anxiety and Depression Scale (HADS; see section 5.2.4.3)
- Ratings of mood and mental alertness (see section 5.2.4.4)
- Cognitive Test Evaluation Questionnaire (CTEQ; see section 5.2.4.5)
- Cognitive Failures Questionnaire (CFQ; see section 5.2.4.6)

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[59] The test still followed the same procedures as Study 1, but different stimuli were used
[60] Words were matched on frequency (Kucera & Francis, 1967), word length and imageability (rating >300). The target word list, and the immediate and delayed distractors were made up of 6 high frequency words (3 long, 3 short), 6 medium frequency words (3 long, 3 short and 6 low frequency words (3 long, 3 short).

- Cognitive Failures Questionnaire for others (CFQ for others)

If a relative or partner of a patient was present during the testing session, and if the patient consented, they had the opportunity to complete the 'Cognitive Failures Questionnaire for others' (Broadbent, Cooper, FitzGerald, & Parkes, 1982; see Appendix T). This questionnaire asked the partner, relative or close friend of the patient to report how many times during the last 6 months the patient had shown any difficulties in everyday life. There are 8 questions, and responses are given on a 5 point Likert scale; very often, quite often, occasionally, very rarely and never. Examples of questions include 'Forgetful, such as forgetting where he/she put things, or appointments, or about what he/she has done?', and 'Disorganised, that is, getting into a muddle when doing something because of lack of planning or concentration?' This questionnaire was included as partners, relatives and close friends had commented during Study 1 that they did not agree with some of the patient reported responses on the CFQ. Higher scores indicate worse subjective cognitive errors.

- Cognitive Difficulties Scale (CDS)

The Cognitive Difficulties Scale (CDS; McNair & Kahn, 1983; see Appendix U) is a 39-item self-report measure of subjective complaints occurring during the previous week relating to immediate and delayed memory, attention, language, temporal orientation, and psychomotor abilities. Participants rated their experience of each item on a 5 point Likert scale, with 0 corresponding to not at all, 1 to rarely, 2 to sometimes, 3 to often, and 4 to very often. Higher total summed scores indicate worse cognitive complaints.

- Debriefing questionnaire

Participants completed a follow-up debriefing questionnaire (see Appendix V) which specifically asked about their experiences of taking part in the follow-up study, and whether they thought their memory and/or attention abilities had changed since they had completed the baseline study.

6.2.5 Physiological Measures

6.2.5.1 Blood glucose

Participants were asked to fast for two hours before the testing session and a single blood glucose measurement was taken using the same procedure as in Study 1 (see Chapter 5, section 5.2.5.1).

6.2.5.2 Carbon monoxide

Carbon monoxide levels were monitored using the same procedure as Study 1 (Chapter 5, section 5.2.5.2).

6.2.6 Procedure

6.2.6.1 Screening

People with CFRD who had taken part in Study 1 were checked for eligibility against the inclusion and exclusion criteria described in Chapter 5 (see section 5.2.2.1 and 5.2.2.2) with the assistance of the CF specialist clinical dietitian using EMIS. As in Study 1, the clinical staff

advised whether it was a suitable time to approach a patient about taking part in the study. People with CF were approached either as an inpatient or outpatient and given a follow up study PIS (see Appendix W). It was reiterated that there were no consequences to their clinical care whether they participated or not. People with CF were given at least 7 days to consider the information, ask questions and to express their interest in the follow-up study.

If people with CF agreed to take part in the follow-up study, written informed consent was obtained (see Appendix X). Participants were also asked to complete a follow up RIQ (see Appendix Y) which asked participants to update their demographic, health and behaviour information since baseline (Study 1).

6.2.6.2 **Testing Session**

Testing was completed either in a hospital setting (inpatient or outpatient) or at a patient's home; time of day was recorded. The testing session followed the same procedure as Study 1 (see Chapter 5, section 5.2.6.2) with the addition of the CDS and CFQ for others after the cognitive tests. Figure 6.1 summarises the procedure. Partners/relatives/friends completed the CFQ for others if present during a testing session. People with CFRD received a £25 Love2Shop Voucher for participating. If testing took place on NHS premises, car parking charges were paid. If the test session could not be arranged to coincide with their health assessment or at their home, their travel expenses were reimbursed up to the value of £20.

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┌─────────────────────────────────────────────┐   ┌──────────────┐
│      Written informed consent obtained        │   │ Recruitment  │
└─────────────────────────────────────────────┘   │     and      │
                      │                             │  screening   │
                      ▼                             │     visit    │
┌─────────────────────────────────────────────┐   │              │
│  Recruitment Information Questionnaire (RIQ)   │   └──────────────┘
└─────────────────────────────────────────────┘
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┌─────────────────────────────────────────────┐
│     LSEQ (Typical night's Sleep last night)   │
│  LSEQ (Typical night's Sleep over past week)  │
│   PSS-10 (Perceived stress over past week)    │
│   PSS-10 (Perceived stress over past month)   │
│                    HADS                        │
│   VAS Ratings of mood and mental alertness    │
└─────────────────────────────────────────────┘
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                      ▼
┌─────────────────────────────────────────────┐
│   Finger prick blood glucose measurement taken │
│         using a GlucoMen® LX meter             │
└─────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────┐      ┌──────────────┐
│     Carbon monoxide level measured using a     │      │              │
│                Smokerlyzer                     │      │   Test day   │
└─────────────────────────────────────────────┘      │              │
                      │                               └──────────────┘
                      ▼
┌─────────────────────────────────────────────┐
│    Cognitive test assessment using CANTAB      │
│              (7 tests in total)                │
└─────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────┐
│                   CTEQ                         │
│                    CFQ                         │
│                CFQ for others                  │
│                    CDS                         │
│           Debriefing Questionnaire             │
└─────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────┐
│   Debriefed and compensated with a £25         │
│            Love2Shop Voucher                   │
│                                                │
│    Car parking charges paid if applicable      │
│                                                │
│  Travel expenses (up for £20) paid if testing was │
│  completed on the Unit outside of their allocated │
│                 appointment                    │
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Figure 6.1 Study 2 flow diagram to indicate the order of screening and test day procedures

6.2.7   NHS Ethical Approval

This study was approved by the Leeds West NHS REC on 12th May 2015 (REF: 13/YH/0219; Substantial amendment 2). Approval from Leeds Teaching Hospitals NHS Trust R&D was

gained on 15th May 2015. Following approval from both NHS REC and R&D, the study was added to the NIHR CRN Portfolio database.

At screening, participants were given written and verbal information about the purpose of the follow up study, all procedures involved and were made aware they could withdraw at any point without having to give a reason. It was made explicit that withdrawing from the study had no consequences for their clinical care. The informed consent of each participant was obtained in writing prior to commencement of the study.

There was the risk of hypoglycaemia occurring on the test day due to fasting for two hours. If hypoglycaemia was detected (<3.9mmol/L) or symptoms were reported by a participant, food and drink were immediately provided to restore a person's blood glucose level to within the normal range and they were withdrawn from the follow up study. This did not occur during the study.

6.2.8 Method of statistical analysis

Cognitive test data were extracted from CANTAB, entered into Excel and checked for accuracy. The delayed VRM data were recorded on a score sheet for each test session prior to entry into Excel, where it was checked. All subjective data were scored, entered and checked for accuracy in Excel.

The analytical approach was reviewed by the independent statistician (Quadt Consultancy BV, NL). A p-value of .05 was considered statistically significant. P values below 0.1 were considered trends. All data were analysed using SPSS version 22.0 (IBM Corp Inc., Armonk, NY, USA). All plotted data represent individual data points and means unless otherwise stated. Where data were transformed in order to normalise the distribution of residuals, the raw data scores are plotted for clarity.

Participant characteristics data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Analysis of participant characteristics was performed to test for changes since baseline using one way repeated measures ANOVAs with time as the within subjects factor for Townsend score, height, weight, BMI, health rating, blood glucose levels (capillary, and plasma), carbon monoxide (COppm and %COHb), anxiety, depression, cognitive failures data, FEV_1, FEV_1% predicted, FVC, FVC% predicted, oxygen saturation, HbA1c, SBP, DBP, pulse, CRP, vitamins A, D and E, serum creatinine, serum urea, and albumin. Changes in education, occupation, microbiology and the number of people receiving IV treatment at the time of testing were analysed using a Chi squared or Fisher's Exact test (when the expected cell frequencies were small). A correlation was performed on the follow up CFQ data with CDS to see the relationship between these two measures.

Cognitive data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Mixed ANCOVA's were performed on the cognitive test data using time as the within subjects factor. As there was an unequal split of males and females, gender was added as a between subjects factor. There was a wide variation in the ages of participants, and the time

point people with CFRD were followed up. Therefore, age and time since baseline were included as covariates to improve model fit. On tests where progression through the different stages/levels of the test was dependent on participant ability, other covariates were added where appropriate. For example, on the PAL test, stages completed was added as a covariate for outcome measures of stages completed on the first trial, total trials and total errors; on the SSP, span length was added as a covariate for the outcome measures of total number of attempts, reaction time and errors. Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS to correct for familywise type 1 error (Roberts & Russo, 1990).

Two way[61] repeated measures ANCOVA's with age and time since baseline as covariates, and gender as a between subjects factor, were performed on the subjective data in SPSS. Subjective data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS.

6.3 Results

6.3.1 Participants

From the 49 people with CFRD at baseline, 36 (23M;13F) were retested.

6.3.1.1 Loss to follow up

Figure 6.2 shows the reasons for loss to follow-up in Study 2.
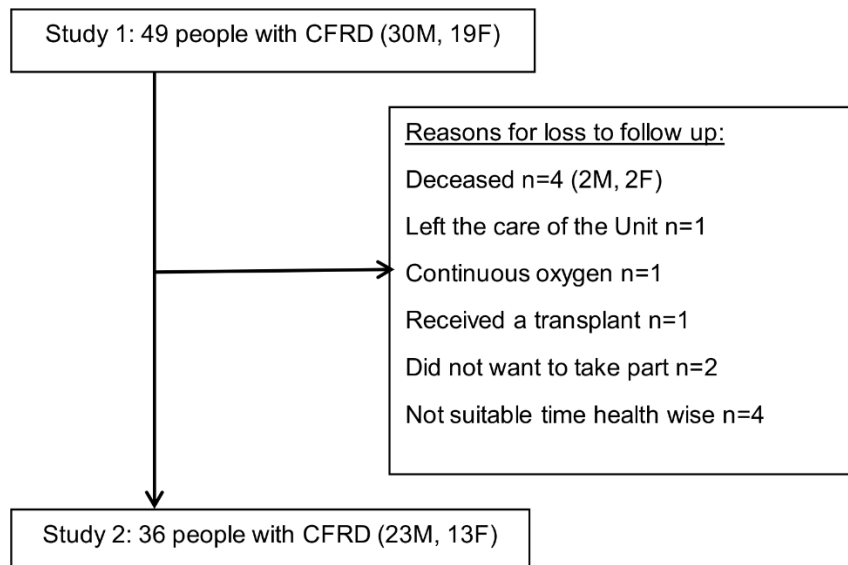
Figure 6.2 Study 2. Reasons for loss to follow up

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[61] For sleep quality, a 2 (time with 2 levels; baseline and follow up) x 2 (period with 2 levels; week and previous night) ANOVA was conducted
For perceived stress, a 2 (time with 2 levels; baseline and follow up) x 2 (period with 2 levels; week and month) ANOVA was conducted

6.3.1.2 **Participant characteristics**

Participants were retested after a period of 19.11 (SD ± 4.67) months. 34 people were heterozygous F508del. Table 6.1 below shows the participant characteristics for CFRD at baseline and follow up.

Table 6.1 Study 2. Participant characteristics at baseline and follow up for people with CFRD

	Baseline N=36 Mean (SE)	Follow up N=36 Mean (SE)	F (1,35)	*p* value	η_p^2
Age (years)	32.03 (1.23)	33.72 (1.22)	265.24	<.001	.883
Height (cm)	168.84 (1.43)	166.74 (1.42)	0.46	.50	.013
Weight (kg)	67.95 (2.14)	68.43 (2.06)	1.45	.24	.04
BMI (kg/m^2)	23.67(0.63)	23.96 (0.60)	1.54	.22	.042
CFRD duration (years)	10.88 (1.21)	12.14 (1.24)	25.72	<.001	.424
Fasting blood glucose (mmol/L)	8.01 (0.37)	7.57 (0.42)	0.60	.45	.017
Plasma blood glucose (mmol/L)	8.03 (0.68)	8.37 (0.60)	0.24	.63	.007
HbA1c (mmol/mol; IFCC)	61.90 (3.52)	58.09 (3.00)	1.76	.19	.049
N= with microvascular complications [62]	0	1			
FEV$_1$	2.03 (0.15)	1.96 (0.13)	4.07	.052	.107
FEV$_1$%predicted	56.00 (3.70)	54.89 (3.45)	3.45	.07	.092
FVC	3.18 (0.17)	3.11 (0.17)	4.00	.054	.105
FVC % predicted	74.75 (3.60)	73.26 (3.46)	4.08	.051	.107
Oxygen saturation (%)	96.47 (0.34)	96.69 (0.34)	0.35	.56	.01
COppm	3.64 (0.23)	3.89 (0.27)	0.63	.43	.018
%COHb	1.23 (0.04)	1.27 (0.04)	0.57	.45	.017
Health rating (1-10)	6.63 (0.28)	6.39 (0.29)	0.92	.34	.026
Anxiety score	6.08 (0.64)	5.94 (0.67)	0.10	.75	.003
Depression score	3.81 (0.50)	4.02 (.50)	0.03	.86	.001
SBP (mmHg)	132.06 (2.74)	135.72 (2.94)	1.08	.31	.03
DBP (mmHg)	78.75 (1.47)	78.33 (1.86)	0.05	.82	.001
Pulse (bpm)	95.25 (2.44)	92.56 (2.56)	1.07	.31	.03
Receiving IV's (n)	15	6	1.85	.21	
CRP (mg/L)	12.87 (2.35)	11.62 (1.59)	0.41	.53	.01
Vitamin A (ng/mL)	1.72 (0.08)	1.99 (0.22)	1.51	.23	.04
Vitamin D (ng/mL)	73.11 (4.45)	71.38 (4.02)	0.15	.71	.004
Vitamin E (ng/mL)	29.03 (1.57)	31.74 (3.17)	1.09	.30	.03
Serum creatinine (µmol/L)	66.56 (2.96)	67.19 (2.22)	0.11	.75	.003
Serum urea (mmol/L)	5.53 (0.28)	5.30 (0.26)	0.69	.41	.019
Albumin (g/L)	42.36 (0.65)	41.19 (0.57)	3.89	.057	.100

[62] Clinically measured or identifiable signs of microvascular disease.

Table 6.1 shows that age and CFRD duration had changed with the passage of time as expected. There were no changes in height, weight BMI, blood glucose level (fasting, plasma), HbA1c, oxygen saturation level, CO (ppm and %COHb), health rating, anxiety and depression score, SBP, DBP, pulse, number of people receiving IV treatment, CRP, vitamin A, D and E, and serum creatinine and urea. The decline in FEV_1, FVC, and FVC% predicted scores showed a marginally significant decline, while FEV_1% predicted showed a trend to decline over time (see Figure 6.3).
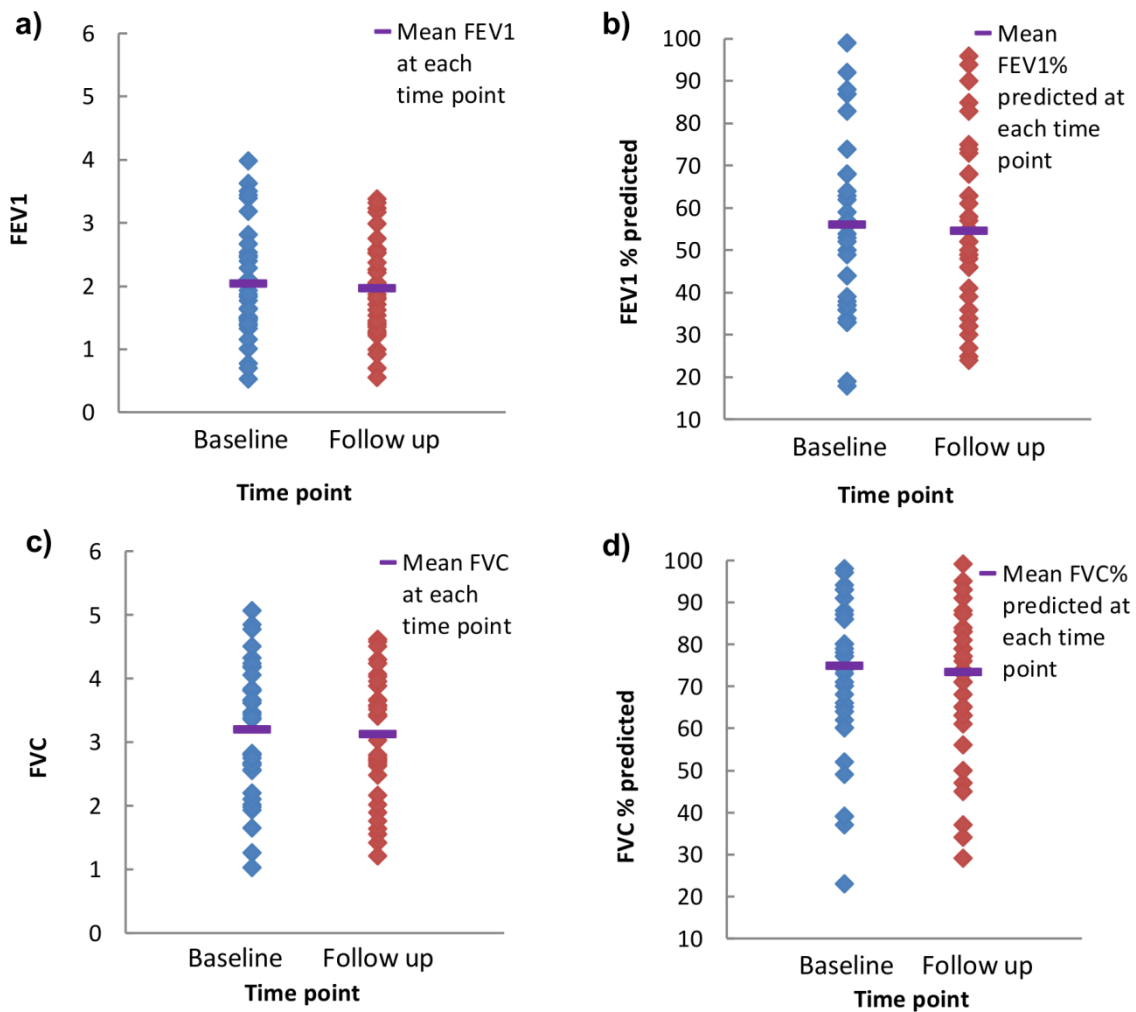
Figure 6.3 Study 2. Distribution of a) FEV1, b) FEV1%predicted, c) FVC and d) FVC% predicted scores at baseline and follow up in people with CFRD

There was a trend for albumin scores to decline over time (see Figure 6.4).
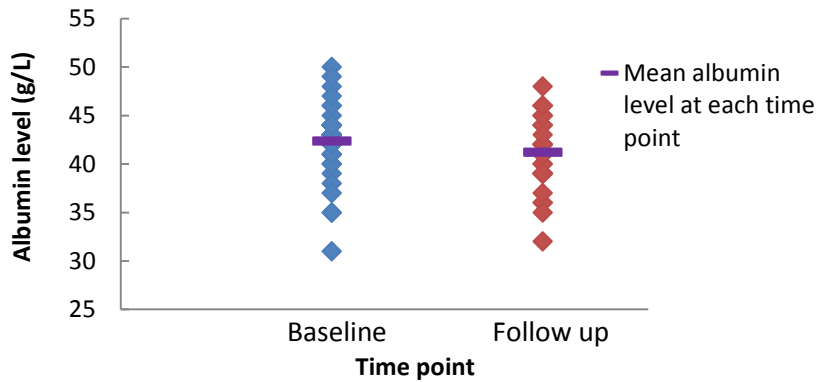
Figure 6.4 Study 2. Distribution of albumin scores at baseline and follow up in people with CFRD

Figures 6.5 shows there was no changed in education except one person had since completed their degree.
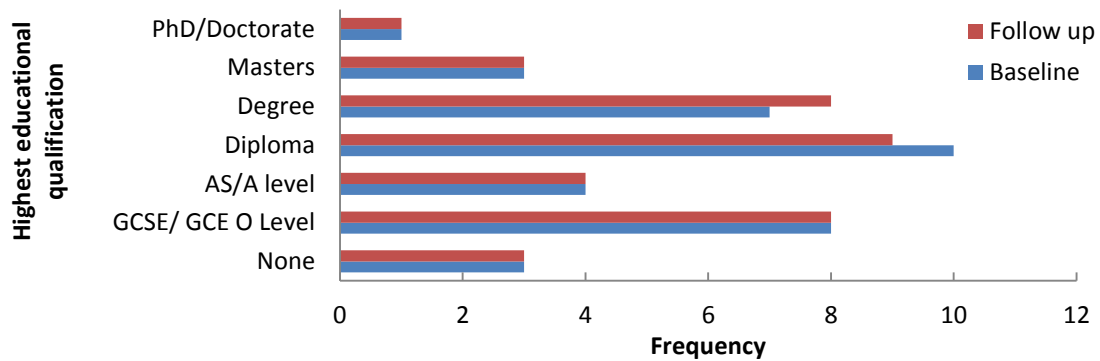
Figure 6.5 Study 2. Frequency of highest education qualification achieved at baseline and follow up in people with CFRD

Figure 6.6 shows that more people with CFRD were employment (full or part time) at follow up due to people having left education. There was no difference in the frequency of unemployment.
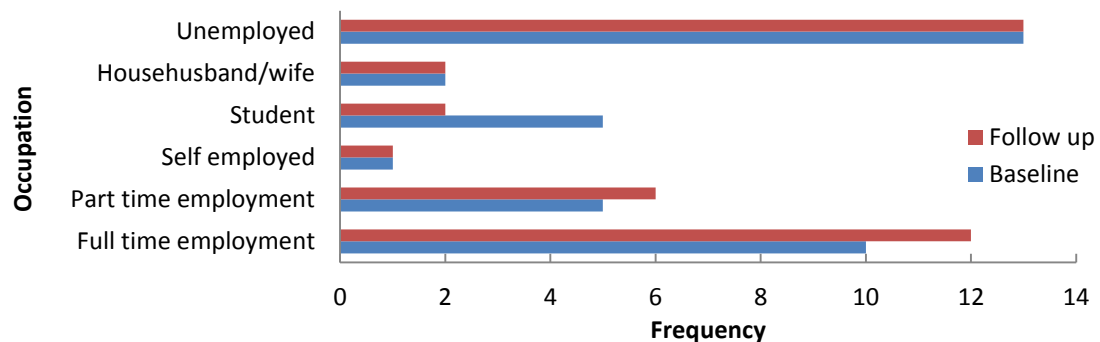
Figure 6.6 Study 2. Frequency of occupation at baseline and follow up in people with CFRD

Figure 6.7 shows there was no change in pulmonary infection except one individual had become *P. aeruginosa* negative (previously chronic *P. aeruginosa*).
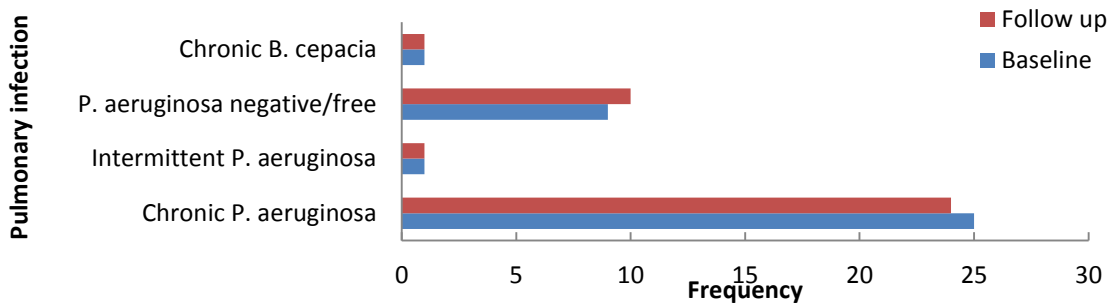
Figure 6.7 Study 2. Frequency of pulmonary infection at baseline and follow up in people with CFRD

There was no difference in blood glucose or HbA1c at baseline and follow up (see Figure 6.8).
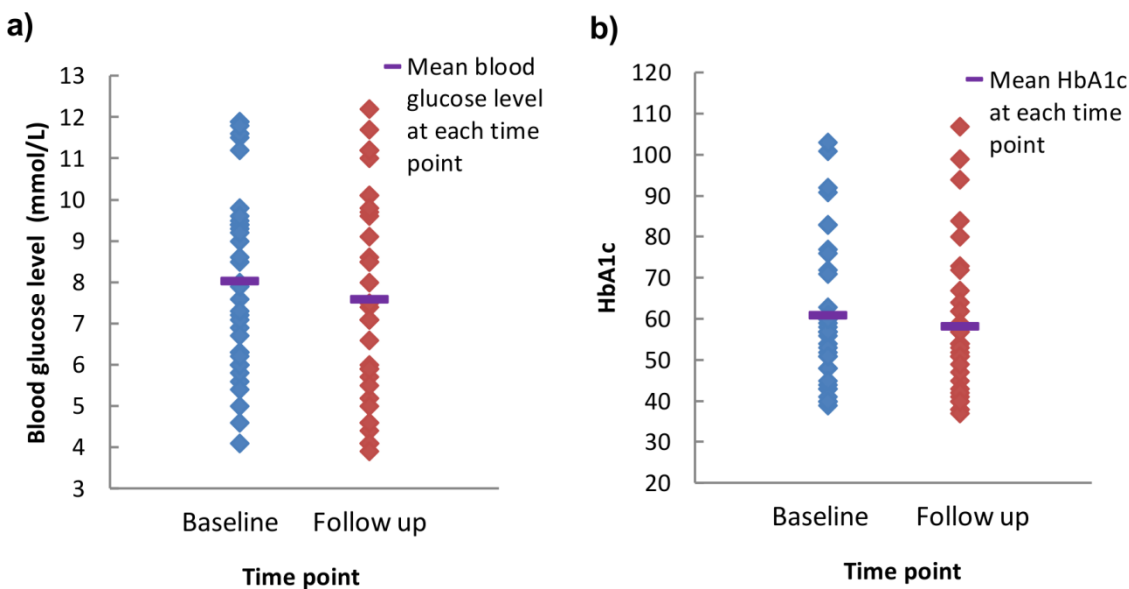
Figure 6.8 Study 2. Distribution of fasting blood glucose levels and HbA1c at baseline and follow up in people with CFRD

Although there was no significant difference in the number of people receiving IV treatment at baseline or follow up, fewer people with CFRD were on IV's at follow up. There was an equal number of people at start, middle and end at follow up. At baseline, more people were starting a course of IV treatment (see Figure 6.9).
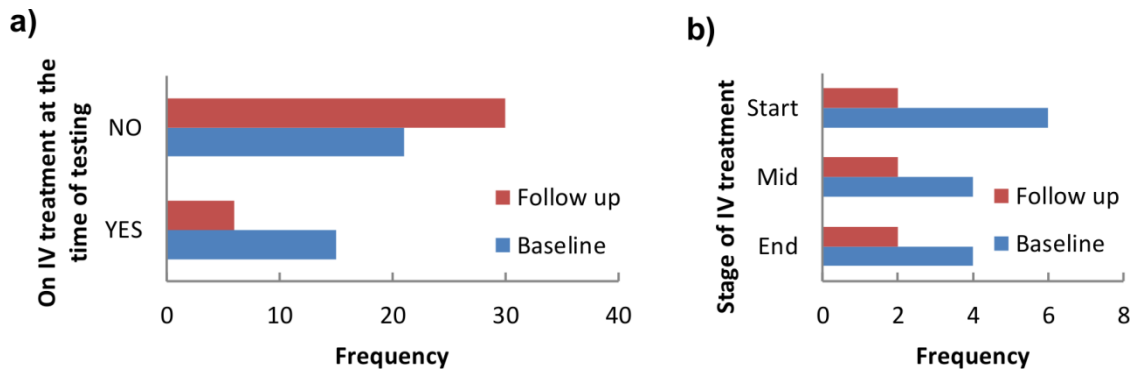
Figure 6.9 Study 2. Frequency of people with CFRD receiving IV treatment at the time of testing and the stage of treatment (start, mid, end), at baseline and follow up

6.3.2 Questionnaires

6.3.2.1 Sleep quality (LSEQ)

6.3.2.1.1 Ease of getting to sleep

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.22$, $p = .64$, $\eta_p^2 = .007$. There was no main effect of gender, $F(1, 32) = 0.09$, $p = .76$, $\eta_p^2 = .003$, time, $F(1, 32) = 1.15$, $p = .29$, $\eta_p^2 = .035$, or period, $F(1, 32) = 0.01$, $p = .92$, $\eta_p^2 < .001$ (see Figure 6.10). There was no time*age interaction $F(1, 32) = 0.000$, $p = .99$, $\eta_p^2 < .001$, but there was a time*gender interaction $F(1, 32) = 5.43$, $p = .026$, $\eta_p^2 = .145$ such that ease of getting to sleep had improved at follow up in both males and females, but to a greater degree in females. There was no significant period*age interaction, $F(1, 32) = 0.09$, $p = .77$, $\eta_p^2 = .003$, and no period*gender interaction, $F(1, 32) = 0.55$, $p = .47$, $\eta_p^2 = .017$. There was no significant time* period, $F(1, 32) = 0.06$, $p = .81$, $\eta_p^2 = .002$, no time*period*age interaction, $F(1, 32) = 0.03$, $p = .86$, $\eta_p^2 = .001$ or time*period*gender interaction, $F(1, 32) = 2.00$, $p = .17$, $\eta_p^2 = .059$.
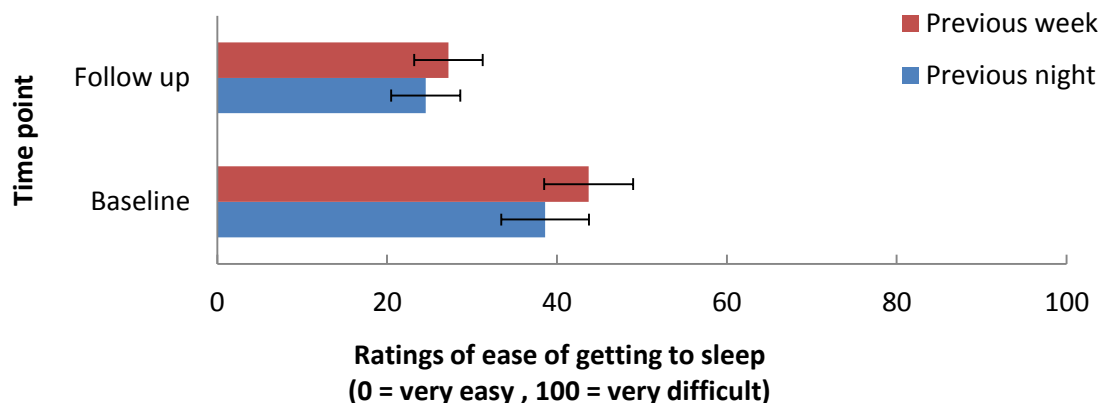
Figure 6.10 Study 2. Mean (±SE) ratings of ease of getting to sleep for the night before the testing session and previous week at baseline and follow up in people with CFRD

6.3.2.1.2 Time to get to sleep

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.64$, $p = .43$, $\eta_p^2 = .020$. There was no main effect of gender, $F(1, 32) = 0.13$, $p = .73$, $\eta_p^2 = .004$, or time, $F(1, 32) = 1.31$, $p = .26$, $\eta_p^2 = .039$, but there was a trend for a main effect of period, $F(1, 32) = 3.38$, $p = .075$, $\eta_p^2 = .096$, such that participants found it quicker to get to sleep the night before a test session compared to the previous week (see Figure 6.11). There was no significant time*age interaction $F(1, 32) = 0.01$, $p = .91$, $\eta_p^2 < .001$, no time*gender interaction $F(1, 32) = 2.30$, $p = .14$, $\eta_p^2 = .067$, no period*age interaction, $F(1, 32) = 1.94$, $p = .17$, $\eta_p^2 = .057$, no period*gender interaction, $F(1, 32) = 0.05$, $p = .82$, $\eta_p^2 = .002$, no time* period interaction, $F(1, 32) = 0.22$, $p = .64$, $\eta_p^2 = .007$, and no time*period*age interaction, $F(1, 32) = 0.16$, $p = .69$, $\eta_p^2 = .005$. There was a significant time*period*gender interaction, $F(1, 32) = 5.11$, $p = .031$, $\eta_p^2 = .138$ such that it took less time to get to sleep the night before the test session compared to the week at both baseline and follow up for males. For females, it took less time getting to sleep the night before the test session than the previous week at follow up, but it took more time to get to sleep before the test session compared to the week at baseline.
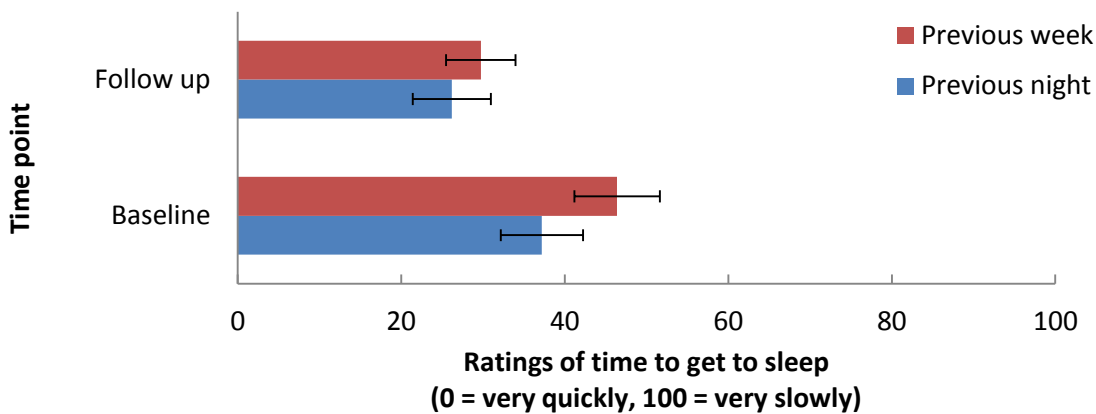
Figure 6.11 Study 2. Mean (±SE) ratings of time to get to sleep for the night before the testing session and previous week at baseline and follow up in people with CFRD

6.3.2.1.3 Restfulness of sleep

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.23$, $p = .63$, $\eta_p^2 = .007$. There was no main effect of gender, $F(1, 32) = 0.05$, $p = .83$, $\eta_p^2 = .001$, time, $F(1, 32) = 2.72$, $p = .11$, $\eta_p^2 = .078$, or period, $F(1, 32) = 0.02$, $p = .90$, $\eta_p^2 = .001$ (see Figure 6.12). There was no significant time*age interaction $F(1, 32) = 1.03$, $p = .32$, $\eta_p^2 = .031$, no time*gender interaction $F(1, 32) = 0.59$, $p = .45$, $\eta_p^2 = .018$, no period*age interaction, $F(1, 32) = 0.22$, $p = .65$, $\eta_p^2 = .007$, no period*gender interaction, $F(1, 32) = 0.06$, $p = .81$, $\eta_p^2 = .002$, no significant time* period, $F(1, 32) = 0.99$, $p = .33$, $\eta_p^2 = .030$, and no time*period*age interaction, $F(1, 32) = 1.68$, $p = .20$, $\eta_p^2 = .050$. There was no significant time*period*gender interaction, $F(1, 32) = 0.32$, $p = .58$, $\eta_p^2 = .010$. Females were more restless at baseline, and more restful at follow up compared to males. Both males and females were more restful the night before a test session than the previous week.
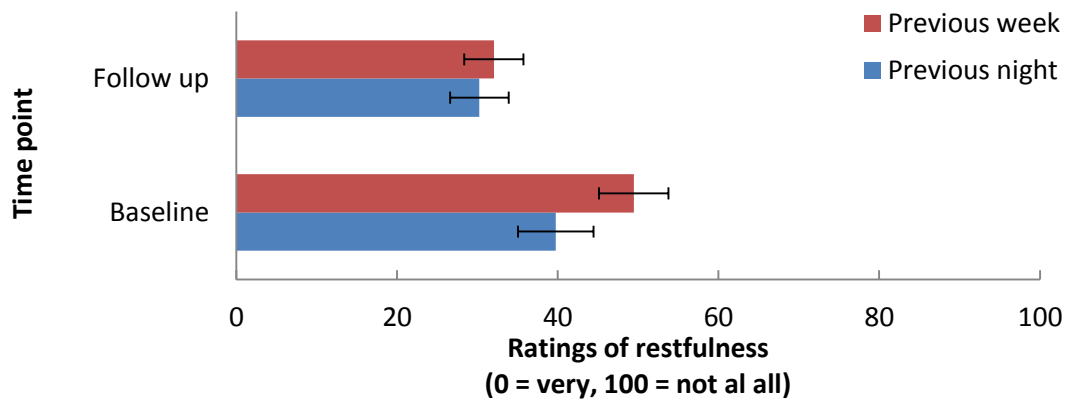
Figure 6.12. Study 2. Mean (±SE) ratings of restfulness of sleep for the night before the testing session and previous week at baseline and follow up in people with CFRD

6.3.2.1.4 Wakefulness during sleep

There was missing data for one participant who did not complete the last week questionnaire at baseline due to time constraints. Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 31) = 0.09$, $p = .77$, $\eta_p^2 = .003$. There was no main effect of gender, $F(1, 31) = 0.000$, $p = .998$, $\eta_p^2 < .001$, time, $F(1, 31) = 0.11$, $p = .75$, $\eta_p^2 = .003$, or period, $F(1, 31) = 0.59$, $p = .45$, $\eta_p^2 = .019$ (see Figure 6.13). There was no significant time*age interaction $F(1, 31) = 0.004$, $p = .95$, $\eta_p^2 < .001$, no time*gender interaction $F(1, 31) = 0.27$, $p = .61$, $\eta_p^2 = .009$, no period*age interaction, $F(1, 31) = 0.04$, $p = .85$, $\eta_p^2 = .001$, period*gender interaction, $F(1, 31) = 2.12$, $p = .16$, $\eta_p^2 = .064$, no significant time* period, $F(1, 31) = 0.26$, $p = .61$, $\eta_p^2 = .008$, and no time*period*age interaction, $F(1, 31) = 0.57$, $p = .46$, $\eta_p^2 = .018$. There was a significant time*period*gender interaction, $F(1, 32) = 1.36$, $p = .025$, $\eta_p^2 = .042$, such that females had fewer periods of wakefulness than males at both baseline and follow up. Both males and females had less periods of wakefulness for the night before a test session compared to the previous week.
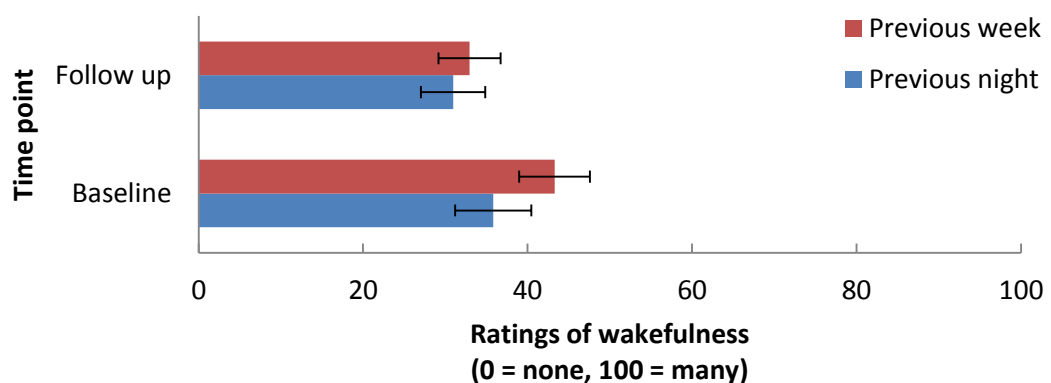
Figure 6.13 Study 2. Mean (±SE) ratings of periods of wakefulness during sleeping for the night before the testing session and previous week at baseline and follow up in people with CFRD

6.3.2.1.5 Ease of waking

There was missing data for one participant who did not complete the last week questionnaire at baseline due to time constraints. Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 31) = 1.37$, $p = .25$, $\eta_p^2 = .042$. There was no main effect of gender, $F(1, 31) = 0.65$, $p = .43$, $\eta_p^2 = .020$, time, $F(1, 31) = 0.009$, $p = .93$, $\eta_p^2 < .001$, or period, $F(1, 31) = 2.69$, $p = .11$, $\eta_p^2 = .080$ (see Figure 6.14). There was no significant time*age interaction $F(1, 31) = 0.05$, $p = .82$, $\eta_p^2 = .002$, no time*gender interaction $F(1, 31) = 0.18$, $p = .68$, $\eta_p^2 = .006$, no period*age interaction, $F(1, 31) = 1.50$, $p = .23$, $\eta_p^2 = .046$, no period*gender interaction, $F(1, 31) = 0.001$, $p = .97$, $\eta_p^2 < .001$, no significant time* period, $F(1, 31) = 0.16$, $p = .69$, $\eta_p^2 = .005$, and no time*period*age interaction, $F(1, 31) = 0.01$, $p = .92$, $\eta_p^2 < .001$. There was no significant time*period*gender interaction, $F(1, 32) = 0.09$, $p = .76$, $\eta_p^2 = .003$ such that females found it easier to wake up in the morning compared to males. However, whereas females found it harder to wake up on the morning of the test session at both baseline and follow up, males found it harder to wake at baseline, but easier at follow up.
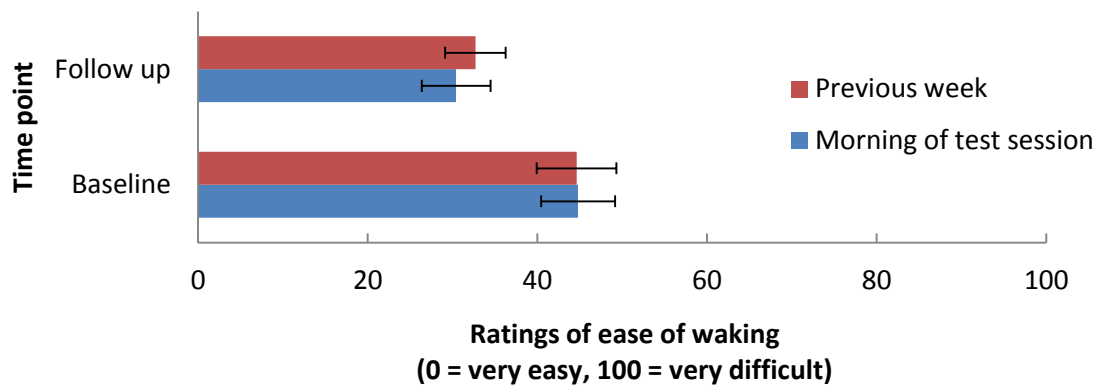
Figure 6.14 Study 2. Mean (±SE) ratings of ease of waking from sleep on the morning of the testing session and for the previous week at baseline and follow up in people with CFRD

6.3.2.1.6 Waking duration

There was missing data for one participant who did not complete the last week questionnaire at baseline due to time constraints. Data were square root transformed due to moderate positive skewness. The covariate of age was a trend, $F(1, 31) = 3.68$, $p = .064$, $\eta_p^2 = .042$, such that older participants reported it took less time to wake up in the morning compared to younger participants. There was no main effect of gender, $F(1, 31) = 0.04$, $p = .84$, $\eta_p^2 = .001$, time, $F(1, 31) = 2.23$, $p = .15$, $\eta_p^2 = .067$, or period, $F(1, 31) = 0.002$, $p = .97$, $\eta_p^2 < .001$ (see Figure 6.15). There was no significant time*age interaction $F(1, 31) = 0.92$, $p = .34$, $\eta_p^2 = .029$, no time*gender interaction $F(1, 31) = 0.002$, $p = .96$, $\eta_p^2 < .001$, no period*age interaction, $F(1, 31) = 0.39$, $p = .54$, $\eta_p^2 = .013$, no period*gender interaction, $F(1, 31) = 0.97$, $p = .33$, $\eta_p^2 = .030$, no significant time* period, $F(1, 31) = 1.22$, $p = .28$, $\eta_p^2 = .038$, no time*period*age interaction, $F(1, 31) = 0.81$, $p = .38$, $\eta_p^2 = .025$, and no time*period*gender interaction, $F(1, 31) = 0.63$, $p = .43$, $\eta_p^2 = .020$.
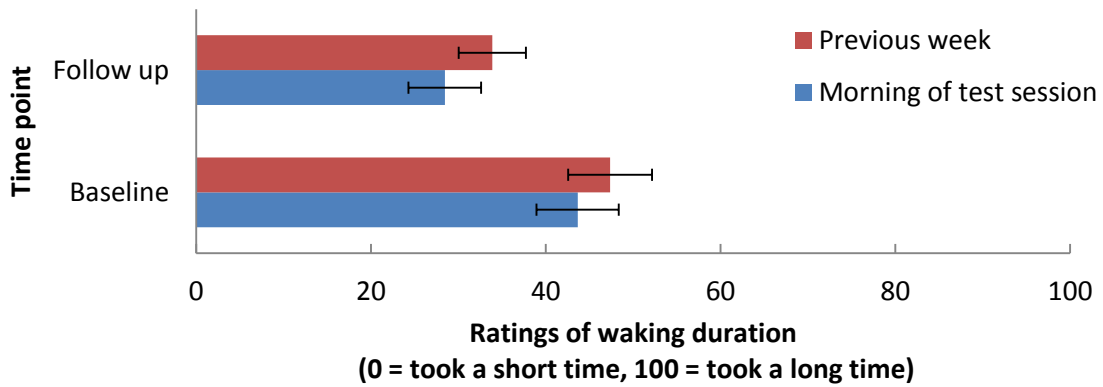
Figure 6.15 Study 2. Mean (±SE) ratings of waking duration on the morning of the testing session and for the previous week, at baseline and follow up in people with CFRD

6.3.2.1.7   Alertness on waking

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 2.49$, $p = .12$, $\eta_p^2 = .072$. There was no main effect of gender, $F(1, 32) = 1.00$, $p = .32$, $\eta_p^2 = .030$, time, $F(1, 32) = 0.68$, $p = .42$, $\eta_p^2 = .021$, or period, $F(1, 32) = 0.06$, $p = .81$, $\eta_p^2 = .002$ (see Figure 6.16). There was no significant time*age interaction $F(1, 32) = 0.05$, $p = .82$ $\eta_p^2 = .002$, no time*gender interaction $F(1, 32) = 0.51$, $p = .48$, $\eta_p^2 = .016$, no period*age interaction, $F(1, 32) = 0.19$, $p = .67$, $\eta_p^2 = .006$, period*gender interaction, $F(1, 32) = 0.007$, $p = .93$, $\eta_p^2 < .001$, no significant time* period, $F(1, 32) = 2.72$, $p = .11$, $\eta_p^2 = .078$, and no time*period*gender interaction, $F(1, 32) = 1.64$, $p = .21$, $\eta_p^2 = .048$. There was a trend for a significant time*period*age interaction, $F(1, 32) = 3.52$, $p = .070$, $\eta_p^2 = .099$ such that older participants were more alert than younger participants, and at baseline, alertness was slightly better on the morning of the test session while at follow up, alertness was better for the previous week.
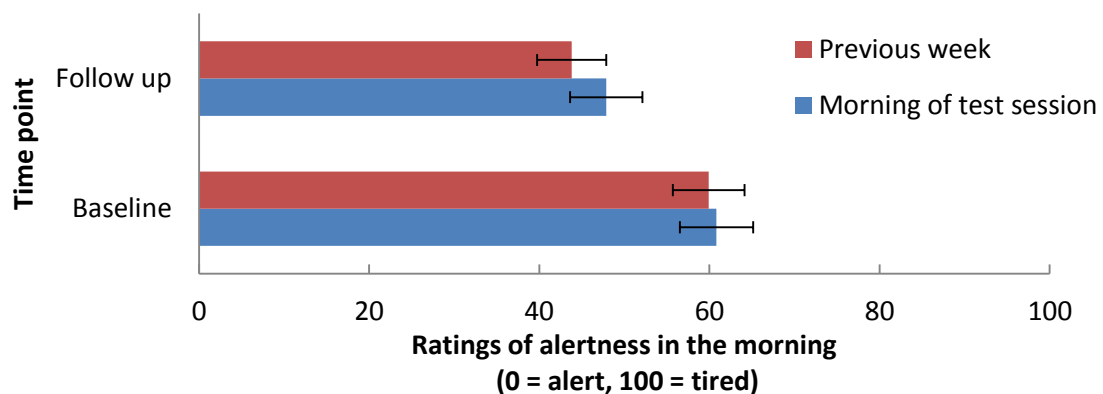
Figure 6.16 Study 2. Mean (±SE) ratings of alertness on the morning of the testing session and for the previous week, at baseline and follow up in people with CFRD

6.3.2.1.8   Alertness 1hour after waking

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 1.75$, $p = .20$, $\eta_p^2 = .052$. There was no main effect of gender, $F(1, 32) = 1.38$, $p = .25$, $\eta_p^2 = .041$, or period, $F(1, 32) = 0.26$, $p = .62$, $\eta_p^2 = .008$, but there was a trend for time, $F(1, 32) = 3.98$, $p = .055$, $\eta_p^2 = .111$, such that participants were more alert one hour after waking at follow up ($p = .004$; see Figure 6.17). There was no significant time*age interaction $F(1, 32) = 1.88$, $p = .18$, $\eta_p^2 = .055$, no time*gender interaction $F(1, 32) = 0.11$, $p = .74$, $\eta_p^2 = .003$, no period*age interaction, $F(1, 32) = 0.42$, $p = .52$, $\eta_p^2 = .013$, no period*gender interaction, $F(1, 32) = 0.84$, $p = .37$, $\eta_p^2 = .026$, no significant time* period, $F(1, 32) = 0.40$, $p = .53$, $\eta_p^2 = .012$, no time*period*age interaction, $F(1, 32) = 0.38$, $p = .54$, $\eta_p^2 = .012$, and no time*period*gender interaction, $F(1, 32) = 0.05$, $p = .83$, $\eta_p^2 = .001$.
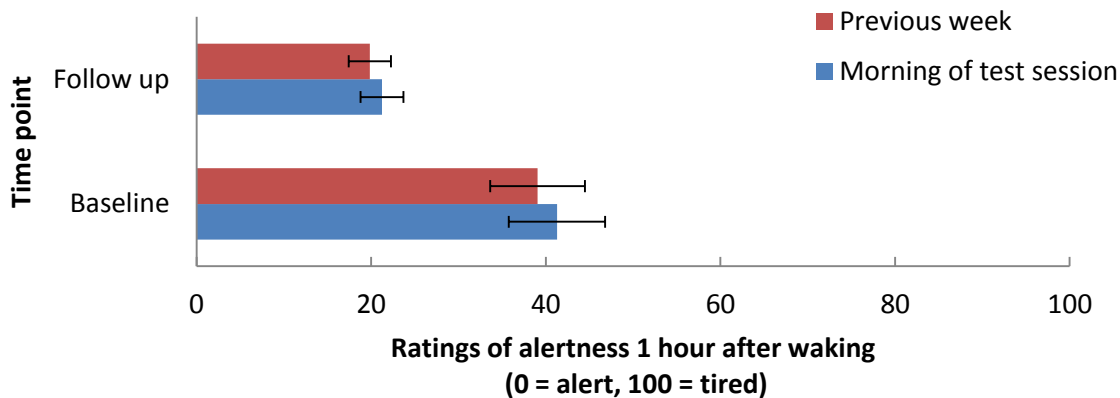
Figure 6.17 Study 2. Mean (±SE) ratings of alertness 1 hour after waking on the morning of the testing session and for the previous week at baseline and follow up in people with CFRD

6.3.2.2   **Perceived stress (PSS)**

One participant did not complete the stress month questionnaire at baseline. Age was not a significant covariate, $F(1, 32) = 1.97$, $p = .17$, $\eta_p^2 = .056$. There was no main effect of gender, $F(1, 32) = 0.29$, $p = .59$, $\eta_p^2 = .009$, time, $F(1, 32) = 2.73$, $p = .11$, $\eta_p^2 = .076$, or period, $F(1, 32) = 0.09$, $p = .77$, $\eta_p^2 = .003$ (see Figure 6.18). There was no significant time*age interaction $F(1, 32) = 1.10$, $p = .30$ $\eta_p^2 = .032$, no time*gender interaction $F(1, 32) = 0.20$, $p = .66$, $\eta_p^2 = .006$, no period*age interaction, $F(1, 32) = 0.07$, $p = .80$, $\eta_p^2 = .002$, but there was a significant period*gender interaction, $F(1, 32) = 7.94$, $p = .008$, $\eta_p^2 = .194$, such that females were more stressed for the previous month than week, while males were slightly more stressed for the previous week. There was no significant time* period interaction, $F(1, 32) = 1.95$, $p = .17$, $\eta_p^2 = .056$, no time*period*gender interaction, $F(1, 32) = 1.82$, $p = .19$, $\eta_p^2 = .052$, and no time*period*age interaction, $F(1, 32) = 0.04$, $p = .85$, $\eta_p^2 = .001$.
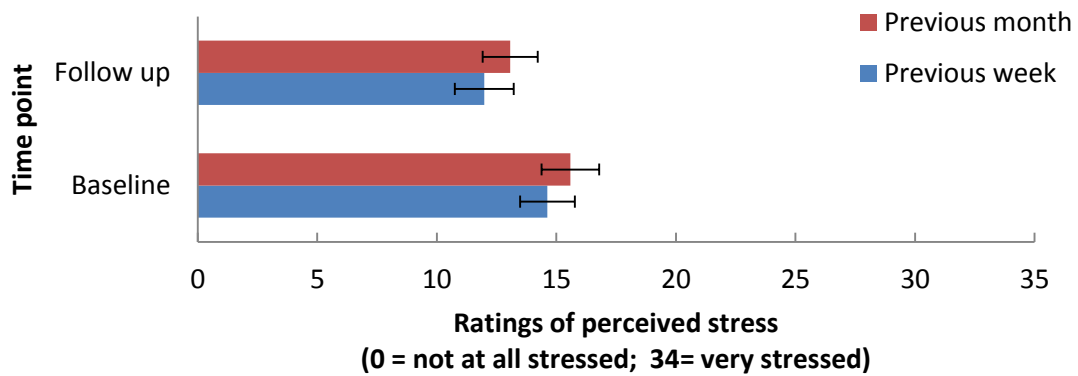
Figure 6.18 Study 2. Perceived stress ratings for the previous month and week before the test session, at baseline and follow up in people with CFRD

6.3.2.3 VAS Ratings of mood and mental alertness

6.3.2.3.1 Contentedness

Age was not a significant covariate, $F(1, 33) = 2.30$, $p = .14$, $\eta_p^2 = .065$. There was a main effect of gender, $F(1, 33) = 6.78$, $p = .014$, $\eta_p^2 = .170$, such that males rated themselves to be more contented than females. There was no significant main effect of time, $F(1, 33) = 0.006$, $p = .94$, $\eta_p^2 < .001$ (see Figure 6.19). There was no significant time*age interaction $F(1, 33) = 0.32$, $p = .58$ $\eta_p^2 = .009$ and no time*gender interaction $F(1, 33) = 0.13$, $p = .72$, $\eta_p^2 = .004$.
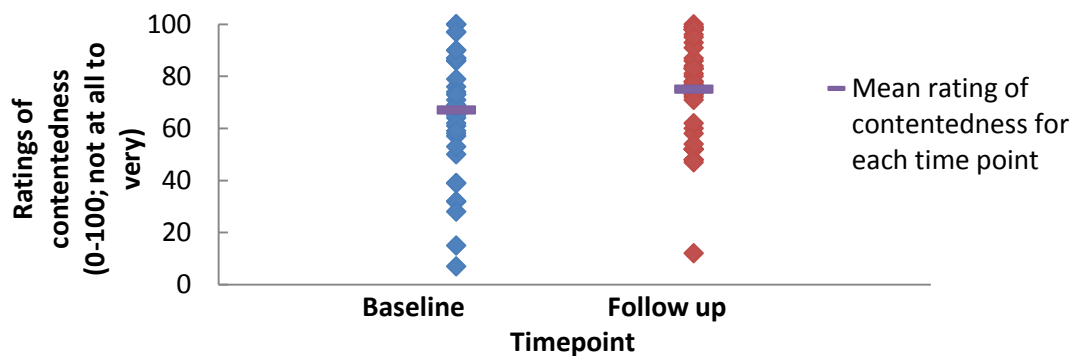
Figure 6.19 Study 2. VAS ratings of contentedness at baseline and follow up in people with CFRD

6.3.2.3.2 Irritability

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 33) = 0.03$, $p = .86$, $\eta_p^2 = .001$. There was no main effect of gender, $F(1, 33) = 0.48$, $p = .50$, $\eta_p^2 = .014$. There was no significant main effect of time, $F(1, 33) = 1.01$, $p = .32$, $\eta_p^2 = .030$ (see Figure 6.20). There was no significant time*age interaction $F(1, 33) = 2.17$, $p = .15$, $\eta_p^2 = .062$, but there was a significant time*gender interaction $F(1, 33) = 5.73$, $p = .022$,

η_p^2 = .148, such that females were considerably less irritable at follow up, while males were slightly more irritable at follow up.
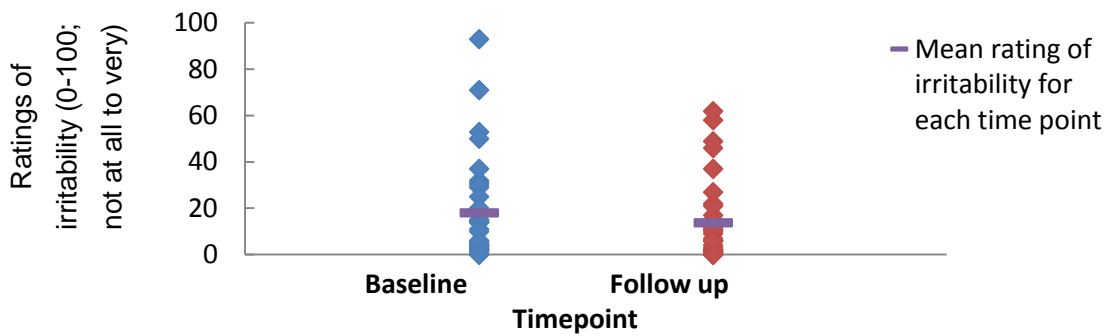
Figure 6.20 Study 2. VAS ratings of irritability at baseline and follow up in people with CFRD

6.3.2.3.3 Sleepiness

Age was not a significant covariate, $F(1, 33) = 0.01$, $p = .91$, $\eta_p^2 < .001$. There was no main effect of gender, $F(1, 33) = 0.64$, $p = .43$, $\eta_p^2 = .019$. There was no significant main effect of time, $F(1, 33) = 0.02$, $p = .88$, $\eta_p^2 = .001$ (see Figure 6.21). There was no significant time*age interaction $F(1, 33) = 0.08$, $p = .78$ $\eta_p^2 = .002$ and no time*gender interaction $F(1, 33) = 2.48$, $p = .13$, $\eta_p^2 = .070$.
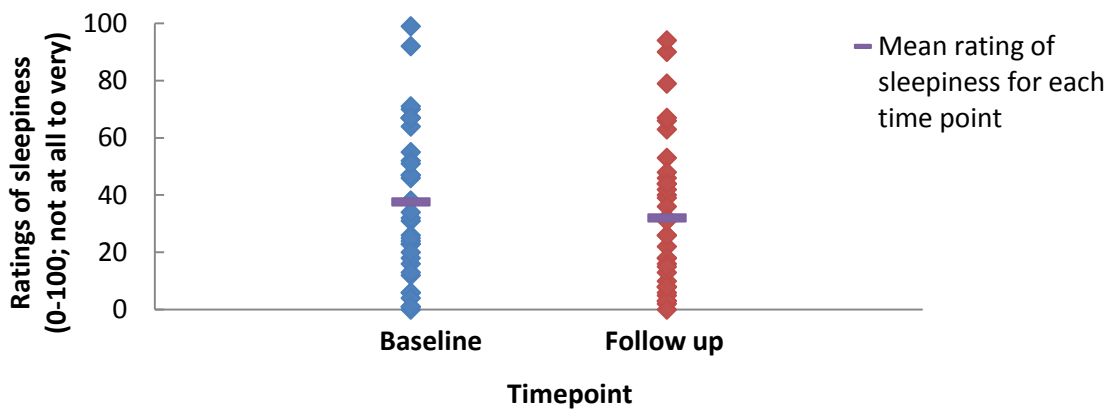
Figure 6.21 Study 2. VAS ratings of sleepiness at baseline and follow up in people with CFRD

6.3.2.3.4 Mental alertness

The covariate for age was a trend, $F(1, 33) = 3.05$, $p = .09$, $\eta_p^2 = .085$, such that older participants rated themselves as less mentally alert than younger participants. There was a main effect of gender, $F(1, 33) = 5.85$, $p = .021$, $\eta_p^2 = .151$, such that females rated themselves to be more mentally alert than males. There was no significant main effect of time, $F(1, 33) = 0.001$, $p = .97$, $\eta_p^2 < .001$ (see Figure 6.22). There was no significant time*age interaction $F(1, 33) = 0.63$, $p = .80$ $\eta_p^2 = .002$ and no time*gender interaction $F(1, 33) = 0.13$, $p = .72$, $\eta_p^2 = .004$.
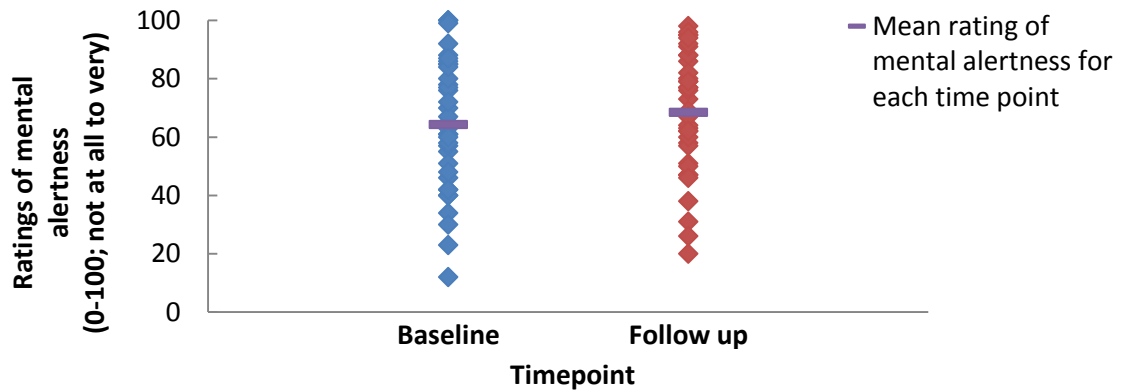
Figure 6.22 Study 2. VAS ratings of mental alertness at baseline and follow up in people with CFRD

6.3.2.3.5 Ability to concentrate

The covariate for age was a trend, $F(1, 33) = 3.21$ $p = .082$, $\eta_p^2 = .089$, such that older participants rated themselves as having less ability to concentrate than younger participants. There was no main effect of gender, $F(1, 33) = 2.23$, $p = .15$, $\eta_p^2 = .063$. There was no significant main effect of time, $F(1, 33) = 0.43$, $p = .52$, $\eta_p^2 = .013$ (see Figure 6.23). There was no significant time*age interaction $F(1, 33) = 0.10$ $p = .92$, $\eta_p^2 < .001$ and no time*gender interaction $F(1, 33) = 1.48$, $p = .23$, $\eta_p^2 = .043$.
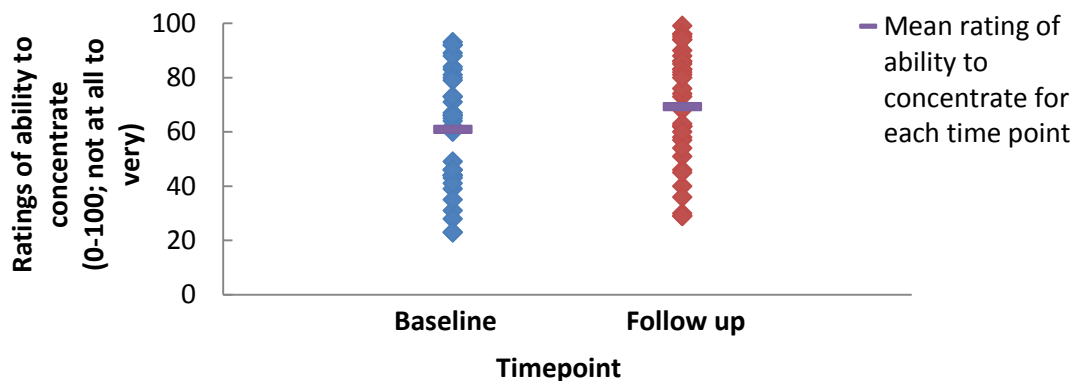
Figure 6.23 Study 2. VAS ratings of ability to concentrate at baseline and follow up in people with CFRD

6.3.2.3.6 Feeling energetic

Age was a significant covariate, $F(1, 33) = 4.24$, $p = .048$, $\eta_p^2 = .089$, such that older participants rated themselves as being less energetic than younger participants. There was no main effect of gender, $F(1, 33) = 0.000$, $p = .998$, $\eta_p^2 < .001$. There was no significant main effect of time, $F(1, 33) = 0.39$, $p = .54$, $\eta_p^2 = .012$ (see Figure 6.24). There was no significant time*age interaction $F(1, 33) = 0.06$ $p = .81$, $\eta_p^2 = .002$ and no time*gender interaction $F(1, 33) = 2.36$, $p = .13$, $\eta_p^2 = .067$.
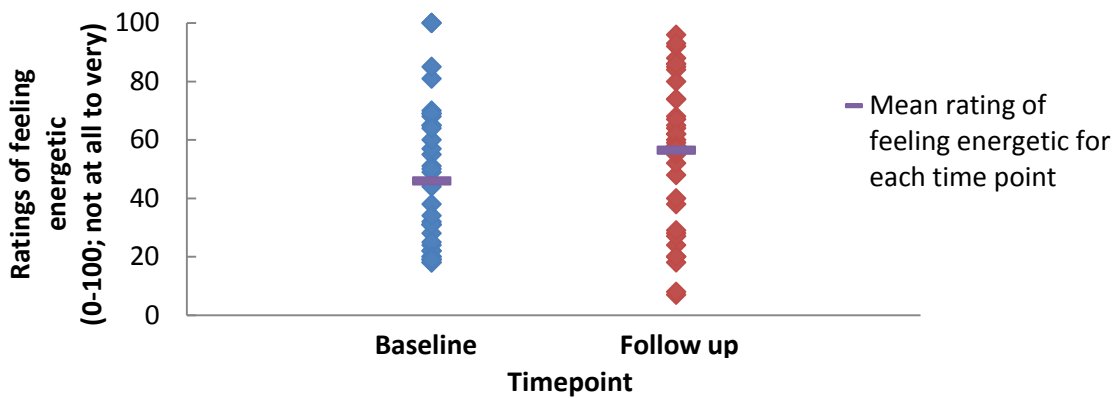
Figure 6.24 Study 2. VAS ratings of feeling energetic at baseline and follow up in people with CFRD

6.3.3 Subjective occurrences of minor daily cognitive errors

6.3.3.1 Cognitive Failures Questionnaire (CFQ)

Figure 6.25 (a) shows the mean number of subjective occurrences of minor daily cognitive errors which occurred in the previous 6 months reported on the CFQ by each group. Age was not a significant covariate, $F(1, 33) = 2.10$, $p = .16$, $\eta_p^2 = .060$. There was no significant main effect of time $F(1, 32) = 0.31$, $p = .58$, $\eta_p^2 = .009$, or gender, $F(1, 33) = 0.45$, $p = .51$, $\eta_p^2 = .013$. There was no significant time*age interaction, $F(1, 32) = 0.04$, $p = .85$, $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 33) = 1.12$, $p = .30$, $\eta_p^2 = .033$.
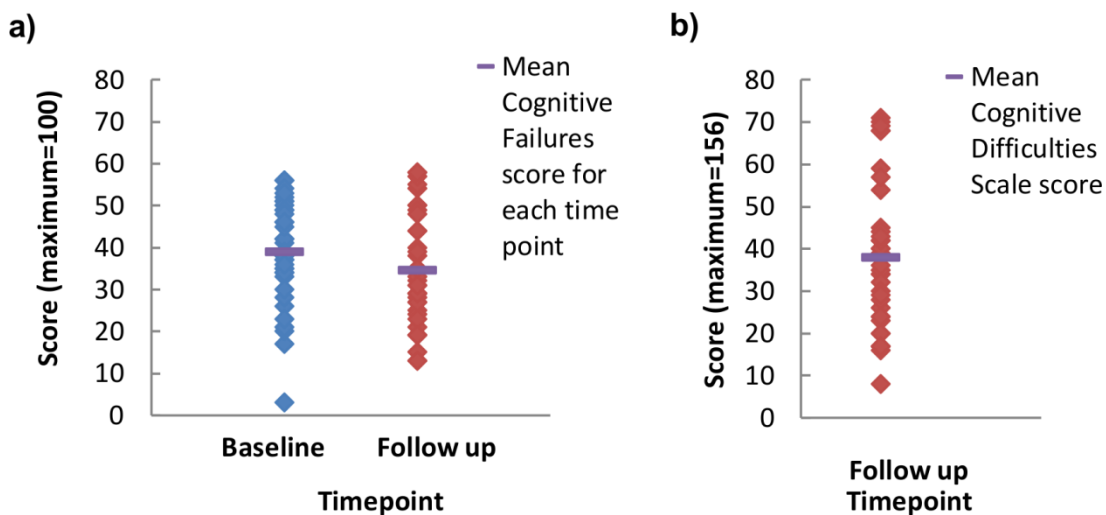
Figure 6.25 Study 2. (a) Cognitive Failures Questionnaire scores at baseline and follow up, and the (b) Cognitive Difficulties Scale score at follow up

6.3.3.2 Cognitive Failures Questionnaire –for others (CFQ-for others)

7 partners/relatives/close friends completed the CFQ-for others at follow up. The mean scores are reported in Table 6.2. The maximum score is 32.

Table 6.2 Study 2. Cognitive Failures Questionnaire –for others score (N=7)

	Mean (SE)
Score	17.00 (2.26)

6.3.3.3 Cognitive Difficulties Scale (CDS)

The CDS was only administered at follow up, however was shown to be highly correlated with the follow up CFQ score, $r(36)=.811$, $p<.001$ (see Figure 6.25b).

6.3.4 Cognitive Tests

Time of day can affect cognitive functioning (Schmidt et al., 2007). The Chi-Square test showed that frequency of participants tested in the morning and afternoon did not differ between baseline and follow up, $\chi^2(2, N = 36) = 0.56$, $p = .51$; see Figure 6.26).
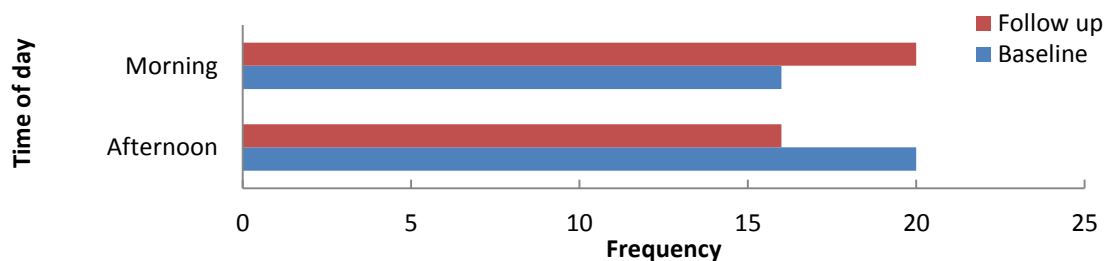
Figure 6.26 Study 2. Frequency of participants tested in the morning and afternoon, at baseline and follow up in people with CFRD

6.3.4.1 Motor Screening Test (MOT)

This test is an index of motor skill assessing both speed and accuracy (see section 5.2.3.3.1). For the outcome measure of total correct, people with CFRD correctly responded to all 10 crosses at baseline and follow up.

6.3.4.1.1 Mean error

Mean error is a measurement of accuracy (see Table 5.4; the mean distance between the centre of the cross and the location the subject touched on the screen). Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 32) = .59$, $p = .59$, $\eta_p^2 = .009$ and time since baseline was not a significant covariate, $F(1, 32) = 0.33$, $p = .57$, $\eta_p^2 = .01$. There was no significant main effect of time $F(1, 32) = 0.58$, $p = .45$, η_p^2

= .018, or gender, $F(1, 32) = 0.57$, $p = .46$, $\eta_p^2 = .017$. There was no significant time*time since baseline interaction, $F(1, 32) = 2.57$, $p = .12$, $\eta_p^2 = .074$, time*age, $F(1, 32) = 0.60$, $p = .44$, $\eta_p^2 = .018$ or time*gender, $F(1, 32) = 0.74$, $p = .40$, $\eta_p^2 = .023$ (see Figure 6.27a).
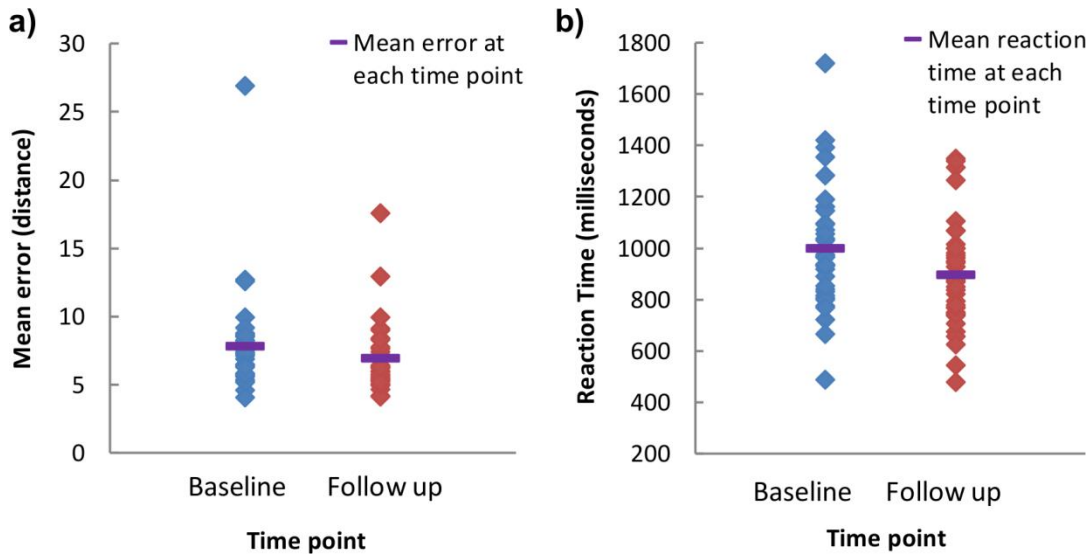
Figure 6.27 Study 2. (a) Mean error (measurement of accuracy) and (b) reaction time (milliseconds) for correct responses on the MOT at baseline and follow up in people with CFRD

6.3.4.1.2   Reaction time for correct responses

Age was not a significant covariate, $F(1, 32) = .2.25$, $p = .14$, $\eta_p^2 = .066$ and time since baseline was not a significant covariate, $F(1, 32) = 0.30$, p $= .59$, $\eta_p^2 = .009$. There was no significant main effect of time $F(1, 32) = 1.48$, $p = .23$, $\eta_p^2 = .044$ or gender, $F(1, 32) = 0.45$, $p = .51$, $\eta_p^2 = .014$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.70$, $p = .41$, $\eta_p^2 = .021$, time*age, $F(1, 32) = 0.96$, $p = .76$, $\eta_p^2 = .003$, or time*gender, $F(1, 32) = 0.19$, $p = .67$, $\eta_p^2 = .006$ (see Figure 6.27b).

6.3.4.2   **Paired Associates Learning (PAL) test**

The outcome measures for the PAL tests are stages completed, stages completed on the first trial, first trial memory score, total trials and total errors (see section 5.2.3.3.2, and Table 5.4 for a definition of each outcome variable).

6.3.4.2.1   Stages completed

There were too few data points to perform analysis for stages completed as participants were at ceiling performance at follow up and all bar one participant completed the 8 stages at baseline. This participant completed 7 stages.

6.3.4.2.2   Stages completed on first trial

Age was a significant covariate, $F(1, 32) = 5.40$, $p = .027$, $\eta_p^2 = .144$. Younger participants completed more stages on the first trial than older participants. Time since baseline was not a significant covariate, $F(1, 32) = 1.61$, $p = .21$, $\eta_p^2 = .048$. There was a trend for a significant main effect of time $F(1, 32) = 3.25$, $p = .081$, $\eta_p^2 = .092$, such that performance at follow up was

significantly better than baseline (p =.03). There was no significant main effect of gender, $F(1, 32) = 0.29$, $p = .60$, $\eta_p^2 = .009$. There was a significant time*age interaction, $F(1, 32) = 3.95$, $p = .007$, $\eta_p^2 = .207$, such that older participants completed more stages on the first trial at follow up, while younger participants completed more stages at baseline. There was a time*gender interaction, $F(1, 32) = 11.46$, $p = .002$, $\eta_p^2 = .264$, such that females performed better at follow up while males performed better at baseline. There was no time*time since baseline interaction, $F(1, 32) = 0.007$, $p = .93$, $\eta_p^2 < .001$. Figure 6.28 shows that performance at follow up was significantly better than baseline.
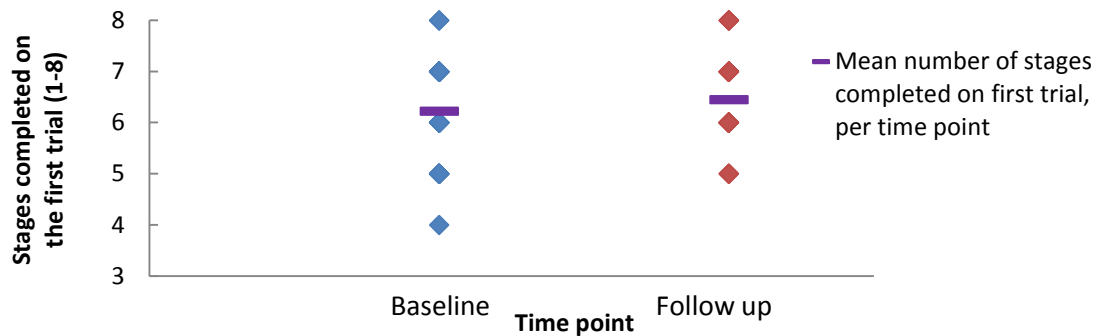
Figure 6.28 Study 2. Number of stages completed on the first trial on the PAL test at baseline and follow up in people with CFRD

6.3.4.2.3 First trial memory score

Data were reflected and a logarithm transformation applied due to substantial negative skewness. Age was a significant covariate, $F(1, 32) = 4.72$, $p = .037$, $\eta_p^2 = .129$. Younger participants correctly located more patterns on the first trial across the test than older participants. Time since baseline was not a significant covariate, $F(1, 32) = 0.76$, $p = .39$, $\eta_p^2 = .023$. There was no significant main effect of time $F(1, 32) = 1.94$, $p = .17$, $\eta_p^2 = .057$, or gender, $F(1, 32) = 1.25$, $p = .27$, $\eta_p^2 = .038$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.28$, $p = .60$, $\eta_p^2 = .009$. There was a significant time*age interaction, $F(1, 32) = 6.22$, $p = .018$, $\eta_p^2 = .163$, such that older participants correctly located more patterns on the first trial at follow up, while younger participants completed more stages at baseline. There was a time*gender interaction, $F(1, 32) = 7.29$, $p = .011$, $\eta_p^2 = .186$, such that females performed better at follow up while males performed better at baseline. Figure 6.29 shows that there was no overall difference between baseline and follow up performance in people with CFRD.
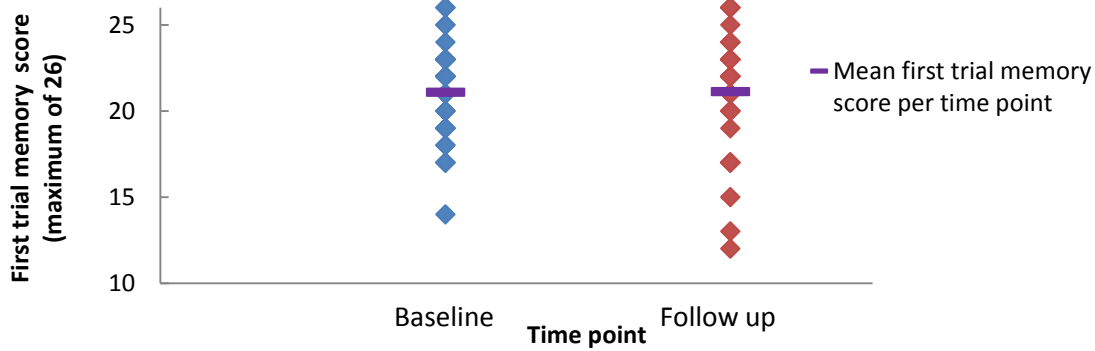
Figure 6.29 Study 2. First trial memory score on the PAL test at baseline and follow up in people with CFRD

6.3.4.2.4 Total trials

Data were inversely transformed due to severe positive skewness. The covariate for age showed a trend, $F(1, 32) = 4.11$, $p = .051$, $\eta_p^2 = .114$. Younger participants tended to need fewer trials than older participants. Time since baseline was not a significant covariate, $F(1, 32) = 1.79$, $p = .19$, $\eta_p^2 = .053$. There was no significant main effect of time $F(1, 32) = 0.16$, $p = .69$, $\eta_p^2 = .005$, or gender, $F(1, 32) = 0.78$, $p = .38$, $\eta_p^2 = .024$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.98$, $p = .33$, $\eta_p^2 = .030$. There was a trend for a significant time*age interaction, $F(1, 32) = 3.31$, $p = .078$, $\eta_p^2 = 094$, such that older participants tended to need more trials at follow up to complete the tests while younger participants needed more trials at baseline. There was a significant time*gender interaction, $F(1, 32) = 5.75$, $p = .022$, $\eta_p^2 = .152$, such that females performed better at baseline while performance was stable in males between baseline and follow up. Figure 6.30 shows that there was no overall difference between baseline and follow up performance for the number of trials needed in order to complete the test.
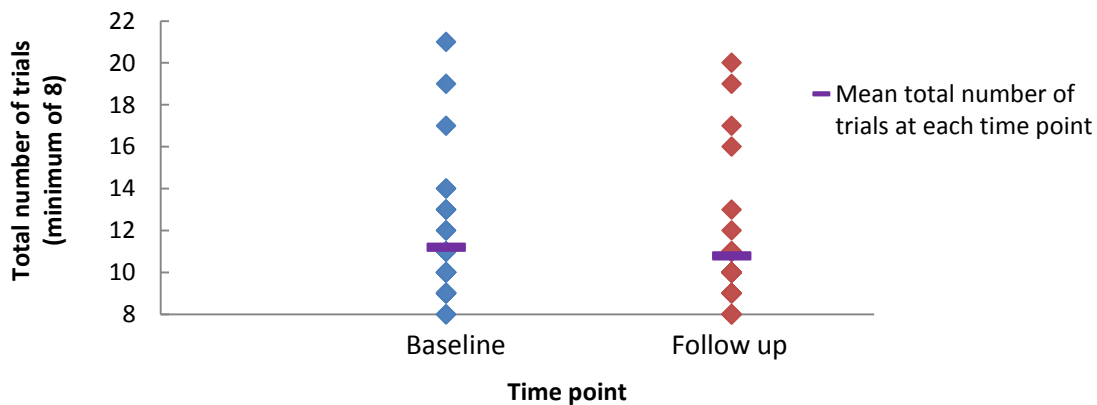
Figure 6.30 Study 2. Total trials on the PAL test at baseline and follow up in people with CFRD

6.3.4.2.5 Total errors

Data were inversely transformed due to severe positive skewness. Age was a significant covariate, $F(1, 32) = 5.17$, $p = .030$, $\eta_p^2 = .139$. Younger participants made fewer errors than

older participants. Time since baseline was not a significant covariate, $F(1, 32) = 1.83$, $p = .19$, $\eta_p^2 = .054$. There was no significant main effect of time $F(1, 32) = 0.23$, $p = .63$, $\eta_p^2 = .007$, or gender, $F(1, 32) = 0.62$, $p = .44$, $\eta_p^2 = .019$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.76$, $p = .39$, $\eta_p^2 = .023$. There was a trend for a significant time*age interaction, $F(1, 32) = 3.05$, $p = .090$, $\eta_p^2 = 087$, such that older participants tended to make more errors at baseline while younger participants made more errors at follow up. There was a significant time*gender interaction, $F(1, 32) = 6.81$, $p = .014$, $\eta_p^2 = .175$, such that females made less errors at follow up while males made less errors at baseline. Figure 6.31 shows that there was no overall difference between baseline and follow up performance for the number of trials needed in order to complete the test.
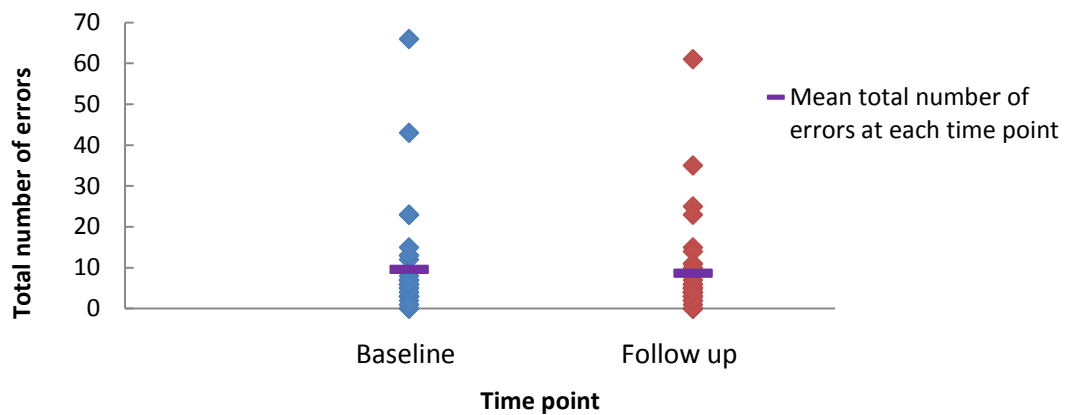
Figure 6.31 Study 2. Total number of errors produced on the PAL test at baseline and follow up in people with CFRD

6.3.4.3 Verbal Recognition Memory (VRM)

The outcome measures for the free recall test are the number of correctly recalled words, the number of novel words and the number of perseverations (number of times a participant repeated a word they had already successfully recalled from the word list). The outcomes measures for the recognition test are correct number of target words and number of false positives (see section 5.2.3.3.3; Table 5.4 for a definition of each outcome variable).

6.3.4.3.1 Immediate free recall

6.3.4.3.1.1 Number of correctly recalled words at immediate recall

Age was not a significant covariate, $F(1, 32) = 1.51$, $p = .23$, $\eta_p^2 = .045$, and time since baseline was not a significant covariate, $F(1, 32) = 0.03$, $p = .86$, $\eta_p^2 = .001$. There was no significant main effect of time $F(1, 32) = 0.14$, $p = .71$, $\eta_p^2 = .004$, but a trend for a main effect of gender, $F(1, 32) = 3.46$, $p = .072$, $\eta_p^2 = .098$, such that females tended to correctly free recall more words than males ($p= .072$). There was no significant time*time since baseline interaction, $F(1, 32) = 2.08$, $p = .16$, $\eta_p^2 = .061$. There was a significant time*age interaction, $F(1, 32) = 6.68$, $p = .015$, $\eta_p^2 = .173$, such that older participants recalled more words at follow up, while younger participants recalled more words at baseline. There was no significant time*gender interaction, $F(1, 32) = 2.35$, $p = .14$, $\eta_p^2 = .068$. Figure 6.32 shows that there was no overall difference

between baseline and follow up performance in the number of words correctly recalled at immediate free recall.
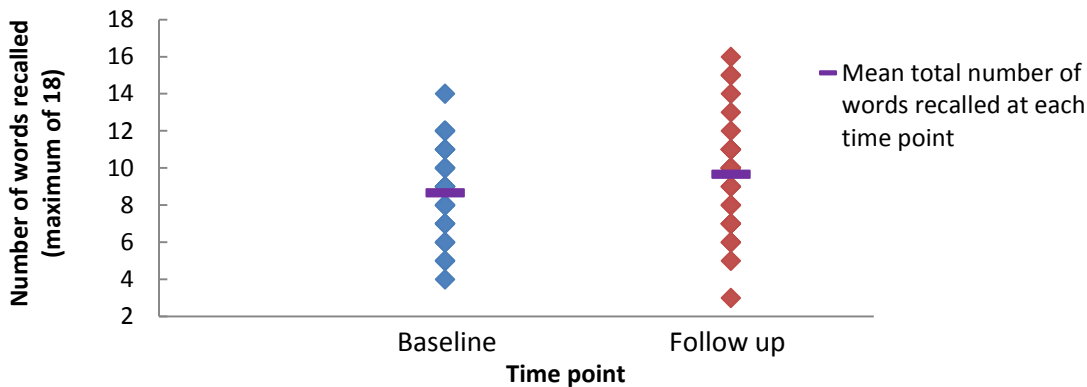
Figure 6.32 Study 2. Number of correctly recalled words at immediate free recall on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.1.2   Number of novel words produced at immediate recall

Data were inversely transformed due to severe positive skewness. Age was not a significant covariate, $F(1, 32) = 0.003$, $p = .96$, $\eta_p^2 < .001$, and time since baseline was not a significant covariate, $F(1, 32) = 0.78$, $p = .38$, $\eta_p^2 = .024$. There was a trend for a significant main effect of time $F(1, 32) = 3.41$, $p = .074$, $\eta_p^2 = .004$, but there were no significant differences on the post hoc tests. There was a significant time*time since baseline interaction, $F(1, 32) = 10.023$, $p = .003$, $\eta_p^2 = .24$, such that people who had a short duration since baseline produced more novel words at baseline, while in those with a longer duration since baseline, more novel words were produced at follow up. There was no significant main effect of gender, $F(1, 32) = 0.54$, $p = .47$, $\eta_p^2 = .017$, no significant time*age interaction, $F(1, 32) = 0.06$, $p = .81$, $\eta_p^2 = .002$, and no significant time*gender interaction, $F(1, 32) = 0.07$, $p = .80$, $\eta_p^2 = .002$. Figure 6.33 shows that 7 people recalled one novel word at baseline, while at follow up 6 people recalled one novel word, and two people recalled 2 novel words; this was not significantly different.
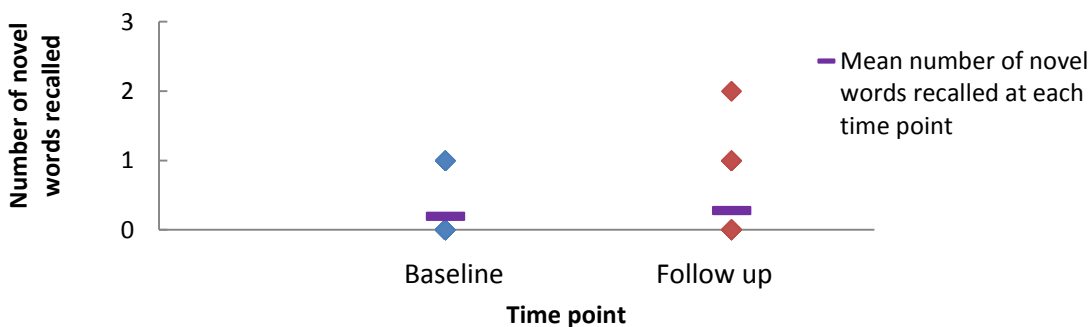
Figure 6.33 Study 2. Number of novel words produced at immediate free recall on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.1.3   Number of perseverations produced at immediate recall

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 32) = 0.52$, $p = .48$, $\eta_p^2 = .016$, and time since baseline was not a significant covariate, $F(1, 32) = 0.13$, $p = .72$, $\eta_p^2 = .004$. There was a significant main effect of gender, $F(1, 32) = 4.39$, $p = .044$, $\eta_p^2 = .121$, such that females made more repetitions of correctly recalled words than males. There was no significant main effect of time $F(1, 32) = 0.69$, $p = .41$, $\eta_p^2 = .021$, no time*time since baseline interaction, $F(1, 32) = 0.46$, $p = .50$, $\eta_p^2 = .014$, no significant time*age interaction, $F(1, 32) = 0.23$, $p = .64$, $\eta_p^2 = .007$, and no significant time*gender interaction, $F(1, 32) = 0.17$, $p = .68$, $\eta_p^2 = .005$. Figure 6.34 shows that at baseline,12 people repeated one word and 3 people repeated 2 words while at follow up, 10 people recalled one word, two people recalled 2 words, and 1 person recalled three words; this was not significantly different
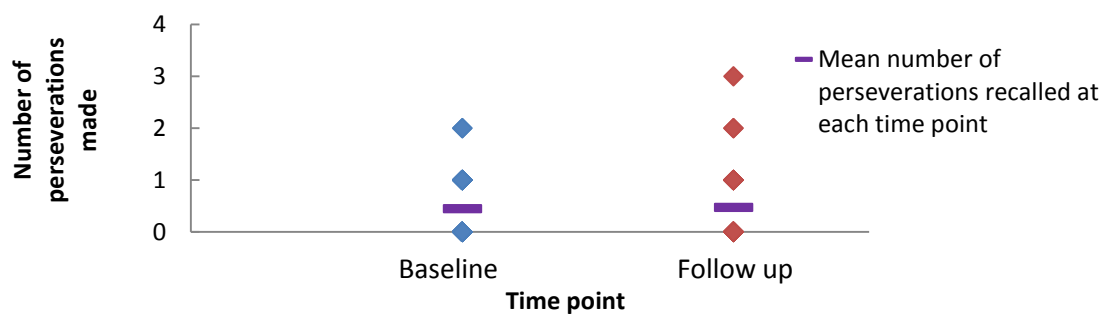
Figure 6.34 Study 2. Number of perseverations at immediate free recall on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.2   Immediate recognition

6.3.4.3.2.1   Total number of correctly recognised target words (recognition task)

Data were reflected and inversely transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 32) = 0.02$, $p = .88$, $\eta_p^2 = .001$, and time since baseline was not a significant covariate, $F(1, 32) = 0.55$, p = .46, $\eta_p^2 = .017$. There was no significant main effect of time $F(1, 32) = 0.08$, p = .28, $\eta_p^2 = .037$, or gender, $F(1, 32) = 0.31$, p = .58, $\eta_p^2 = .009$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.10$, p = .75, $\eta_p^2 = .003$, no significant time*age interaction, $F(1, 32) = 1.78$, p = .19, $\eta_p^2 = .053$, and no significant time*gender interaction, $F(1, 32) = 0.009$, p = .92, $\eta_p^2 < .001$. Figure 6.35 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recognised target words at immediate recognition.
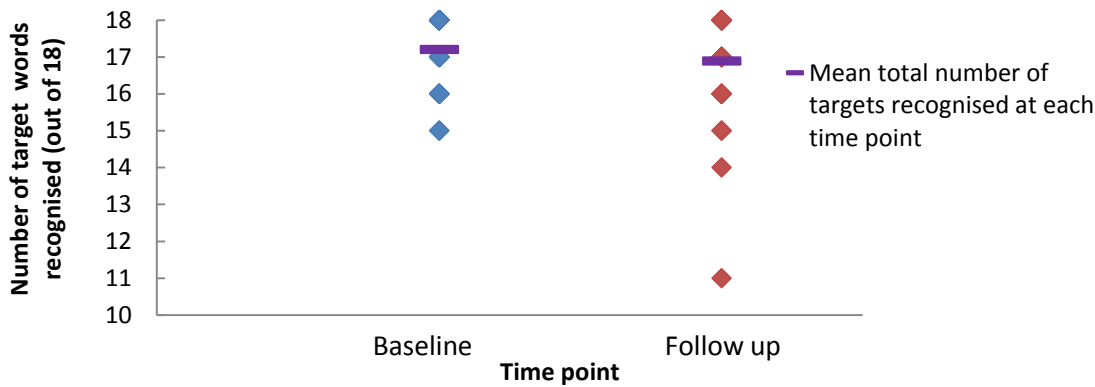
Figure 6.35 Study 2. Total number of correctly recognised target words at immediate recognition on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.2.2 Total number of false positives (recognition task)

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 32) = 1.19$, $p = .28$, $\eta_p^2 = .036$, and time since baseline was not a significant covariate, $F(1, 32) = 0.57$, $p = .46$, $\eta_p^2 = .018$. There was no significant main effect of time $F(1, 32) = 0.17$, $p = .69$, $\eta_p^2 = .005$, or gender, $F(1, 32) = 0.83$, $p = .37$, $\eta_p^2 = .025$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.18$, $p = .67$, $\eta_p^2 = .006$, no significant time*age interaction, $F(1, 32) = 0.03$, $p = .86$, $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 0.78$, $p = .39$, $\eta_p^2 = .024$. Figure 6.36 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recognised target words at immediate recognition.
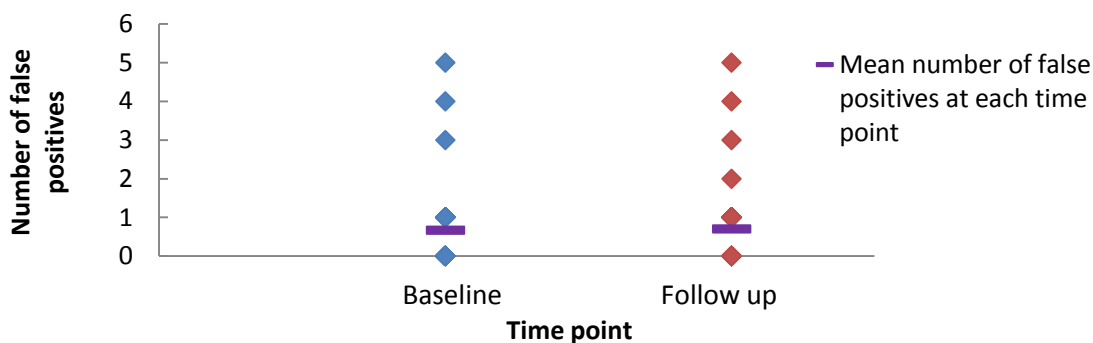
Figure 6.36 Study 2. Total number of false positives produced at immediate recognition on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.3 Delayed free recall

6.3.4.3.3.1 Total number of correctly recalled words at delayed recall

Age was not a significant covariate, $F(1, 32) = 0.29$, $p = .60$, $\eta_p^2 = .009$ and time since baseline was not a significant covariate, $F(1, 32) = 0.68$, $p = .42$, $\eta_p^2 = .021$. There was no significant main effect of time $F(1, 32) = 0.41$, $p = .53$, $\eta_p^2 = .013$, or gender, $F(1, 32) = 2.34$, $p = .14$, $\eta_p^2 = .068$. There was no significant time*time since baseline interaction, $F(1, 32) = 2.66$, $p = .11$,

η_p^2 = .077, no significant time*age interaction, F(1, 32) = 0.95, p = .34, η_p^2 = .029, and no significant time*gender interaction, F(1, 32) = 0.003, p = .95, η_p^2 < .001. Figure 6.37 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recalled words at delayed free recall.
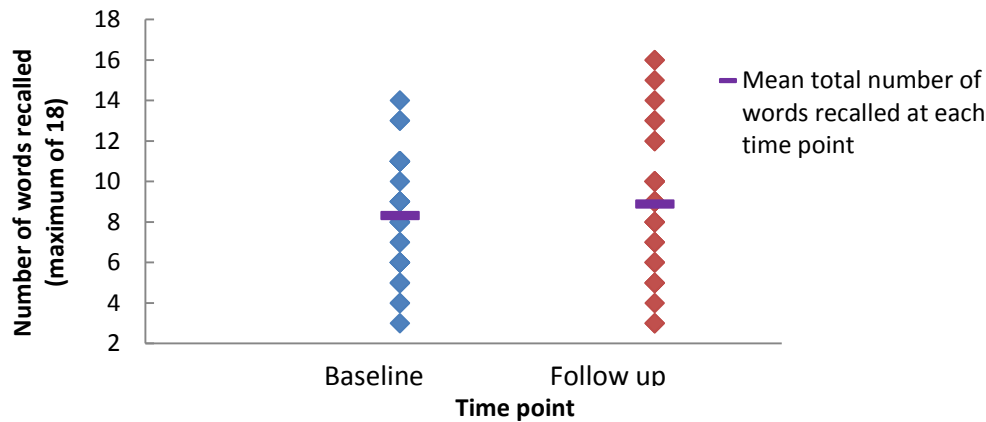
Figure 6.37 Study 2. Total number of correctly recalled words at delayed recall on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.3.2 Number of novel words produced at delayed recall

Data were substantially positively skewed and therefore a logarithm transformation was applied. Age was not a significant covariate, $F(1, 32) = 1.01$, $p = .32$, $\eta_p^2 = .031$, and time since baseline was not a significant covariate, $F(1, 32) = 0.61$, $p = .44$, $\eta_p^2 = .019$. There was no main effect of gender, $F(1, 32) = 0.17$, $p = .69$, $\eta_p^2 = .005$, but there was a significant main effect of time $F(1, 32) = 56.210$, $p < .001$, $\eta_p^2 = .637$, such that more novel words were produced at baseline ($p < .001$). There was no time*time since baseline interaction, $F(1, 32) = 0.01$, $p = .91$, $\eta_p^2 < .001$, no significant time*age interaction, $F(1, 32) = 1.19$, $p = .28$, $\eta_p^2 = .036$ and no significant time*gender interaction, $F(1, 32) = 0.17$, $p = .68$, $\eta_p^2 = .005$. Figure 6.38 shows that at baseline, 10 people recalled one novel word, two people recalled two novel words, and 2 people recalled 3 novel words, while at follow up 5 people recalled one novel word and four recalled 2 novel words; this was significantly different.
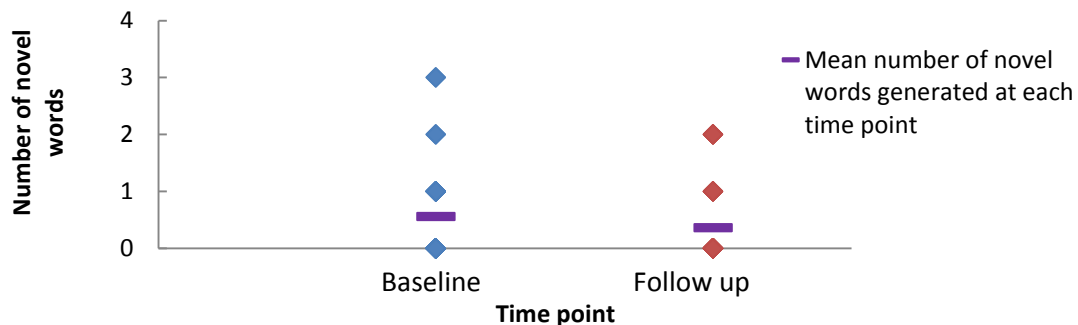
Figure 6.38 Study 2. Number of novel words produced at delayed free recall on the VRM test, at baseline and follow up, in people with CFRD

6.3.4.3.3.3 Number of perseverations words produced at delayed recall

Data were substantially positively skewed and therefore a logarithm transformation was applied. Age was not a significant covariate, $F(1, 32) = 0.06$, $p = .81$, $\eta_p^2 = .002$, and time since baseline was not a significant covariate, $F(1, 32) = 2.27$, $p = .14$, $\eta_p^2 = .066$. There was no significant main effect of time $F(1, 32) = 0.40$, $p = .53$, $\eta_p^2 = .012$, or gender, $F(1, 32) = 0.66$, $p = .42$, $\eta_p^2 = .020$. There was a significant time*time since baseline interaction, $F(1, 32) = 4.28$, $p = .047$, $\eta_p^2 = .118$, such that people made more repetitions at follow up with a shorter duration since baseline, while more repetitions were made at baseline with a longer duration since baseline. There was no significant time*age interaction, $F(1, 32) = 1.17$, $p = .29$, $\eta_p^2 = .035$, and no significant time*gender interaction, $F(1, 32) = 0.55$, $p = .46$, $\eta_p^2 = .017$. Figure 6.39 shows that at baseline, 6 people repeated one word, three people repeated 2 words, and one person repeated 3 words, while at follow up, 8 people recalled one word, 1 person recalled two words, and two people recalled three words; this was not significantly different.
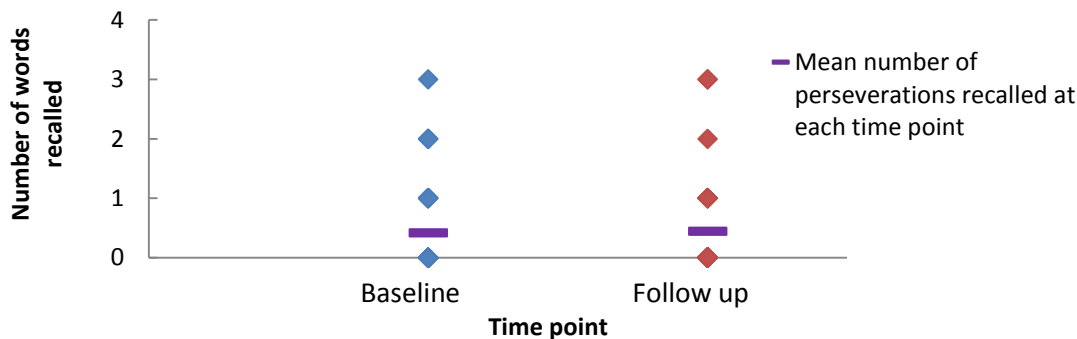
Figure 6.39 Study 2. Number of perseverations at delayed free recall on the VRM test at baseline and follow up in people with CFRD

6.3.4.3.4 Delayed recognition

6.3.4.3.4.1 Total number of correctly recognised target words (recognition task)

Data were severely negatively skewed and therefore reflected and an inverse transformation was applied. Age was not a significant covariate, $F(1, 32) = 0.90$, $p = .35$, $\eta_p^2 = .027$, but time since baseline was a significant covariate, $F(1, 32) = 5.00$, $p = .032$, $\eta_p^2 = .135$. A longer duration was a predictor for fewer correctly recognised target words. There was no significant main effect of time $F(1, 32) = 0.04$, $p = .85$, $\eta_p^2 = .001$, or gender, $F(1, 32) = 0.30$, $p = .59$, $\eta_p^2 = .009$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.26$, $p = .61$, $\eta_p^2 = .008$, no significant time*age interaction, $F(1, 32) = 0.02$, $p = .89$, $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 0.10$, $p = .30$, $\eta_p^2 = .034$. Figure 6.40 shows that there was no difference in the number of correctly recognised target words at baseline and follow up.
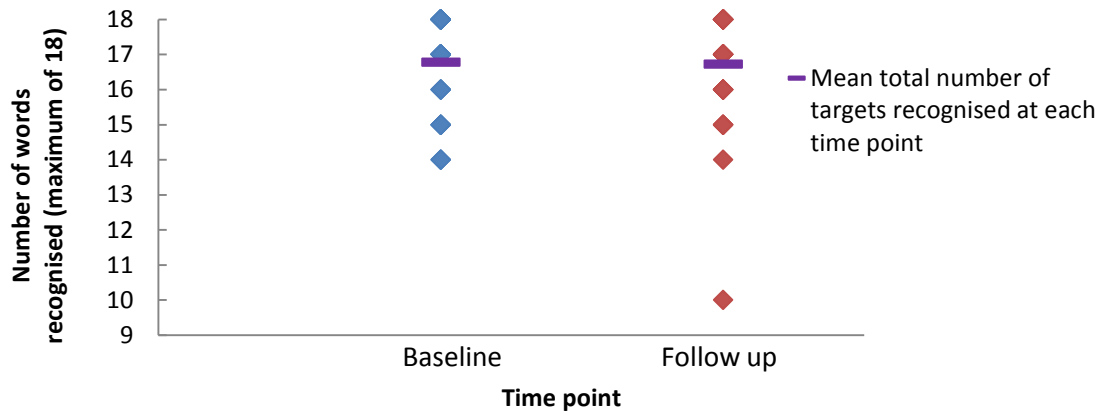
Figure 6.40 Study 2. Total number of correctly recognised target words at delayed recognition on the VRM test, at baseline and follow up, in people with CFRD

6.3.4.3.4.2   Total number of false positives (recognition task)

Data were substantially positively skewed and therefore a logarithm transformation was applied. Age was not a significant covariate, $F(1, 32) = 0.15$, $p = .70$, $\eta_p^2 = .005$, and time since baseline was not a significant covariate, $F(1, 32) = 0.74$, $p = .40$, $\eta_p^2 = .023$. There was no significant main effect of time $F(1, 32) = 0.05$, $p = .82$, $\eta_p^2 = .002$, or gender, $F(1, 32) = 0.42$, $p = .52$, $\eta_p^2 = .013$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.18$, $p = .68$, $\eta_p^2 = .005$, no significant time*age interaction, $F(1, 32) = 0.008$, $p = .93$, $\eta_p^2 < .001$, and no significant time*gender interaction, $F(1, 32) = 0.61$, $p = .44$, $\eta_p^2 = .019$. Figure 6.41 shows that at baseline, seven people produced 1 false positive, one person produced 2, two people produced 3, and one person produced 4, while at follow up, six people produced one false positive, two people produced 2, one person produced three, one person produced 4 and one person produced 5; this was not significantly different.
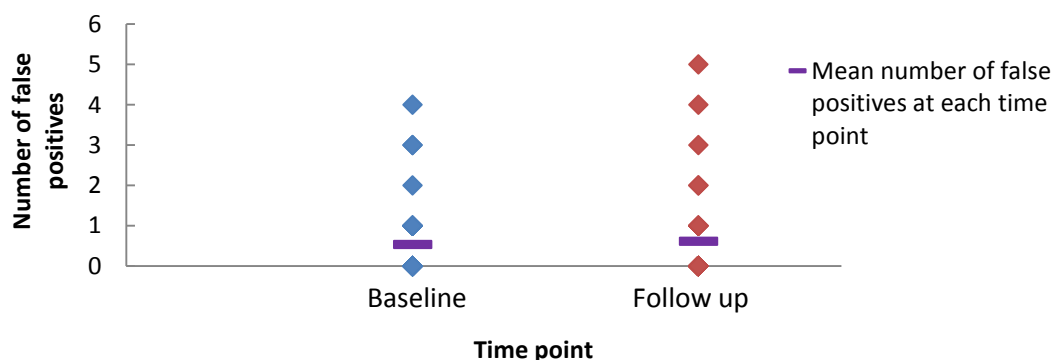
Figure 6.41 Study 2. Total number of false positives produced at delayed recognition on the VRM test, at baseline and follow up, in people with CFRD

6.3.4.4 **Pattern Recognition Memory (PRM)**

The outcome measures for immediate and delayed are the number of correctly recognised patterns and the reaction time to recognise the patterns (see section 5.2.3.3.4; Table 5.4 for a definition of each outcome variable).

6.3.4.4.1 Immediate pattern recognition

6.3.4.4.1.1 Number of correctly recognised patterns

Data were reflected and inverse transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 32) = 0.21$, $p = .65$, $\eta_p^2 = .006$, and time since baseline was not a significant covariate, $F(1, 32) = 0.77$, $p = .39$, $\eta_p^2 = .024$. There was no significant main effect of time $F(1, 32) = 0.02$, $p = .90$, $\eta_p^2 = .001$, or gender, $F(1, 32) = 0.13$, $p = .72$, $\eta_p^2 = .004$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.12$, $p = .73$, $\eta_p^2 = .004$, no significant time*age interaction, $F(1, 32) = 0.25$, $p = .62$, $\eta_p^2 = .008$, and no significant time*gender interaction, $F(1, 32) = 0.51$, $p = .48$, $\eta_p^2 = .016$. Figure 6.42 shows that there was no difference in the number of correctly recognised patterns at immediate recognition at baseline and follow up.
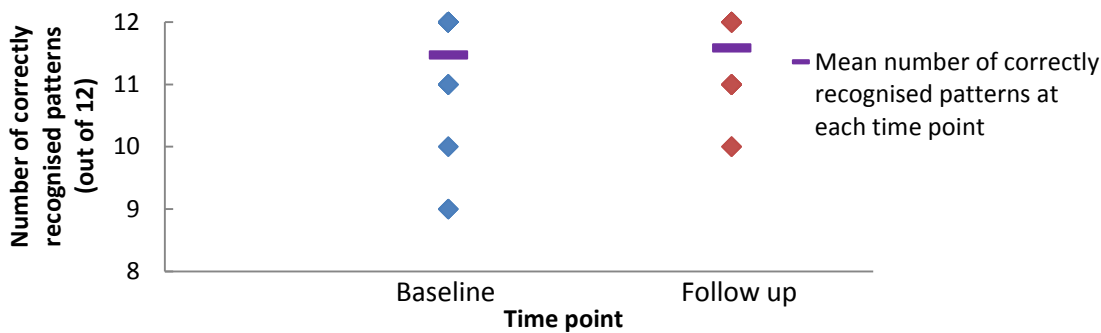
Figure 6.42 Study 2. Number of correctly recognised patterns at immediate recognition on the PRM test, at baseline and follow up in people with CFRD

6.3.4.4.1.2 Reaction time for correctly recognised patterns

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.16$, $p = .69$, $\eta_p^2 = .005$, and time since baseline was not a significant covariate, $F(1, 32) = 2.41$, $p = .13$, $\eta_p^2 = .070$. There was a trend for a significant main effect of gender, $F(1, 32) = 3.29$, $p = .079$, $\eta_p^2 = .093$, such that females tended to be faster at responding than males ($p = .079$). There was no significant main effect of time $F(1, 32) = 0.60$, $p = .44$, $\eta_p^2 = .018$, and no significant time*time since baseline interaction, $F(1, 32) = 0.64$, p $= .43$, $\eta_p^2 = .020$, no significant time*age interaction, $F(1, 32) = 0.003$, $p = .95$, $\eta_p^2 < .001$, and no significant time*gender interaction, $F(1, 32) = 1.08$, $p = .31$, $\eta_p^2 = .033$. Figure 6.43 shows that there was no difference in the reaction to correctly recognised patterns at immediate recognition at baseline and follow up.
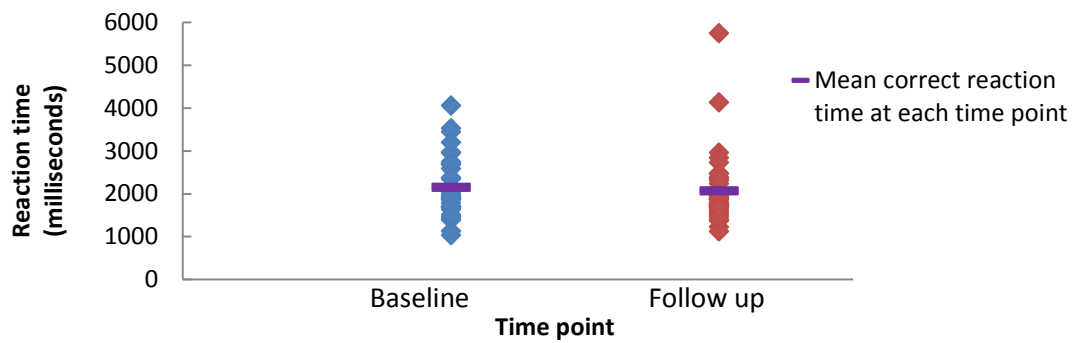
Figure 6.43 Study 2. Reaction time for correctly recognised patterns at immediate recognition on the PRM test, at baseline and follow up in people with CFRD

6.3.4.4.2   Delayed pattern recognition

6.3.4.4.2.1   Number of correctly recognised patterns

Data were severely negatively skewed and therefore were reflected square and an inverse transformation was applied. Age was not a significant covariate, $F(1, 32) = 0.89$, $p = .35$, $\eta_p^2 = .027$, and time since baseline was not a significant covariate, $F(1, 32) = 0.04$, $p = .85$, $\eta_p^2 = .001$. There was no significant main effect of time $F(1, 32) = 0.007$, $p = .94$, $\eta_p^2 < .001$, or gender, $F(1, 32) = 1.33$, $p = .26$, $\eta_p^2 = .040$.   There was no significant time*time since baseline interaction, $F(1, 32) = 0.13$, p $= .72$, $\eta_p^2 = .004$, no significant time*age interaction, $F(1, 32) = 1.22$, $p = .28$, $\eta_p^2 = .037$, and no significant time*gender interaction, $F(1, 32) = 1.10$, $p = .30$, $\eta_p^2 = .033$. Figure 6.44 shows that there was no difference in the number of correctly recognised patterns at delayed recognition at baseline and follow up.
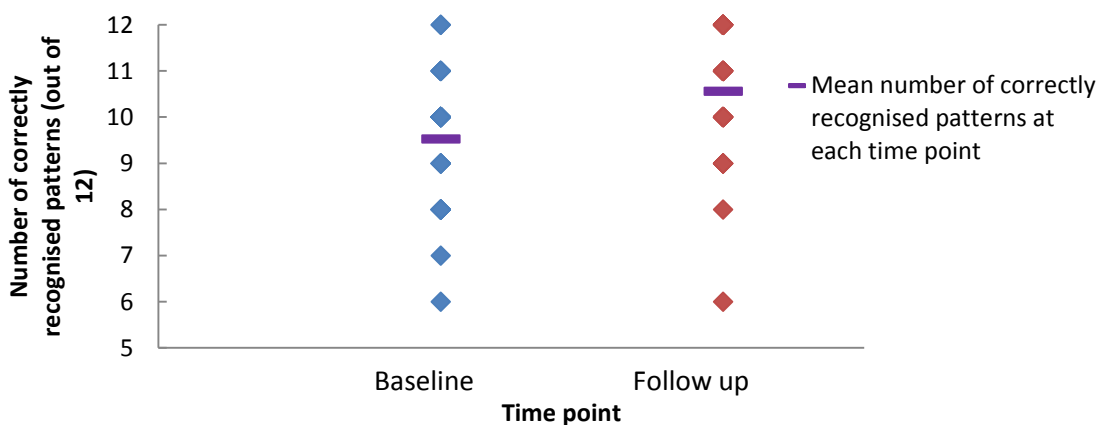
Figure 6.44 Study 2. Number of correctly recognised patterns at delayed recognition on the PRM test, at baseline and follow up, in people with CFRD

6.3.4.4.2.2   Reaction time for correctly recognised patterns

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.05$, $p = .83$, $\eta_p^2 = .002$ and time since baseline was not a significant covariate, $F(1, 32) = .000$, $p = .99$, $\eta_p^2 < .001$. There was no significant main effect

of time $F(1, 32) = 1.46$, $p = .24$, $\eta_p^2 = .044$, but there was a significant main effect of gender, $F(1, 32) = 5.15$, $p = .03$, $\eta_p^2 = .139$, such that females were faster at responding than males ($p = .03$). There was no significant time*time since baseline interaction, $F(1, 32) = 0.001$, $p = .98$, $\eta_p^2 < .001$ and no significant time*age interaction, $F(1, 32) = 1.07$, $p = .31$, $\eta_p^2 = .032$, but a trend for a significant time*gender interaction, $F(1, 32) = 3.63$, $p = .066$, $\eta_p^2 = .102$, such that reaction times were faster at follow up, and females responded faster than males. Figure 6.45 shows that there was no difference in reaction time in correctly recognising patterns at delayed recognition at baseline and follow up.
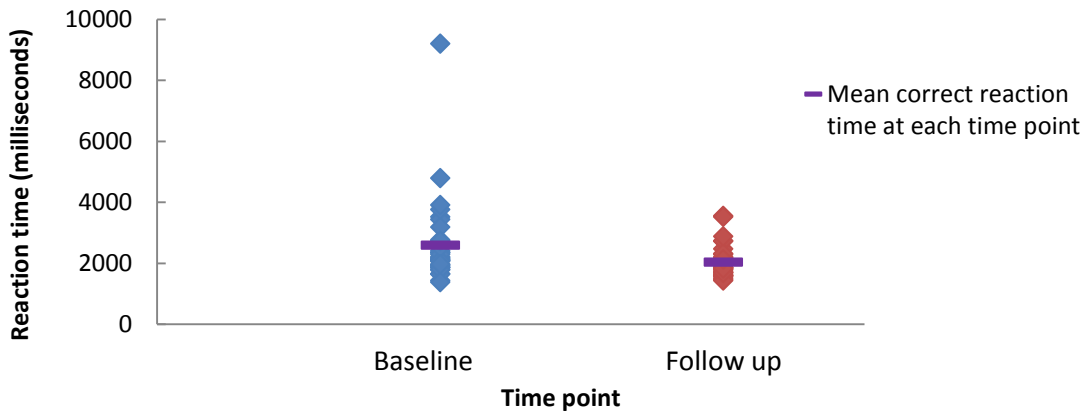
Figure 6.45 Study 2. Reaction time for correctly recognised patterns at delayed recognition on the PRM test, at baseline and follow up in people with CFRD

6.3.4.5 Rapid Visual Processing (RVP)

There are a total of 36 target sequences to detect (see section 5.2.5.3.5) on the four minute task (9 per minute). The outcome measures for the RVP tests are: total hits, total hits at each minute, total false alarms, total false alarms at each minute, reaction time for hits, reaction time for hits at each minute, A' prime, and B' prime (see section 5.2.3.3.5, and Table 5.4 for a definition of each outcome variable).

6.3.4.5.1 Total hits (correct detections of target sequences)

Age was not a significant covariate, $F(1, 32) = 0.43$, $p = .52$, $\eta_p^2 = .013$ but time since baseline was a significant covariate, $F(1, 32) = 5.10$, $p = .031$, $\eta_p^2 = .137$. A longer duration since baseline was a predictor for fewer correctly detected hits at follow up. There was no significant main effect of time $F(1, 32) = 0.73$, $p = .40$, $\eta_p^2 = .022$, or gender, $F(1, 32) = 1.62$, $p = .21$, $\eta_p^2 = .048$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.14$, $p = .72$, $\eta_p^2 = .004$, no significant time*age interaction, $F(1, 32) = 1.45$, $p = .24$, $\eta_p^2 = .043$, and no significant time*gender interaction, $F(1, 32) = 0.68$, $p = .42$, $\eta_p^2 = .021$. Figure 6.46 shows that there was no difference in the number of target sequences correctly detected at baseline and follow up.
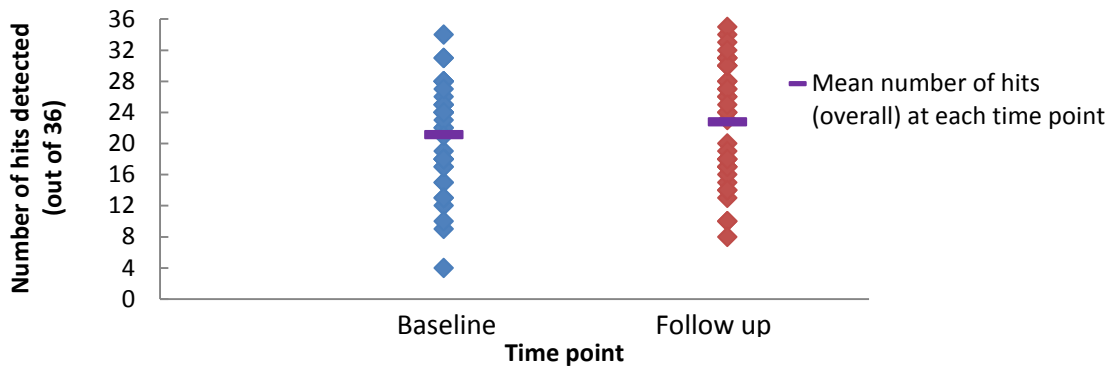
Figure 6.46 Study 2. Total hits (correct detections) on the RVP test at baseline and follow up in people with CFRD

6.3.4.5.2 Total false alarms

Age was a significant covariate, $F(1, 32) = 4.61$, $p = .04$, $\eta_p^2 = .126$. Younger participants produced more false alarms than older participants. Time since baseline was not a significant covariate, $F(1, 32) = 0.009$, $p = .93$, $\eta_p^2 < .001$. There was no significant main effect of time $F(1, 32) = 0.03$, $p = .87$, $\eta_p^2 = .001$, or gender, $F(1, 32) = .000$, $p = .99$, $\eta_p^2 < .001$. There was no significant time*time since baseline interaction, $F(1, 32) = 2.31$, $p = .14$, $\eta_p^2 = .067$, no significant time*age interaction, $F(1, 32) = 2.00$, $p = .17$, $\eta_p^2 = .059$, and no significant time*gender interaction, $F(1, 32) = 2.76$, $p = .11$, $\eta_p^2 = .079$. Figure 6.47 shows that there was no difference in the number of false alarms produced at baseline and follow up.
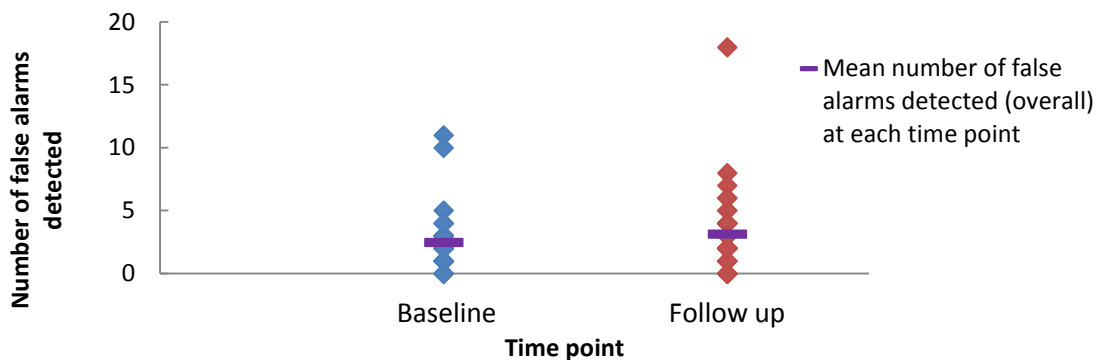
Figure 6.47 Study 2. Total number of false alarms produced on the RVP test, at baseline and follow up, in people with CFRD

6.3.4.5.3 Mean reaction time for hits

Age was not a significant covariate, $F(1, 32) = 1.27$, $p = .27$, $\eta_p^2 = .038$. The covariate for time since baseline showed a trend, $F(1, 32) = 3.60$, $p = .067$, $\eta_p^2 = .101$. Reaction times tended to be slower with a longer duration since baseline. There was no significant main effect of time $F(1, 32) = 0.29$, $p = .60$, $\eta_p^2 = .009$, or gender, $F(1, 32) = .40$, $p = .53$, $\eta_p^2 = .012$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.28$, $p = .60$, $\eta_p^2 = .009$, no significant time*age interaction, $F(1, 32) = 0.07$, $p = .80$, $\eta_p^2 = .002$, and no significant time*gender

interaction, $F(1, 32) = 0.92$, $p = .35$, $\eta_p^2 = .028$. Figure 6.48 shows that there was no difference in the number of false alarms produced at baseline and follow up.
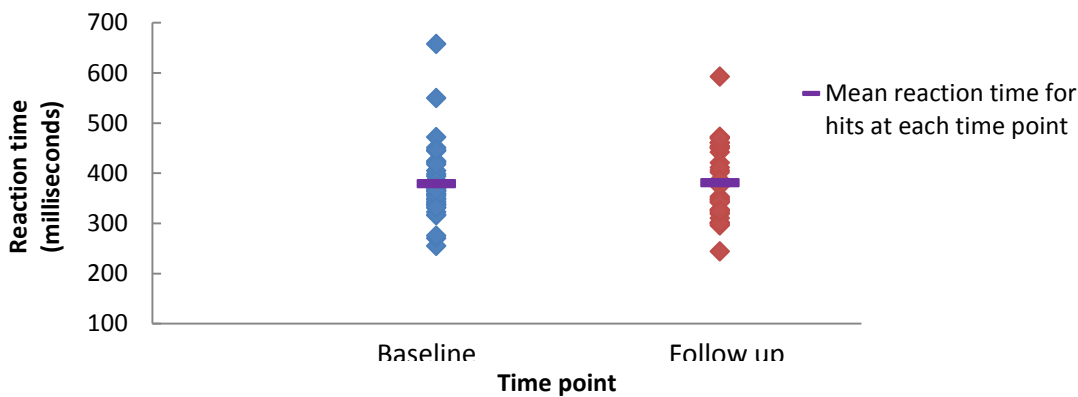
Figure 6.48 Study 2. Mean reaction time for hits on the RVP test, at baseline and follow up, in people with CFRD

6.3.4.5.4 A' Prime

Age was not a significant covariate, $F(1, 32) = 0.61$, $p = .44$, $\eta_p^2 = .019$. Time since baseline was a significant covariate, $F(1, 32) = 5.21$ $p = .029$, $\eta_p^2 = .140$. Sensitivity to detecting targets was lower with a longer duration since baseline. There was no significant main effect of time $F(1, 32) = 0.80$, $p = .38$, $\eta_p^2 = .025$, or gender, $F(1, 32) = 1.62$, $p = .21$, $\eta_p^2 = .048$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.12$, $p = .91$, $\eta_p^2 < .001$, no significant time*age interaction, $F(1, 32) = 2.18$, $p = .15$, $\eta_p^2 = .064$, and no significant time*gender interaction, $F(1, 32) = 1.55$, $p = .22$, $\eta_p^2 = .046$. Figure 6.49 shows that there was no difference in the sensitivity to responding to targets at baseline and follow up.
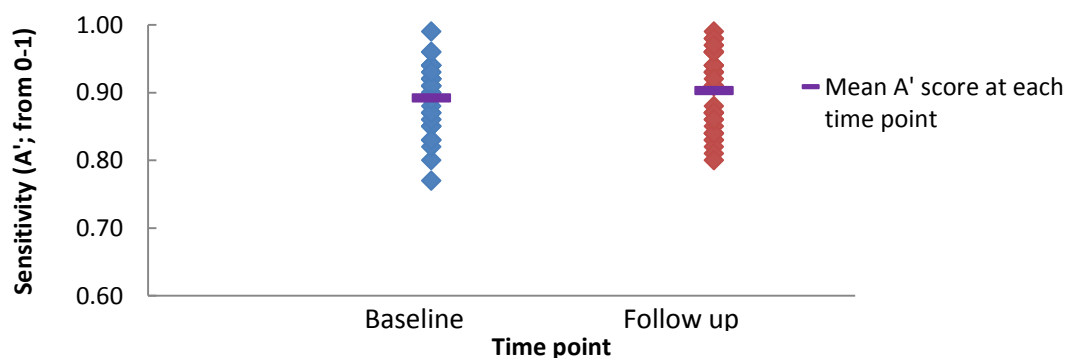
Figure 6.49 Study 2. A' prime (Sensitivity to the target, regardless of response tendency) on the RVP test, at baseline and follow up in people with CFRD

6.3.4.5.5 B' Prime

Data were reflected and an inverse transformation applied due to severe negative skewness. Age was a significant covariate, $F(1, 32) = 6.30$, $p = .017$, $\eta_p^2 = .164$. Older participants were

more biased in their responding than younger participants. Time since baseline was not a significant covariate, $F(1, 32) = 0.53$, $p = .47$, $\eta_p^2 = .016$. There was no significant main effect of time $F(1, 32) = 0.80$, $p = .38$, $\eta_p^2 = .025$, or gender, $F(1, 32) = 0.006$, $p = .94$, $\eta_p^2 < .001$. There was a significant time*time since baseline interaction, $F(1, 32) = 5.57$, $p = .025$, $\eta_p^2 = .148$, a trend for a significant time*age interaction, $F(1, 32) = 2.18$, $p = .15$, $\eta_p^2 = .064$, but no significant time*gender interaction, $F(1, 32) = 1.55$, $p = .22$, $\eta_p^2 = .046$. Participants who had a shorter duration performed worse at baseline compared to follow up, while participants who had a longer duration performed better at baseline than follow up. Furthermore, younger participants performed better at baseline, while older participants performed better at follow up. Figure 6.50 shows that although there was no difference in bias in responding at baseline and follow up, one participant at follow made a considerable number of false alarms indicating a guessing response.
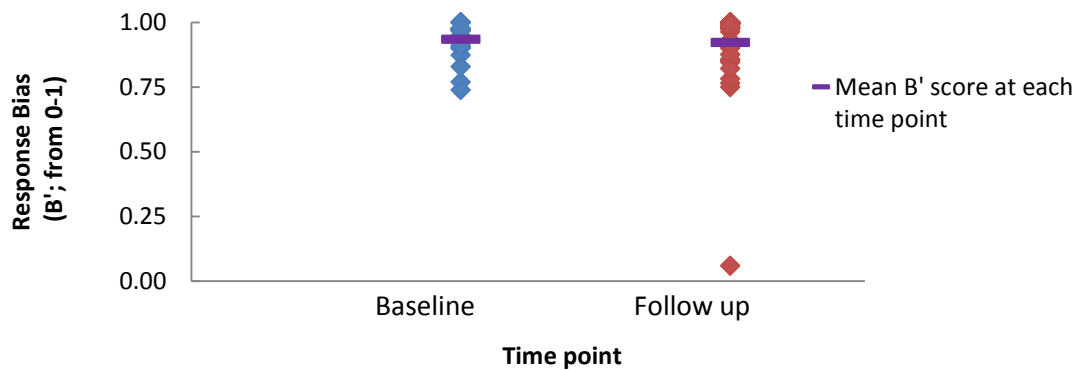
Figure 6.50 Study 2. B' prime (tendency to respond regardless of whether the target sequence is present) on the RVP test, at baseline and follow up in people with CFRD

6.3.4.6 Spatial span (SSP)

The outcome measures for SSP are span length, number of attempts (overall and per level), reaction time (mean time to first and last response), and errors (total and usage; see section 5.2.3.3.6, and Table 5.4 for a definition of each outcome variable). As the degree of test completion varies as a function of individual performance (i.e. test difficulty increases with each span length (2-9) and the test terminates if a sequence is not successfully recalled at 'n' span length after 3 attempts), span length was included as a covariate in the analyses for all subsequent SSP outcome measures.

6.3.4.6.1 Span length (longest number sequence successfully recalled)

The covariate for age was a trend, $F(1, 32) = 2.98$, $p = .094$, $\eta_p^2 = .085$. Older participants tended to reach a lower span length than younger participants. Time since baseline was not a significant covariate, $F(1, 32) = 0.32$, $p = .58$, $\eta_p^2 = .010$. There was no significant main effect of time $F(1, 32) = 1.94$, $p = .17$, $\eta_p^2 = .057$, or gender, $F(1, 32) = 2.46$, $p = .13$, $\eta_p^2 = .071$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.14$, $p = .71$, $\eta_p^2 = .004$, no significant time*age interaction, $F(1, 32) = 2.58$, $p = .12$, $\eta_p^2 = .075$, and no significant

time*gender interaction, $F(1, 32) = 0.58$, $p = .45$, $\eta_p^2 = .018$. Figure 6.51 shows that there was no difference highest span length achieved at baseline and follow up.
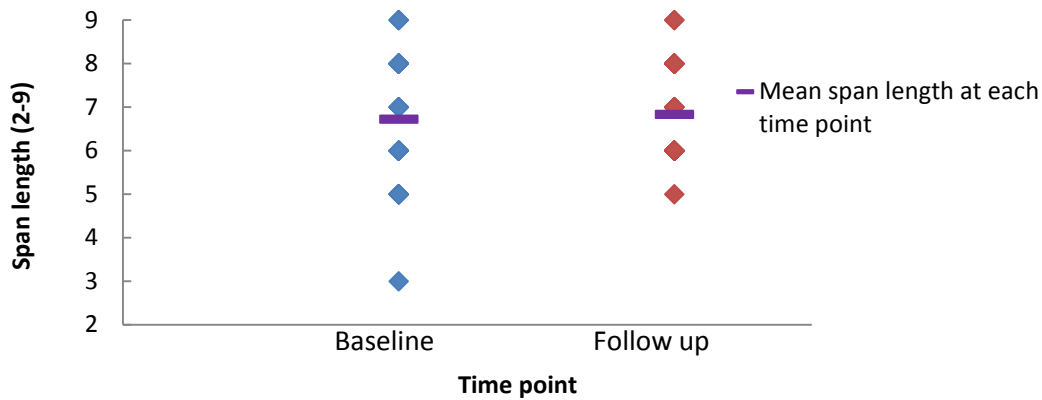
Figure 6.51 Study 2. Span length (longest number sequence successfully recalled; 2-9) on the SSP test, at baseline and follow up in people with CFRD

6.3.4.6.2   Total number of attempts

Age was a significant covariate, $F(1, 31) = 4.52$, $p = .042$, $\eta_p^2 = .127$. Older participants made less attempts than younger participants. Time since baseline was not a significant covariate, $F(1, 31) = 1.08$, $p = .31$, $\eta_p^2 = .034$ but span length was a significant covariate, $F(1, 31) = 5.35$, $p = .028$, $\eta_p^2 = .147$. There was no significant main effect of time $F(1, 31) = 0.79$, $p = .38$, $\eta_p^2 = .025$, or gender, $F(1, 31) = 1.46$, $p = .24$, $\eta_p^2 = .044$. There was no significant time*time since baseline interaction, $F(1, 31) = 1.85$, $p = .18$, $\eta_p^2 = .057$, and no significant time*gender interaction, $F(1, 31) = 0.19$, $p = .67$, $\eta_p^2 = .006$. There was a significant time*age interaction, $F(1, 31) = 8.43$, $p = .007$, $\eta_p^2 = .214$, such that younger participants made less attempts at follow up, while older participants made less attempts at baseline. Figure 6.52 shows that there was no difference highest span length achieved at baseline and follow up.
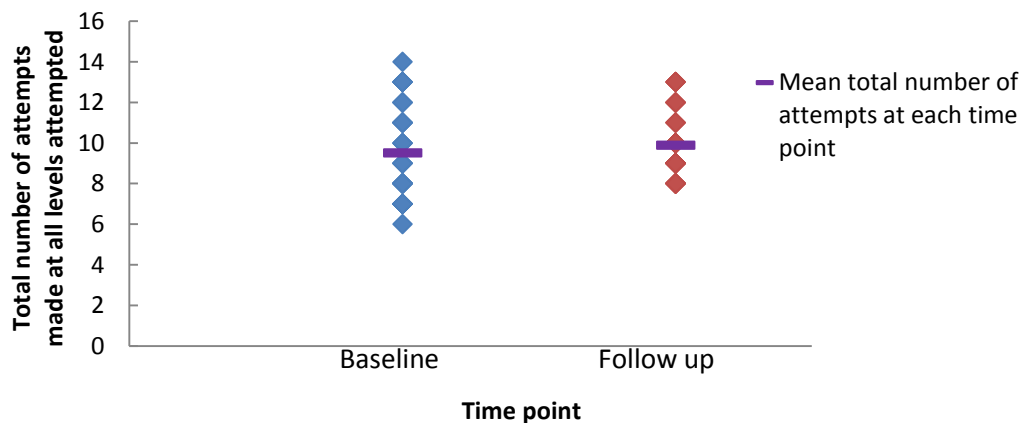
Figure 6.52 Study 2. Total number of attempts made at all levels reached on the SSP test, at baseline and follow up, in people with CFRD

6.3.4.6.3   Reaction time outcome measures on the SSP test

6.3.4.6.3.1   Mean time to first response

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 32) = 0.002$, $p = .97$, $\eta_p^2 < .001$, and time since baseline was not a significant covariate, $F(1, 32) = 1.47$, $p = .29$, $\eta_p^2 = .035$. There was no significant main effect of time $F(1, 32) = 0.53$, $p = .47$, $\eta_p^2 = .016$, or gender, $F(1, 32) = 2.71$, $p = .11$, $\eta_p^2 = .078$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.23$, $p = .64$, $\eta_p^2 = .007$, no significant time*age interaction, $F(1, 32) = 0.76$, $p = .39$, $\eta_p^2 = .023$, and no significant time*gender interaction, $F(1, 32) = 0.19$, $p = .66$, $\eta_p^2 = .006$. Figure 6.53 shows that there was no difference in mean time to first response at baseline and follow up.
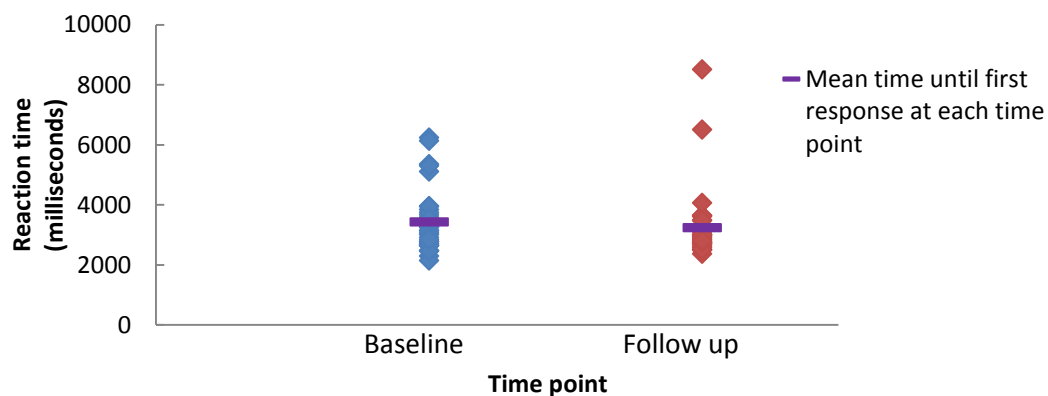
Figure 6.53 Study 2. Mean time to first response (milliseconds) on the SSP test at baseline and follow up, in people with CFRD

6.3.4.6.3.2   Mean time to last response

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 32) = 0.39$, $p = .54$, $\eta_p^2 = .012$, and time since baseline was not a significant covariate, $F(1, 32) = 0.05$, $p = .82$, $\eta_p^2 = .002$. There was no significant main effect of time $F(1, 32) = 0.52$, $p = .48$, $\eta_p^2 = .016$, but there was a significant main effect of gender, $F(1, 32) = 5.99$, $p = .020$, $\eta_p^2 = .158$, such that males were slower to the last response than females. There was no significant time*time since baseline interaction, $F(1, 32) = 0.14$, $p = .71$, $\eta_p^2 = .004$, no significant time*age interaction, $F(1, 32) = 1.24$, $p = .28$, $\eta_p^2 = .037$, and no significant time*gender interaction, $F(1, 32) = 0.04$, $p = .85$, $\eta_p^2 = .001$. Figure 6.54 shows that there was no difference in mean time to last response at baseline and follow up.
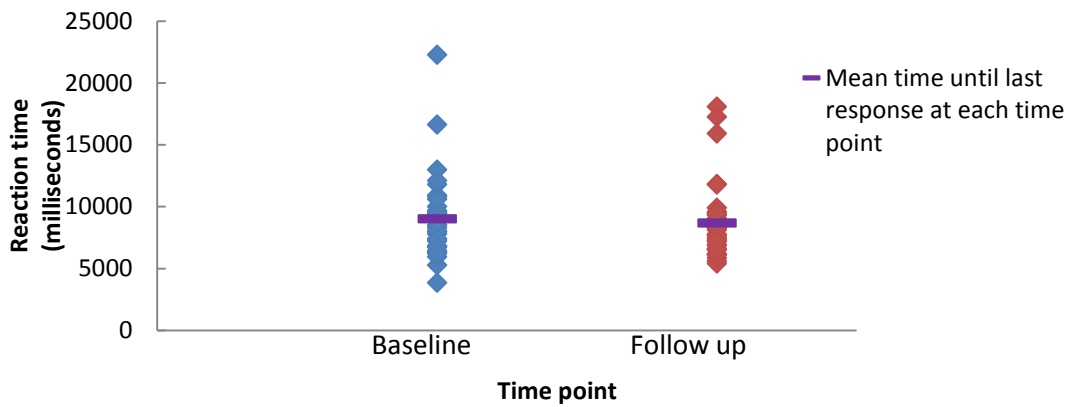
Figure 6.54 Study 2. Mean time to last response (milliseconds) on the SSP test at baseline and follow up, in people with CFRD

6.3.4.6.4   Errors

6.3.4.6.4.1   Total errors

Age was a significant covariate, $F(1, 32) = 4.49$, $p = .042$, $\eta_p^2 = .123$, but time since baseline was not a significant covariate, $F(1, 32) = 2.49$, $p = .12$, $\eta_p^2 = .072$. Younger participants made more errors than older participants. There was no significant main effect of time $F(1, 32) = 0.90$, $p = .35$, $\eta_p^2 = .027$, or gender, $F(1, 32) = 0.26$, $p = .35$, $\eta_p^2 = .027$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.26$, $p = .62$, $\eta_p^2 = .008$, no significant time*age interaction, $F(1, 32) = 0.91$, $p = .35$, $\eta_p^2 = .028$, and no significant time*gender interaction, $F(1, 32) = 0.10$, $p = .76$, $\eta_p^2 = .003$. Figure 6.55 shows that there was no difference in total errors at baseline and follow up.
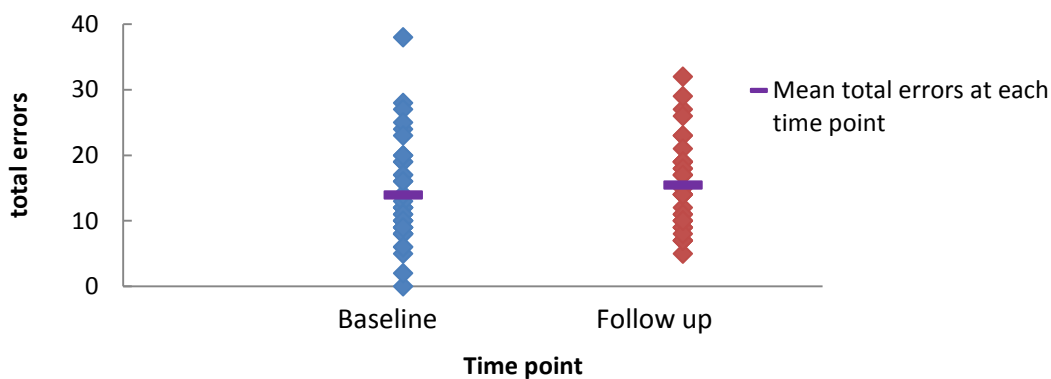
Figure 6.55 Study 2. Total number of errors produced whilst recalling sequences on the SSP test at baseline and follow up, in people with CFRD

6.3.4.6.4.2   Total usage errors

Age was not a significant covariate, $F(1, 32) = 0.03$, $p = .86$, $\eta_p^2 = .001$, and time since baseline was not a significant covariate, $F(1, 32) = 2.08$, $p = .16$, $\eta_p^2 = .061$. There was no significant main effect of time $F(1, 32) = 0.34$, $p = .56$, $\eta_p^2 = .011$, or gender, $F(1, 32) = 0.30$, $p = .59$, η_p^2

= .009. There was no significant time*time since baseline interaction, $F(1, 32) = 0.18$, $p = .67$, $\eta_p^2 = .006$, no significant time*age interaction, $F(1, 32) = 2.81$, $p = .10$, $\eta_p^2 = .081$, and no significant time*gender interaction, $F(1, 32) = 0.06$, $p = .80$, $\eta_p^2 = .002$. Figure 6.56 shows that there was no difference in total usage errors at baseline and follow up.
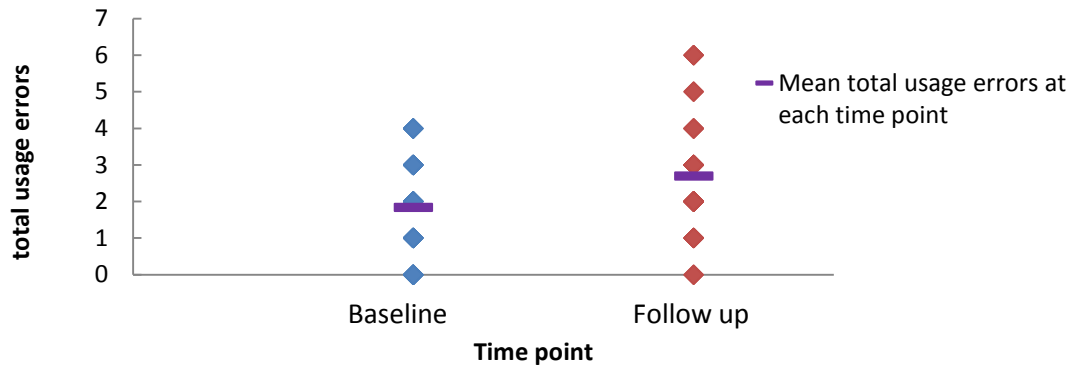
Figure 6.56 Study 2. Total number of usage errors produced on the SSP test, at baseline and follow up, in people with CFRD

6.3.4.7 Attention switching task (AST)

A total of 160 responses were required per test administration. The outcome measures for AST are accuracy (correct trials), reaction time for correct trials, errors (omission and commission), congruency cost, and switch cost (see section 5.2.3.3.7, and Table 5.4 for a definition of each outcome variable). As there were an unequal number of switched and non-switched trials, reaction time for switched and non-switched trials and switch cost should be treated with some degree of caution.

6.3.4.7.1 Total correct trials

6.3.4.7.1.1 Total correct trials (overall accuracy)

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 32) = 0.01$, $p = .92$, $\eta_p^2 < .001$, and time since baseline was not a significant covariate, $F(1, 32) = 0.003$, $p = .96$, $\eta_p^2 < .001$. There was no significant main effect of gender, $F(1, 32) = 0.004$, $p = .95$, $\eta_p^2 < .001$. There was a marginally significant main effect of time $F(1, 32) = 4.07$, $p = .052$, $\eta_p^2 = .113$, but there were no differences on the post hocs. There was no significant time*time since baseline interaction, $F(1, 32) = 0.77$, $p = .39$, $\eta_p^2 = .024$, no significant time*age interaction, $F(1, 32) = 2.36$, $p = .13$, $\eta_p^2 = .069$, and no significant time*gender interaction, $F(1, 32) = 2.753$, $p = .11$, $\eta_p^2 = .079$. Figure 6.57 shows that there was no difference in total correct trials at baseline and follow up.
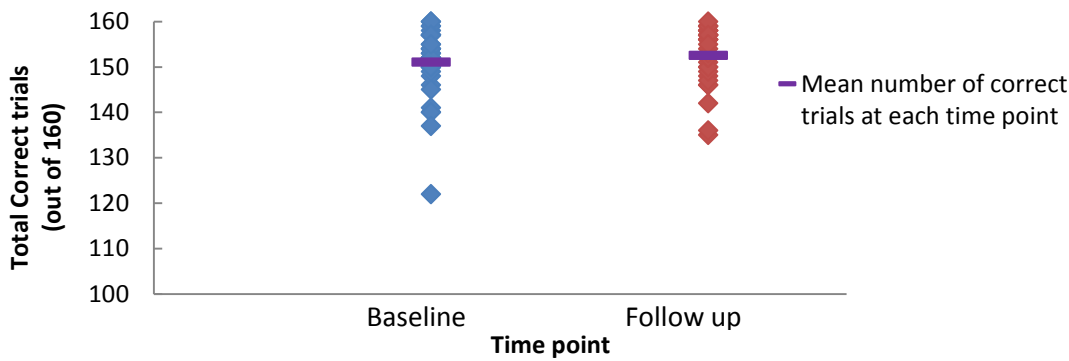
Figure 6.57 Study 2. Total number of correct trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.1.2 Mean reaction time for total correct trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.20$, $p = .65$, $\eta_p^2 = .006$, but the covariate for time since baseline was a trend, $F(1, 32) = 3.13$, $p = .087$, $\eta_p^2 = .089$. Reaction time tended to be slower at follow up compared to baseline. There was no significant main effect of gender, $F(1, 32) = 0.77$, $p = .39$, $\eta_p^2 = .024$, and of time $F(1, 32) = 0.004$, $p = .95$, $\eta_p^2 < .001$. There was no significant time*time since baseline interaction, $F(1, 32) = 1.85$, $p = .18$, $\eta_p^2 = .055$, no significant time*age interaction, $F(1, 32) = 0.06$, $p = .81$ $\eta_p^2 = .002$, and no significant time*gender interaction, $F(1, 32) = 2.11$, $p = .16$, $\eta_p^2 = .062$. Figure 6.58 shows that there was no difference in reaction time for correct trials at baseline and follow up.
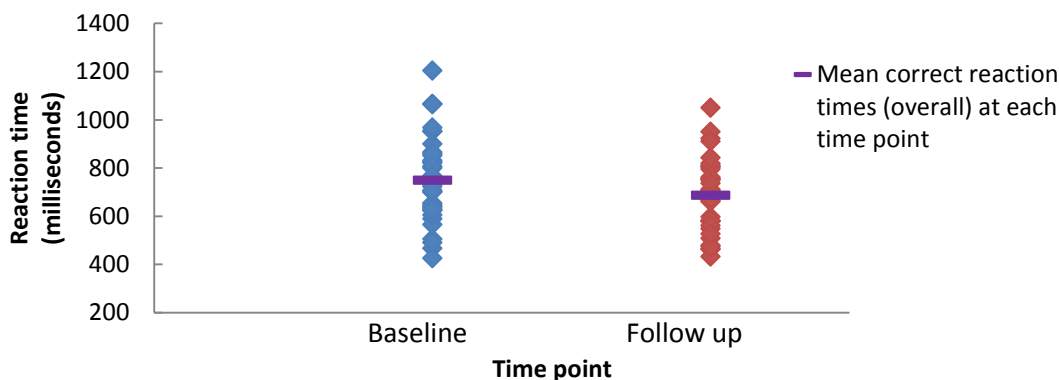
Figure 6.58 Study 2. Reaction time for correct trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.2 Direction trials

6.3.4.7.2.1 Total correct trials with direction as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 32) = 0.09$, $p = .77$, $\eta_p^2 = .003$, and time since baseline was not a significant covariate, $F(1, 32) = 0.07$, $p = .80$, $\eta_p^2 = .002$. There was no significant main effect of gender, $F(1, 32) = 2.116$, $p = .16$, $\eta_p^2 = .062$, or time $F(1, 32) = 2.83$, $p = .10$, $\eta_p^2 = .081$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.98$, $p = .33$, $\eta_p^2 = .030$,

and no significant time*age interaction, $F(1, 32) = 1.07$, $p = .31$, $\eta_p^2 = .032$, but there was a trend for a significant time*gender interaction, $F(1, 32) = 3.83$, $p = .059$, $\eta_p^2 = .107$, such that females correctly responded to more trials than males at both time points, but at follow up, males correctly responded to more than at baseline, while females correctly responded to less than at baseline. Figure 6.59 shows that there was no difference in the total number of correct direction trials at baseline and follow up.
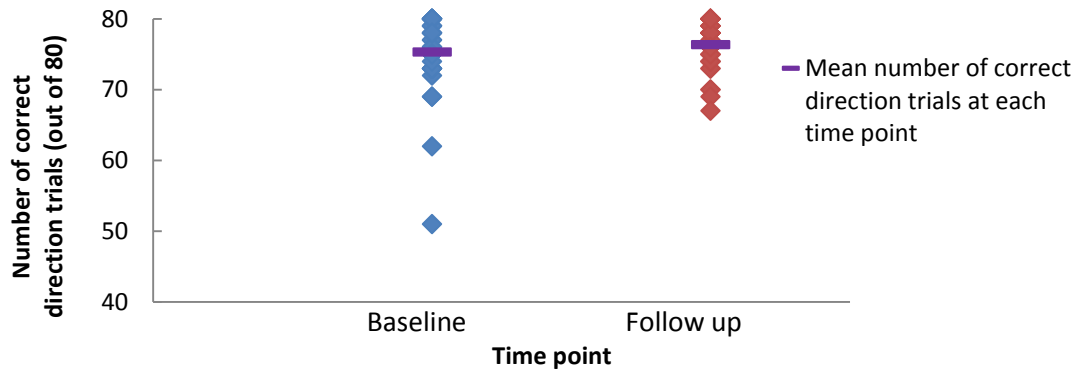
Figure 6.59 Study 2. Number of correct direction trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.2.2   Reaction time for correct trials with direction as the rule

Age was not a significant covariate, $F(1, 32) = 0.37$, $p = .55$, $\eta_p^2 = .012$, and time since baseline was not a significant covariate, $F(1, 32) = 2.70$, $p = .11$, $\eta_p^2 = .078$. There was no significant main effect of gender, $F(1, 32) = 1.76$, $p = .19$, $\eta_p^2 = .052$, and of time $F(1, 32) = 0.32$, $p = .58$, $\eta_p^2 = .010$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.47$, $p = .50$, $\eta_p^2 = .014$, no significant time*age interaction, $F(1, 32) = 0.24$, $p = .63$ $\eta_p^2 = .007$, and a trend for a significant time*gender interaction, $F(1, 32) = 3.10$, $p = .088$, $\eta_p^2 = .088$. Figure 6.60 shows that there was no difference in reaction time for direction trials at baseline and follow up.
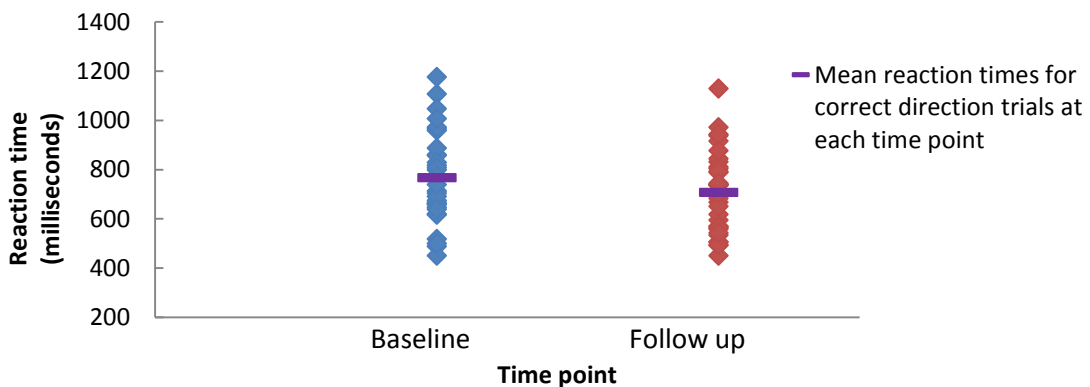
Figure 6.60 Study 2. Reaction time for correct direction trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.3 Side trials

6.3.4.7.3.1 Total correct trials with side as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. Age was not a significant covariate, $F(1, 32) = 0.02$, $p = .88$, $\eta_p^2 = .001$, and time since baseline was not a significant covariate, $F(1, 32) = 0.11$, $p = .74$, $\eta_p^2 = .003$. There was no significant main effect of gender, $F(1, 32) = 2.25$, $p = .14$, $\eta_p^2 = .066$, or time $F(1, 32) = 1.31$, $p = .26$, $\eta_p^2 = .039$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.000$, $p = .99$, $\eta_p^2 < .001$, and no significant time*age interaction, $F(1, 32) = 1.59$, $p = .22$, $\eta_p^2 = .047$, and no significant time*gender interaction, $F(1, 32) = 0.81$, $p = .38$, $\eta_p^2 = .025$. Figure 6.61 shows that there was no difference in total number of correct side trials at baseline and follow up.
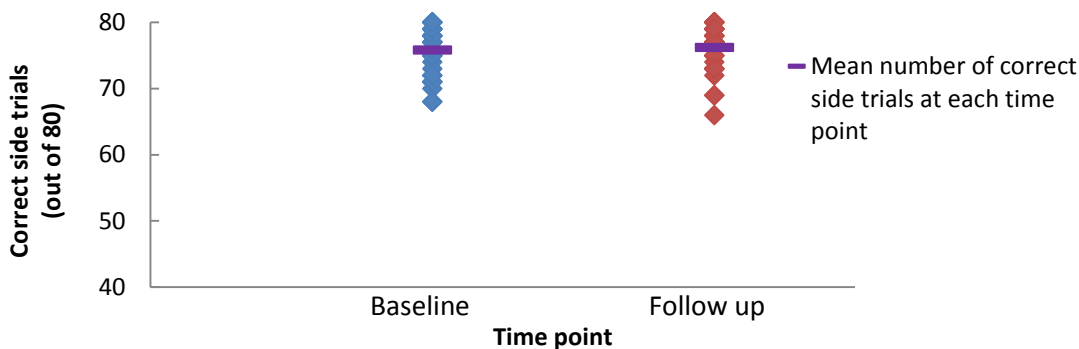
Figure 6.61 Study 2. Number of correct side trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.3.2 Reaction time for correct trials with side as the rule

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.20$, $p = .65$, $\eta_p^2 = .006$, but the covariate for time since baseline was a trend, $F(1, 32) = 3.55$, $p = .069$, $\eta_p^2 = .100$. There was a trend for reaction times to be slower at follow up compared to baseline. There was no significant main effect of gender, $F(1, 32) = 0.18$, $p = .68$, $\eta_p^2 = .006$, and of time $F(1, 32) = 0.36$, $p = .55$, $\eta_p^2 = .011$. There was a trend for a significant time*time since baseline interaction, $F(1, 32) = 3.84$, $p = .059$, $\eta_p^2 = .107$, such that reaction time was slightly slower at follow up in participants with less time since baseline, while reaction times were faster at follow up in participants with a longer duration since baseline. There was no significant time*age interaction, $F(1, 32) = 0.02$, $p = .88$, $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 1.08$, $p = .31$, $\eta_p^2 = .033$. Figure 6.62 shows that there was no difference in reaction times for correct side trials at baseline and follow up.
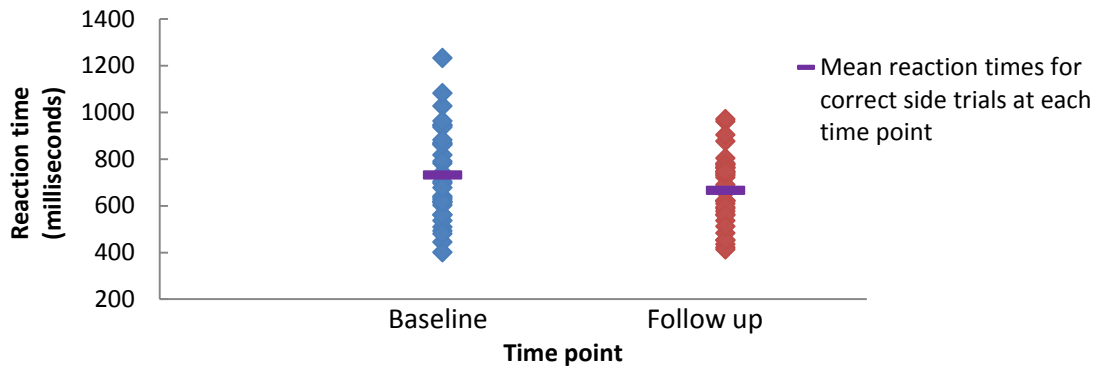
Figure 6.62 Study 2. Reaction time for correct side trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.4 Congruent trials

6.3.4.7.4.1 Total correct congruent trials

Data were reflected and inversely transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 32) = 0.12$, $p = .73$, $\eta_p^2 = .004$, and time since baseline was not a significant covariate, $F(1, 32) = 0.13$, $p = .73$, $\eta_p^2 = .004$. There was no significant main effect of gender, $F(1, 32) = 1.10$, $p = .30$, $\eta_p^2 = .033$, or time $F(1, 32) = 0.63$, $p = .43$, $\eta_p^2 = .019$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.04$, $p = .84$, $\eta_p^2 = .001$, and no significant time*age interaction, $F(1, 32) = 1.09$, $p = .31$, $\eta_p^2 = .033$, but there was a trend for a significant time*gender interaction, $F(1, 32) = 3.63$ $p = .066$, $\eta_p^2 = .102$, such that males correctly responded to more trials at baseline than females, but at follow up, females correctly responded to more trials while males correctly responded to less trials. Figure 6.63 shows that there was no difference in the number of correct congruent trials at baseline and follow up.
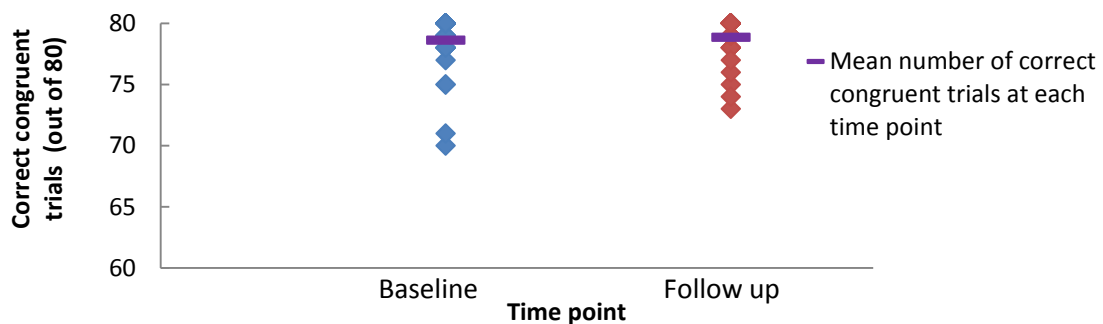
Figure 6.63 Study 2. Number of correct congruent trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.4.2 Reaction time for correct congruent trials

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 0.59$, $p = .45$, $\eta_p^2 = .018$, but the covariate for time since baseline was a significant, $F(1, 32) = 4.30$, $p = .046$, $\eta_p^2 = .119$. Reaction time was slower at follow up compared to baseline. There was no significant main effect of gender, $F(1, 32) = 0.80$, $p = .38$, $\eta_p^2 = .024$, and time $F(1, 32) = 0.04$, $p = .84$, $\eta_p^2 = .001$. There was no significant time*time

since baseline interaction, $F(1, 32) = 2.15$, $p = .15$, $\eta_p^2 = .063$, no significant time*age interaction, $F(1, 32) = 0.02$, $p = .89$, $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 2.53$, $p = .12$, $\eta_p^2 = .073$. Figure 6.64 shows that there was no difference in reaction times for correct congruent trials at baseline and follow up.
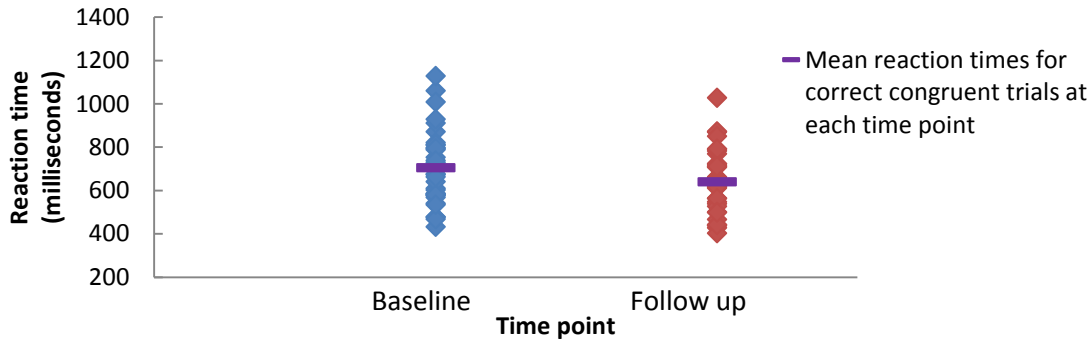
Figure 6.64 Study 2. Reaction time for correct congruent trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.5 Incongruent trials

6.3.4.7.5.1 Total correct incongruent trials

Data were reflected and a logarithm transformation was applied due to substantial negative skewness. Age was not a significant covariate, $F(1, 32) = 0.01$, $p = .92$, $\eta_p^2 < .001$, and time since baseline was not a significant covariate, $F(1, 32) = 0.01$, $p = .92$, $\eta_p^2 < .001$. There was no significant main effect of gender, $F(1, 32) = 0.08$, $p = .78$, $\eta_p^2 = .003$. There was a significant main effect of time $F(1, 32) = 5.76$, $p = .022$, $\eta_p^2 = .152$, but there were no differences on the post hocs. There was no significant time*time since baseline interaction, $F(1, 32) = 2.02$, $p = .17$, $\eta_p^2 = .059$, and no significant time*age interaction, $F(1, 32) = 2.19$, $p = .15$, $\eta_p^2 = .064$. There was a trend for a significant time*gender interaction, $F(1, 32) = 3.20$, $p = .083$, $\eta_p^2 = .091$, such that females correctly responded to less trials at follow up compared to baseline, while performance in males was stable over time. Figure 6.65 shows that there was no difference in the total number of correct incongruent trials at baseline and follow up.
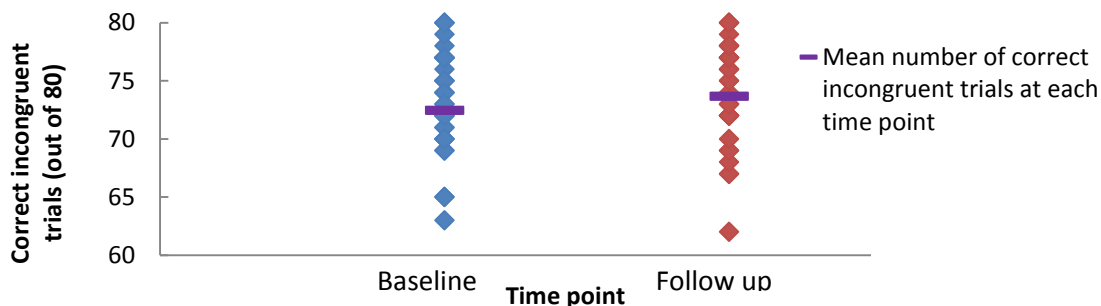
Figure 6.65 Study 2. Number of correct incongruent trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.5.2   Reaction time for correct incongruent trials

Age was not a significant covariate, $F(1, 32) = 0.09$, $p = .77$, $\eta_p^2 = .003$, and time since baseline was not a significant covariate, $F(1, 32) = 2.34$, $p = .14$, $\eta_p^2 = .068$. There was no significant main effect of gender, $F(1, 32) = 0.62$, $p = .44$, $\eta_p^2 = .019$, and time $F(1, 32) = 0.009$, $p = .92$, $\eta_p^2 < .001$. There was no significant time*time since baseline interaction, $F(1, 32) = 1.62$, $p = .21$, $\eta_p^2 = .048$, no significant time*age interaction, $F(1, 32) = 0.20$, $p = .66$ $\eta_p^2 = .006$, and no significant time*gender interaction, $F(1, 32) = 1.38$, $p = 25$, $\eta_p^2 = .041$. Figure 6.66 shows that there was no difference in reaction time for correct incongruent trials at baseline and follow up.
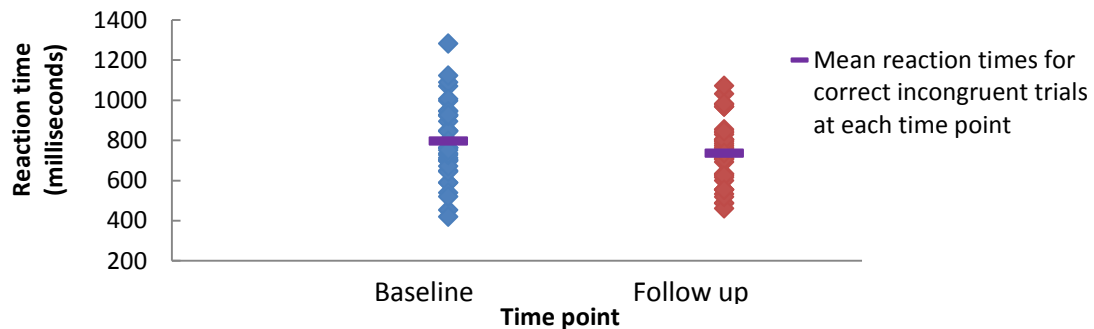
Figure 6.66 Study 2. Mean reaction time for correct incongruent trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.6   Switched trials

6.3.4.7.6.1   Proportion of correct switched trials

Data were reflected and inversely transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 32) = 0.12$ $p = .73$, $\eta_p^2 = .004$, and time since baseline was not a significant covariate, $F(1, 32) = 0.13$, $p = .73$, $\eta_p^2 = .004$. There was no significant main effect of gender, $F(1, 32) = 0.48$, $p = .49$, $\eta_p^2 = .015$. There was a significant main effect of time $F(1, 32) = 5.56$, $p = .025$, $\eta_p^2 = .148$, but there were no differences on the post hocs. There was no significant time*time since baseline interaction, $F(1, 32) = 0.94$, $p = .34$, $\eta_p^2 = .028$, but there was a trend for a significant time*age interaction, $F(1, 32) = 3.16$, $p = .085$ $\eta_p^2 = .090$, and a significant time*gender interaction, $F(1, 32) = 9.31$, $p = .005$, $\eta_p^2 = .225$, such that females correctly responded to less trials at baseline compared to males, but at follow up females correctly responded to more trials than males. Younger participants correctly responded to more trials at follow up, while older participants correctly responded to more trials at baseline. Figure 6.48 shows that there was no difference in the proportion of correct switched trials at baseline and follow up.
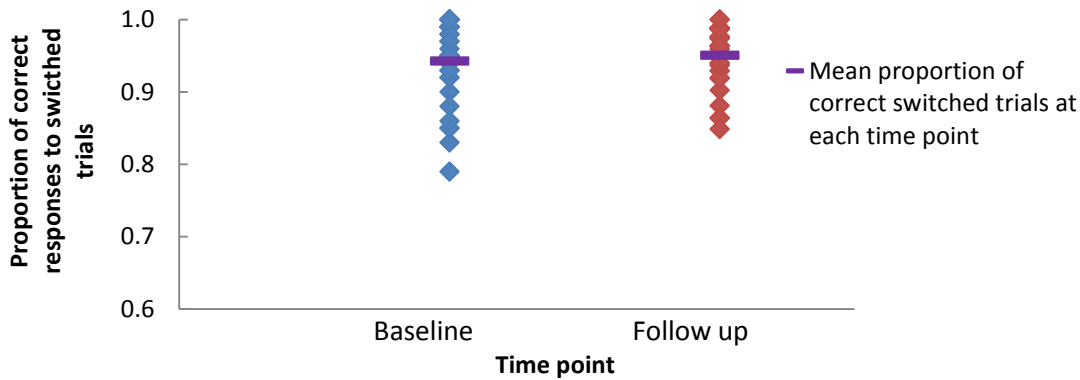
Figure 6.67 Study 2. Proportion of correct switched trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.6.2 Reaction time for correct switched trials

Age was not a significant covariate, $F(1, 32) = 1.26$ $p = .27$, $\eta_p^2 = .038$, and time since baseline was not a significant covariate, $F(1, 32) = 2.86$, $p = .10$, $\eta_p^2 = .082$. There was no significant main effect of gender, $F(1, 32) = 0.88$, $p = .36$, $\eta_p^2 = .027$, and time $F(1, 32) = 0.002$, $p = .96$, $\eta_p^2 < .001$. There was no significant time*time since baseline interaction, $F(1, 32) = 1.22$, $p = .28$, $\eta_p^2 = .037$, no significant time*age interaction, $F(1, 32) = 0.05$, $p = .83$ $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 0.97$, $p = .33$, $\eta_p^2 = .029$. Figure 6.68 shows that there was no difference in reaction time for correct switched trials at baseline and follow up.
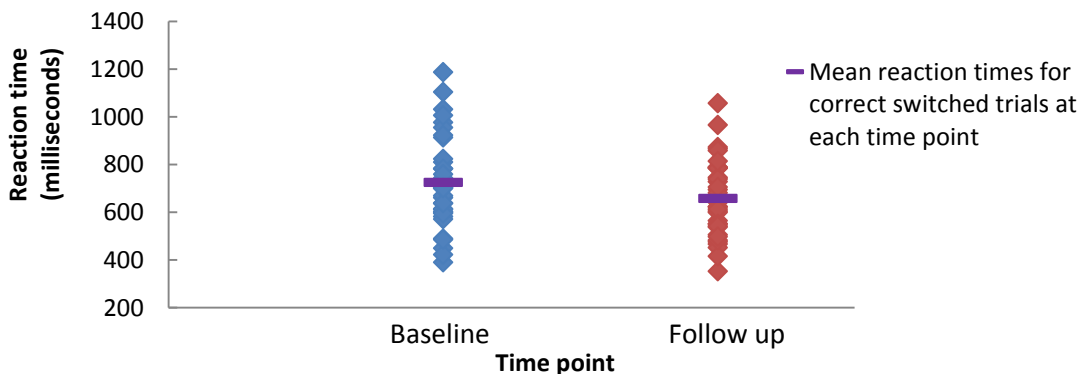
Figure 6.68 Study 2. Reaction time for correct switched trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.7 Non switched trials

6.3.4.7.7.1 Proportion of correct non switched trials

Data were reflected and inversely transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 32) = 0.35$ $p = .56$, $\eta_p^2 = .011$, and time since baseline was not a significant covariate, $F(1, 32) = 1.02$, $p = .32$, $\eta_p^2 = .031$. There was no significant main effect of gender, $F(1, 32) = 1.09$, $p = .30$, $\eta_p^2 = .033$, and time $F(1, 32) = 0.40$, $p = .53$, $\eta_p^2 = .090$. There was a trend for a significant time*time since baseline interaction, $F(1, 32) = 3.15$ $p = .086$, $\eta_p^2 = .090$, but there were no differences on the post hocs. There was no significant time*age

interaction, $F(1, 32) = 1.16$, $p = .29$ $\eta_p^2 = .035$, and no significant time*gender interaction, $F(1, 32) = 2.53$, $p = .12$, $\eta_p^2 = .073$. Figure 6.69 shows that there was no difference in the proportion of correct non switched trials at baseline and follow up.
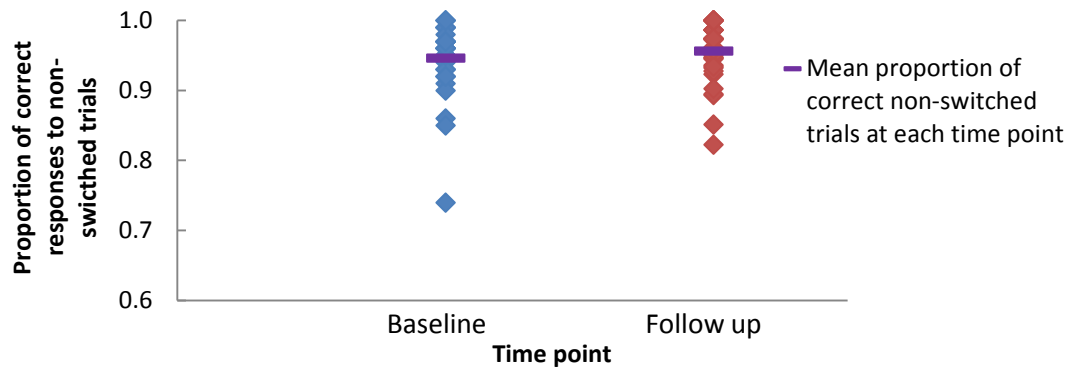
Figure 6.69 Study 2. Proportion of correct non-switched trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.7.2   Reaction time for correct non switched trials

Age was not a significant covariate, $F(1, 32) = 0.001$ $p = .98$, $\eta_p^2 < .001$, but the covariate for time since baseline was a trend, $F(1, 32) = 4.00$, $p = .054$, $\eta_p^2 = .111$. Longer duration since baseline was a predictor for slower reaction times. There was no significant main effect of gender, $F(1, 32) = 0.48$, $p = .50$, $\eta_p^2 = .015$, and time $F(1, 32) = 0.14$, $p = .72$, $\eta_p^2 = .004$. There was a trend for a significant time*time since baseline interaction, $F(1, 32) = 4.10$, $p = .051$, $\eta_p^2 = .114$, such that there was no difference in reaction time in those tested after a short duration since follow up, but reaction time was better at follow up in those tested after a longer period of time. There was no significant time*age interaction, $F(1, 32) = 0.22$, $p = .64$ $\eta_p^2 = .007$, and a trend for a significant time*gender interaction, $F(1, 32) = 3.12$, $p = .087$, $\eta_p^2 = .089$, such that both males and females responded faster at follow up, but females got considerably quicker. Figure 6.70 shows that there was no difference in reaction time for correct non switched trials at baseline and follow up.
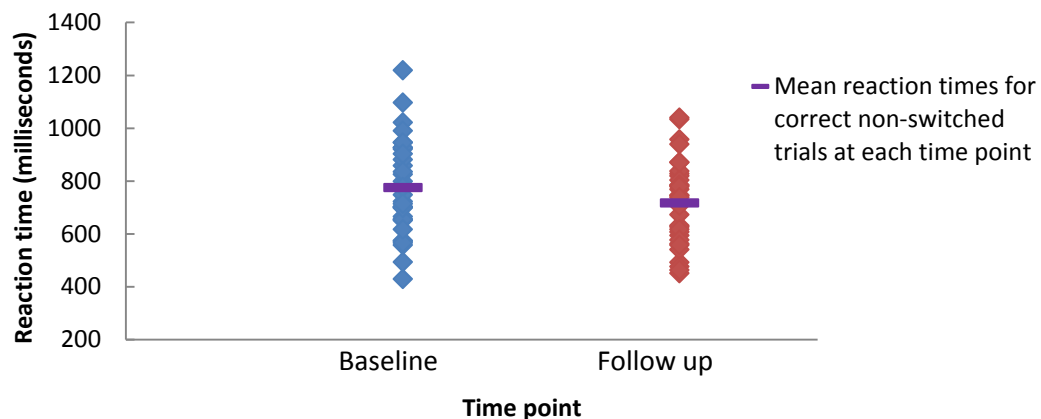
Figure 6.70 Study 2. Reaction time for correct non switched trials on the AST at baseline and follow up, in people with CFRD

6.3.4.7.8 Omission errors

Data were inverse transformed due to severe positive skewness. Age was not a significant covariate, $F(1, 32) = 0.01$ $p = .92$, $\eta_p^2 < .001$, but the covariate for time since baseline was a trend, $F(1, 32) = 3.08$, $p = .089$, $\eta_p^2 = .088$, such that a longer duration since baseline was a predictor for more omission errors. There was no significant main effect of gender, $F(1, 32) = 0.66$, $p = .80$, $\eta_p^2 = .002$, and of time $F(1, 32) = 0.06$, $p = .82$, $\eta_p^2 = .002$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.38$, $p = .55$, $\eta_p^2 = .012$, no significant time*age interaction, $F(1, 32) = 0.02$, $p = .88$ $\eta_p^2 = .001$, and no significant time*gender interaction, $F(1, 32) = 1.50$, $p = .23$, $\eta_p^2 = .045$. Figure 6.71 shows that there was no difference in omission errors at baseline and follow up.
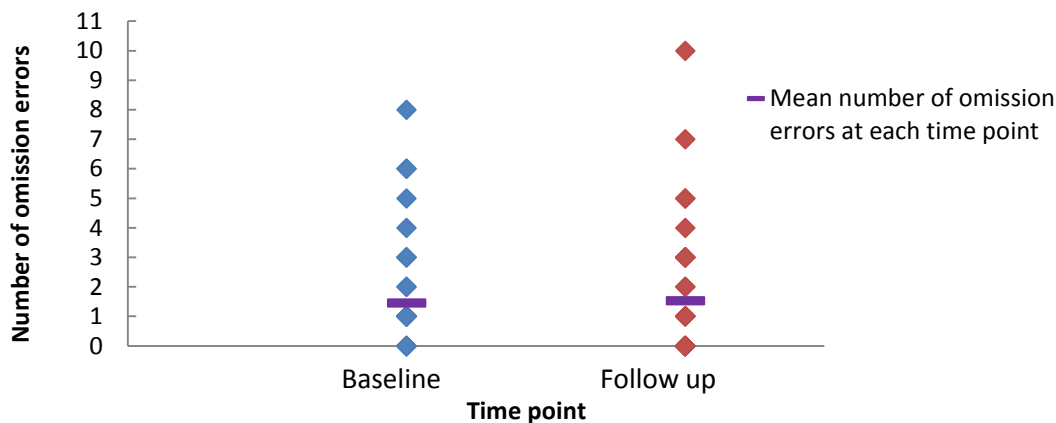
Figure 6.71 Study 2. Total number of omission errors produced on the AST at baseline and follow up, in people with CFRD

6.3.4.7.9 Commission errors

There were too few data points to perform analysis for commission errors. This showed that participants did not, on the whole, respond too soon, either prior to the end of the pre-empt window or prior to the stimulus being shown, at both baseline and follow up.

6.3.4.7.10 Congruency cost

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 32) = 1.84$ $p = .19$, $\eta_p^2 = .054$, and time since baseline was not a significant covariate, $F(1, 32) = 0.74$, $p = .40$, $\eta_p^2 = .023$. There was no significant main effect of gender, $F(1, 32) = 0.58$, $p = .81$, $\eta_p^2 = .002$, and of time $F(1, 32) = 0.43$, $p = .52$, $\eta_p^2 = .013$. There was no significant time*time since baseline interaction, $F(1, 32) = 0.44$, $p = .51$, $\eta_p^2 = .014$, no significant time*age interaction, $F(1, 32) = 0.14$, $p = .71$ $\eta_p^2 = .004$, and no significant time*gender interaction, $F(1, 32) = 0.39$, $p = .54$, $\eta_p^2 = .012$. Figure 6.72 shows that there was no difference congruency cost (difference in reaction time between congruent and incongruent trials) at baseline and follow up.
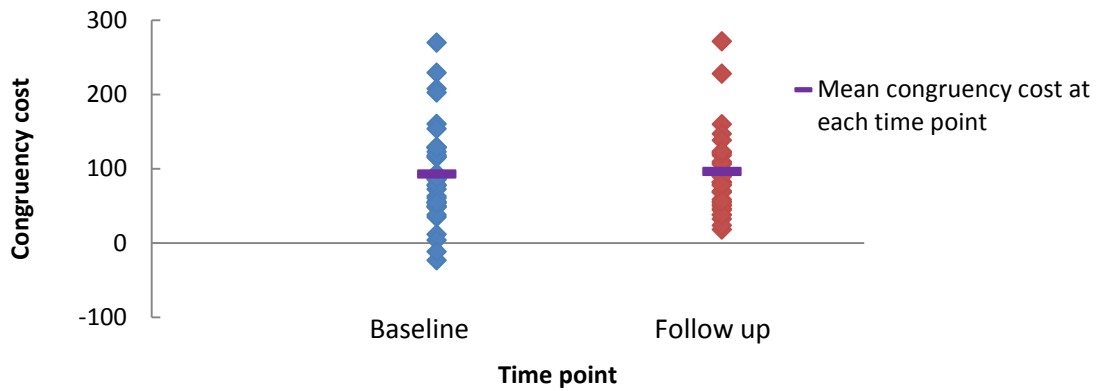
Figure 6.72 Study 2. Congruency cost for correct trials (subtraction of congruent from incongruent reaction times for correct trials) on the AST at baseline and follow up, in people with CFRD

6.3.4.7.11 Switch cost

Age was a significant covariate, $F(1, 32) = 7.38$, $p = .01$, $\eta_p^2 = .187$, but time since baseline was not a significant covariate, $F(1, 32) = 0.17$, $p = .69$, $\eta_p^2 = .005$. Older age was a predictor of a negative switch cost. There was no significant main effect of gender, $F(1, 32) = 0.49$, $p = .49$, $\eta_p^2 = .015$, and time $F(1, 32) = 0.32$, $p = .58$, $\eta_p^2 = .013$. There was no significant time*time since baseline interaction, $F(1, 32) = 1.01$, $p = .32$, $\eta_p^2 = .031$, no significant time*age interaction, $F(1, 32) = 0.08$, $p = .78$ $\eta_p^2 = .003$, and no significant time*gender interaction, $F(1, 32) = 0.71$, $p = .41$, $\eta_p^2 = .022$. Figure 6.73 shows that there was no difference in switch cost at baseline and follow up.
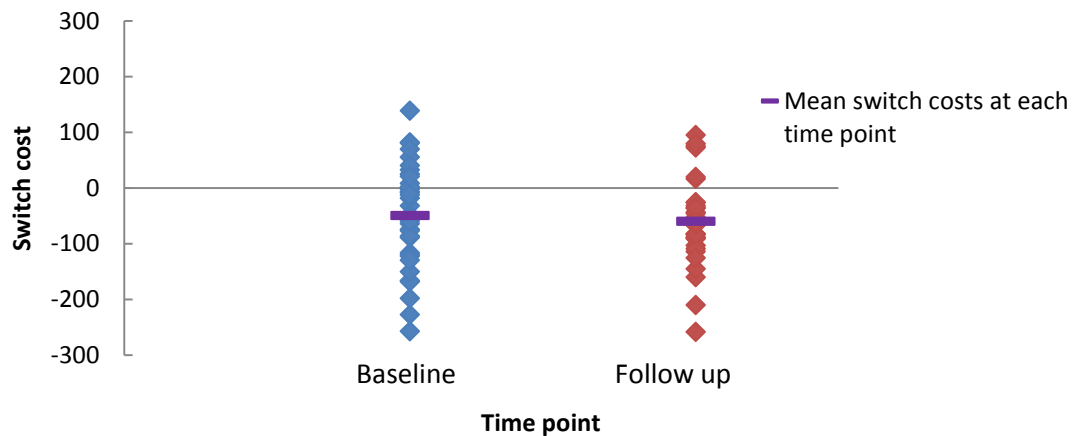
Figure 6.73 Study 2. Switch cost for correct trials (subtraction of switched from non switched reaction times) on the AST at baseline and follow up, in people with CFRD

6.3.5   Cognitive test evaluation questionnaire (CTEQ)

Table 6.3 shows the participants scores on the CTEQ at baseline and follow up.

Table 6.3 Study 2. Subjective experience of completing the cognitive test battery in people with CFRD at baseline and follow up

	Baseline N=36 Mean (SE)	Follow up N=36 Mean (SE)	F (1,32)	*p* value	η_p^2
Time pressure	32.00 (4.02)	28.49 (4.02)	0.17	.68[63]	.005
Test difficulty	47.44 (3.24)	42.58 (3.10)	0.60	.45[64]	.018
Ability to concentrate	81.56 (2.51)	82.36 (3.04)	0.56	.46[65]	.017
Effort	86.14 (1.87)	84.92 (2.39)	0.09	.76[66]	.003
Performance	56.22 (2.96)	58.69 (2.52)	3.85	.058[67]	.104
Frustration	47.14 (3.48)	46.58 (3.91)	0.38	.54	.011

There was no difference in baseline and follow up scores for cognitive test difficulty, perceived time pressure, ability to concentrate, effort, and frustration experienced in completing the cognitive tests. There was a trend for participants to report they had performed better at follow up. Females rated that they concentrated significantly more (*p*=.03) and tried significantly harder (*p*=.026) and tended to find the tests less difficult at follow up (*p*=.071) than males. Younger participants tended to rate they had performed better at follow up while older participants thought they performed better at baseline (*p*=.068). Figure 6.74 and Figure 6.75 show the distribution of ratings of which was the hardest and easiest test respectively. At baseline and follow up, the RVP test was rated as the hardest. Ratings of which tests participants found easiest had changed at follow up. At baseline, more participants rated the VRM test as the easiest, while at follow up, the PRM test was rated as the easiest.
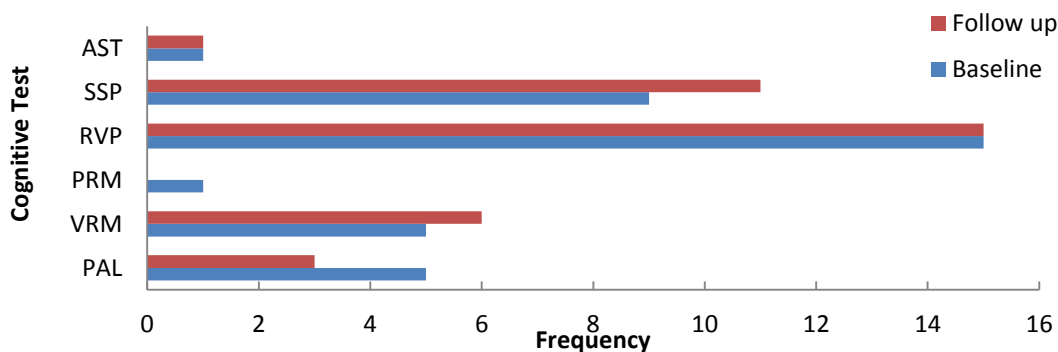
Figure 6.74 Study 2. Distribution of which was the hardest test from the cognitive battery at baseline and follow up in people with CFRD

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[63] Square root transformed due to moderate positive skewness.

[64] Square root transformed due to moderate positive skewness. Time*gender interaction shows females found the tests less difficult at follow up.

[65] Reflected and logarithm transformed due to substantial negative skewness. Females concentrated significantly more than males.

[66] Reflected and logarithm transformed due to substantial negative skewness.

[67] Reflected and square root transformed due to moderate negative skewness. No significant differences on the post hocs. Time*age interaction shows younger participants thought they performed better at follow up while older participants thought they performed better at baseline
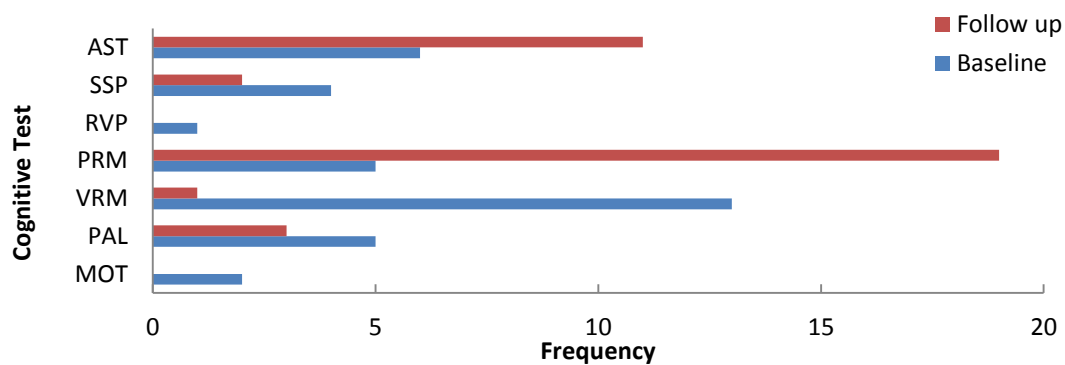
Figure 6.75 Study 2. Distribution of which was the easiest test from the cognitive battery at baseline and follow up in people with CFRD

6.4 Summary of findings

6.4.1 Participant characteristics

- From the 49 people with CFRD at baseline, 36 (23M; 13F) were retested.
- Participants were retested after a period of 19.11 (SD ± 4.67) months. 34 people were heterozygous F508del.
- There were no significant differences in clinical characteristics between baseline and follow up for weight, BMI, blood glucose (capillary, plasma), HbA1c, oxygen saturation levels, number of people receiving IV treatment, CO (ppm and %COHb), health rating, anxiety and depression levels, SBP, DBP, pulse, CRP, vitamin A,D,E, serum creatinine and serum urea, and cognitive failures score.
- There was a trend for worse lung function (FEV1, FEV1% predicted, FVC, FVC% predicted) and albumin.
- There were no differences in education except one person had since completed their degree. More people were in employment as an effect of people leaving education, but the same number of people was unemployed.
- There was no difference in the time of day testing took place.

6.4.2 Findings from the cognitive tests (Aim 1)

A detailed summary of the outcomes for each test is presented in Table 6.4. Taken together, the cognitive assessments indicated that:

- There was no change in cognitive performance over a period of 1-3 years.
- Females improved on immediate verbal memory, and reaction time for pattern recognition.
- Younger participants improved on visual memory and new pattern learning, and working memory. However, the tendency to achieve a higher span length was at the expense of making more attempts and errors.
- A longer time since baseline was predictive of worse attention and processing speed and cognitive flexibility (AST, RVP).

Table 6.4 Study 2. Summary of cognitive test outcomes for Aim 1: Changes in cognitive function over time; baseline and follow up   ('+' better performance, '-' worse performance, '0' no difference)

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Effect of gender	Age	Time since baseline
MOT	Mean error	0	0	0	0
	Reaction time	0	0	0	0
PAL	Stages completed	0	0	0	0
	Stages completed on first trial	+	0	Younger +	0
	First trial memory score	0	0	Younger +	0
	Total trials	0	0	Younger +	0
	Total errors	0	0	Younger +	0
VRM	Immediate free recall	0	Female +	0	0
	Immediate novel words	(trend)+	0	0	0
	Immediate perseverations	0	Female -	0	0
	Immediate target recognition	0	0	0	0
	Immediate false alarm recognition	0	0	0	0
	Delayed free recall	0	0	0	0
	Delayed novel words	+	0	0	0
	Delayed perseverations	0	0	0	0
	Delayed target recognition	0	0	0	Longer -
	Delayed false alarm recognition	0	0	0	0

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Effect of gender	Age	Time since baseline
PRM	Immediate number correct	0	0	0	0
	Immediate reaction time	0	(trend) Female +	0	0
	Delayed Number correct	0	0	0	0
	Delayed reaction time	0	Female +	0	0
RVP	Total hits	0	0	0	Longer -
	False Alarms	0	0	Younger -	0
	Mean reaction time for hits	0	0	0	Longer -
	A' Prime	0	0	0	Longer -
	B' Prime	0	0	Younger +	0
SSP	Span length	0	0	(trend) Younger +	0
	Total number of attempts	0	0	Younger -	0
	Mean time to first response	0	0	0	0
	Mean time to last response	0	Male -	0	0
	Total errors	0	0	Younger -	0
	Total usage errors	0	0	0	0
AST	Total correct trials	0	0	0	0
	Mean reaction time for correct trials	0	0	0	Longer -
	Correct direction trials	0	0	0	0
	Mean reaction time for direction trials	0	0	0	0
	Correct side trials	0	0	0	0
	Mean reaction time for side trials	0	0	0	Longer -
	Correct congruent trials	0	0	0	0

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Effect of gender	Age	Time since baseline
AST *continued*	Mean reaction time for congruent trials	0	0	0	Longer -
	Correct incongruent trials	0	0	0	0
	Mean reaction time for incongruent trials	0	0	0	0
	Correct switched trials	0	0	0	0
	Mean reaction time for switched trials	0	0	0	0
	Correct non-switched trials	0	0	0	0
	Mean reaction time for non-switched trials	0	0	0	0
	Omission errors	0	0	0	Longer -
	Commission errors	0	n/a	n/a	n/a
	Congruency cost	0	0	0	0
	Switch cost	0	0	Younger -	0

6.4.3   Findings from the subjective ratings questionnaires (Aim 2 and 3)

- Overall sleep quality did not differ between baseline and follow up. There was no difference in sleep quality between the night before the test session and the previous week except participants found it quicker to get to sleep the night before a test session.

- There were gender differences regarding sleep quality for ease and time getting to sleep, periods of wakefulness and ease of waking.

- Older participants reported being more alert on waking than younger participants, and at baseline, alertness was slightly better on the morning of the test session while at follow up, alertness was better for the previous week.

- Overall, perceived stress was not different at follow up, and there was no difference between the previous week and month. However, females reported they felt more stressed for the previous month than week, while males were slightly more stressed for the previous week.

- There was no difference in mood at follow up compared to baseline. Males reported they were more content than females while females reported they were more mentally alert. Females reported they were less irritable at follow up while males reported being slightly more irritable. Older participants reported feeling less mentally alert, lower ability to concentrate and less energetic than younger participants.

- There was a trend for participants to feel their performance had improved at follow up. There were no other differences on other cognitive workload measures.

- There were no differences in the number of subjective minor daily cognitive errors made within the past 6 months. The number of errors made within the past week (CDS) correlated highly with made within 6 months (CFQ).

- The RVP test was rated the hardest test at both baseline and follow up. The VRM test was rated the easiest at baseline and the PRM at follow up.

6.5   Discussion

The first aim of this study was to investigate whether cognitive function had changed in people with CFRD during a 1-3 year period. The second aim was to investigate whether the number of subjective cognitive daily errors had remained stable over this period of time. The third aim was to investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period. It was hypothesised that changes in glycaemic control, severity of lung function disease and mood would influence the profile of cognitive function in people with CFRD.

6.5.1   Aim 1: To investigate whether cognitive function had changed in people with CFRD during a 1-3 year period

The present study found there were no overall changes in cognitive function over a 1-3 year period in people with CFRD (see section 6.4.2). Therefore people with CFRD have some degree of impairment relative to controls (Study 1; Chapter 5) on domains of visual memory and new

pattern learning, verbal memory, attention and processing speed, spatial working memory and cognitive flexibility, but cognitive function does not appear to decline over a period of 1-3 years.

Chronic hyperglycaemia and duration of diabetes have been proposed to contribute to the development of cognitive impairment in people with T1DM and T2DM (see Chapter 3, section 3.2.3.3). People had been diagnosed with CFRD for, on average, 12 years at follow up. Over the period of 1-3 years, glycaemic control had remained stable. As glucose regulation and cognitive function are tightly linked, it is therefore unlikely that cognitive function would have changed. It is suggested that as HbA1c levels had remained stable, this may have been a protective factor against cognitive decline in people with CFRD. This suggestion is supported by West et al. (2014) who found an association between the duration of T2DM and cognitive function, which was modulated by glycaemic control.

Ryan (2006) had used the CANTAB PAL test investigating the impact improved glycaemic control (due to insulin sensitizers or secretagogues) in people with T2DM. Fasting plasma blood glucose levels were improved within 24 weeks, and this improved glycaemic control was associated with a reduction in the number of errors on the PAL test. Although the present study found that overall performance was stable, being younger people was predictive of improvement on this test. This was also a finding in Study 1. Therefore, impairment in visual memory and new pattern learning is reflective of older age. Therefore, as people with CFRD get older, declines in visual memory and new pattern learning may become more apparent.

Jacobson et al. (2007) found that HbA1c levels greater than 72 mmol/mol in people with T1DM were associated with worse psychomotor and processing speed, compared to people who had levels below 57 mmol/mol. There was minimal change in HbA1c in the present study which might explain why there was no overall decline in processing speed. Conversely, a longer time since baseline was predictive of worse attention and processing speed and cognitive flexibility. This suggests that the minimum time to follow up was to shorter time to fully detect decline in these domains, and suggests that in fact there is a progressive decline in processing speed and cognitive flexibility in people with CFRD.

6.5.1.1 Subjective evaluation of cognitive performance

There were no differences on the cognitive workload measures except for perceived performance (see section 6.4.2). Participants thought they had done better on the tests at follow up. This may be reflective of the testing procedure being less novel, causing a reduction in anxiety levels and nervousness allowing them to focus more on the task in hand. However, there was no difference in perceived test difficulty, or levels of concentration during the tests. Furthermore, no improvement in performance was seen objectively, which reflects the disparity between objective and subjective cognitive performance.

At follow up, RVP was still rated as the hardest test. As there were no differences in concentration or perceived test difficulty, this reflects the impairment in attention and slowing in processing speed. The easiest test had changed from VRM to PRM. Study 1 (Chapter 5) found that people with CFND and controls rated the PRM as the easiest. At follow up, people with CFRD reported more novel words, but there was no change in their free recall (for words in the

list to remember) which suggests that verbal memory may have slightly declined due to more guessing and intrusions of words not present in the word list in order to maintain baseline accuracy.

6.5.2 Aim 2: To investigate whether the number of subjective cognitive daily errors had remained stable over a period of 1-3 years in people with CFRD.

There was no difference in the subjective reporting of daily minor cognitive daily errors which have occurred in the past 6 months (CFQ) at follow up. This suggests that participants do not perceive their cognitive function has declined in the time since baseline. This may be explained as there was no change in depressive symptomology which has shown to affect ratings of cognitive errors. Scores on the CDS, which asked participants to rate the number of cognitive errors occurring within the past week, were found to be highly correlated with the number of errors reported on the CFQ.

6.5.3 Aim 3: To investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period.

People with CFRD showed a trend for a decline in lung function scores over a period of 1-3 years. However, as there was no evidence of decline in cognitive performance, this suggests there may be some delay between changes within the brain due to a reduction in lung function and cognitive performance. Conversely, it may be that glycaemic control is a stronger mechanism for cognitive impairment in people with CFRD over that of a decline in lung function. Therefore the stability of glycaemic control was a protective factor against decline in people with CFRD.

Clinically measured or identifiable signs of retinopathy were present in one person at follow up. Therefore, it is not possible to conclude whether microvascular complications in CFRD are associated with cognitive impairment. No patient showed signs of clinically evident macrovascular disease. The lack of clinically detected signs of microvascular disease may be an explanation for a lack of cognitive decline in people with CFRD.

Depression has been associated with an increased risk of cognitive dysfunction (Papazacharias & Nardini, 2012). As the levels of depression had remained stable in people with CFRD, this may explain why no decline in cognitive function was observed. The consistent finding that RVP was the hardest test (in both Study 1 and the present study) may be explained by elevated levels of depressive symptoms in people with CFRD resulting in a deficit in attention (Weiland-Fiedler et al., 2004). However, it has been suggestive in section 6.5.1 that there is evidence of a decline in processing speed in people who had a longer time since baseline testing. Therefore, some degree of cognitive impairment in people with CFRD may be independent of depressive symptomology and a longer follow up period would allow investigation into whether the slowing in processing speed becomes a stronger effect despite people with CFRD suffering from depression.

The improvement seen by females on immediate verbal memory, and reaction time for pattern recognition may to some extent be explained by gender differences in cognitive abilities and mood. Females commonly show a beneficial advantage to verbal memory (Zaidi, 2010). The reduction in anxiety levels in conjunction with the gender advantage may explain why improvement was seen on verbal memory at follow up. Although males tend to show an advantage for visual - spatial memory (Zaidi, 2010), females reported that they were more mentally alert than males. PRM was rated as the easiest test, and therefore it is suggested that pattern recognition required less cognitive load than responding to tasks which require high cognitive demand such RVP and AST. As females reported they were more mentally alert than males, the ease of the test in combination with alertness may have contributed to the faster reaction times seen for pattern recognition.

6.6 **Conclusion**

There were no differences in cognitive function over a 1-3 year period in people with CFRD. However, gender and age differences were observed for verbal, visual, and working memory. A longer duration since baseline testing was predictive of a slowing in processing speed and cognitive flexibility. There were no differences in clinical characteristics except a trend for a decline in lung function. In light of this, it is suggested that there may be some delay between changes in lung function and changes within the brain. Conversely, it may be that glycaemic control is a stronger mechanism for cognitive impairment in people with CFRD over that of a decline in lung function.

Chapter 7

Cognitive function in post transplant people with CFRD (CFRDTx), relative to people with CFRD who have not undergone transplantation and healthy controls (Study 3)

7.1 Introduction

Chapter 1 described the progressive nature of CF disease. Although advances in treatment and care have increased the median predicted survival of people with CF, most die from respiratory failure (Elborn, Balfour-Lynn, & Bilton, 2015). Lung transplantation is the only viable treatment option for those with end-stage CF lung disease, capable of restoring people toward normal respiratory health and improving quality of life (Hirche et al., 2014; Inci et al., 2012). Chapter 2 (section 2.3.7) reviews the literature examining cognitive function in people with CF who have end stage lung disease. Impairments are commonly seen in the domains of verbal memory and executive function and to a lesser extent cognitive flexibility. It is therefore plausible that lung transplantation, as well as improving respiratory health, may also influence cognitive functioning.

7.1.1 Transplantation and survival rates post transplantation in CF

The ability to perform transplants, as well as the increase in the number of lung transplants per year, has steadily contributed to the increasing median survival rate in CF (P. Stewart, Yankaskas, & Egan, 2014). Bilateral lung transplantation is the most widely used technique (Liou, Adler, Cahill, et al., 2001) and 25% of all lung transplants in the world are for people with CF. CF is the third major indication for lung transplant in Europe, (Hirche et al., 2014), and the second major indication in the US (Liou, Adler, Cahill, et al., 2001). Using the Cystic Fibrosis Foundation Patient Registry (CFFPR), a 5 year survivorship model has been validated (Liou, Adler, Fitzsimmons, et al., 2001). Using the model, people with CF who had <30% predicted survival benefitted from lung transplantation (Liou, Adler, Cahill, et al., 2001). However, lung transplantation is not a cure for CF and itself is the second major cause of death in CF (Liou, Adler, Cahill, et al., 2001).

Transplantation also necessitates additional prescribed treatment such as immunosuppressant agents, which themselves cause complications, and therefore treatment burden is not necessarily decreased. Nevertheless, people with CF have better outcomes post-transplant than other clinical groups, such as those with chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis (Corris, 2013; Hackman, Snell, & Bach, 2014).

7.1.2 Factors affecting survival rates post transplantation

Reported post-transplant survival rates of people with CF are 81% in the first year, 58% up to 3 years, and 49% after 5 years (Aris, Routh, Puma, Heath, & Gilligan, 2001). People with CF have the best survival after transplantation amongst all causes (60% at 5 years) and it can significantly

improve their quality of life (Samano et al., 2013). However, acute rejection, diabetes, bronchiolitis obliterans syndrome (BOS)[68] and pathogen colonisation can affect survival rates.

7.1.2.1 Post-transplant diabetes

Post-transplant diabetes is a distinct clinical entity and a common complication after solid organ transplantation (Ollech et al., 2008). Despite CF being a strong risk factor for developing diabetes following transplantation (Quattrucci et al., 2005; Ye, Kuo, Sampaio, Jiang, & Bunnapradist, 2011), the aetiology of post transplant diabetes in CF is not clear (Kelly & Moran, 2013). This often results in diabetes in the post-transplant period in CF being referred to as CFRD. Diabetes is thought to be induced post-transplant in those with CF as a result of the underlying pancreatic dysfunction in conjunction with the effect of glucocorticoids and immunosuppression therapy with tacrolimus and cyclosporine. Furthermore, the operation itself may contribute to the development of diabetes too as a result of causing a major stress response which can result in impaired glucose metabolism (Hadjiliadis et al., 2005).

Diabetes in the post transplant period is a significant morbidity in people with CF. Even during the first year after lung transplantation, the presence of diabetes has been shown to negatively affect transplantation outcomes (i.e. significantly increasing the likelihood of hospitalisation for infections and acute rejection as well as increased incidence and earlier onset of BOS (Zamora, Edwards, Weill, Astor, & Nicolls, 2004)). However, the risk of mortality is higher in people with CF who have diabetes pre-transplant than people who developed diabetes post-transplant (Belle-van Meerkerk et al., 2012). It has been suggested that duration of diabetes (i.e. presence of chronic insulin deficiency) may be correlated with post-transplant clinical deterioration (Bradbury, Shirkhedkar, Glanville, & Campbell, 2009).

The choice of immunosuppression therapy is also a risk factor for developing diabetes post-transplant in people with CF (Ye et al., 2011). Calcineurin inhibitors can reduce β cell function (Sunni, Bellin, & Moran, 2013). The most commonly used calcineurin inhibitor in recipients at 1 and 5 years post lung transplant is tacrolimus (Christie et al., 2009; Dipchand et al., 2015). The risk of developing post-transplant diabetes is increased in those prescribed tacrolimus compared to cyclosporine (Ye et al., 2011). This can be explained by the fact tacrolimus is more diabetogenic than cyclosporine. Therefore, having CF and being treated with the immunosuppressive drug tacrolimus are two important risk factors for developing diabetes after lung transplantation.

It is important to note that lung transplantation does not always have a negative effect on the health of a person with CF. Transplant recipients have been shown to experience improved glucose control at 1 and 2 years post transplant (Valour et al., 2013). It is therefore plausible that improvement in glucose control may have an effect on cognitive functioning in the post transplant period. Improved glucose control may occur in people whose endogenous insulin

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[68] A form of chronic lung allograft dysfunction that affects a majority of lung transplant recipients and is the principal factor limiting long-term transplant survival. Results in inflammatory obstruction of the lungs tiniest airways (bronchioles). The bronchioles become damaged and inflamed which leads to excessive scarring that blocks the airways.

secretion was affected by a decline in respiratory health and in whom the development of CFRD was mainly due to insulin resistance. Despite being prescribed immunosuppressive agents which can alter insulin resistance, the large reduction in infection and inflammation of the respiratory system can improve insulin resistance over that induced by post-transplant medication.

7.1.2.2 **Pancreatic status**

People with CF who are PI are at an increased risk of developing CFRD later in life. It is therefore plausible that these people are at higher risk of developing diabetes post-transplant. In a retrospective study of 77 PI people with CF who underwent lung transplantation, 38 (49.4%) had developed diabetes post-transplant (Hadjiliadis et al., 2005). Of these 38 people, 22 had been diagnosed with CFRD prior to transplantation whereas 16 had no prior evidence of CFRD. Of the 16 people who had diabetes post-transplant, 11 developed it within the first 6 months, with a median time of 80 days. This highlights that diabetes occurs frequently in the early months post transplantation in people who are PI; however, it can still develop after this period. The risk of developing diabetes decreases after the first 6 months due to the reduction of corticosteroids over time; corticosteroids cause insulin resistance and IGT, particularly in PI people with CF due to their susceptibility to developing diabetes. This suggests that a longer duration since transplant may be associated with better cognitive functioning due to a reduction in insulin resistance and IGT.

7.1.2.3 **Pathogen colonisation**

Pathogen colonisation can also have a negative effect on survival in the post-transplant period. By the time transplantation is considered in the progressive course of CF disease, the majority of people are colonised by P. *aeruginosa*; however, the majority of research has shown this pathogen to have minimal impact on transplantation outcomes (Hadjiliadis, 2007). Conversely, colonisation and infection with B. *cepacia* has been shown to significantly affect post-transplant outcomes and mortality in people with CF (Aris et al., 2001; Chaparro et al., 2001; Snell, de Hoyos, Krajden, Winton, & Maurer, 1993). However, the high post-transplant mortality rate of those infected with B. *cepacia* has contributed to this pathogen being a contraindication to transplantation.

7.1.3 **Cognitive function in people with CF who have undergone transplantation**

Previous research has investigated whether transplantation can cause changes in cognitive function in children and adults. Although the samples tend to be heterogeneous, people with CF tend to be younger than other transplant recipients and therefore the studies often make this differentiation between participants in the results.

7.1.3.1 **Cognitive function in children and adolescents with CF who have undergone either heart, or heart-lung transplantation**

Wray and colleagues (Wray, Long, Radley-Smith, & Yacoub, 2001) examined cognitive function after returning to school following transplantation at time points of 6 months, 1, 3, and 5 years

in 81 children and adolescents (mean age 10.2 years, range 5-17 years; CF n=13) who had received either a heart (n=47) or heart-lung transplant (n=34). Compared to a healthy control group (n=44, matched on age, gender and SES), overall IQ and academic attainment were significantly lower, but still within the normal range at all time points. Interestingly, those with CF performed better than those with other initial diseases. Longitudinal examination of cognitive function for people with CF is hindered by the fact that some patients at 3 and 5 years were either above the age range which the test was appropriate for, they were transplanted close to the end of the study period, or had died. Nevertheless, the results highlight that children and adolescents who have undergone transplantation experience cognitive deficits compared to their peers.

In 2006, Wray and Radley-Smith assessed psychological functioning (development, cognitive and academic) in a group of 34 children and adolescents (mean age 7.9 years, range 1.3-15.3 years) at 1 and 3 years post heart or heart-lung transplantation (Wray & Radley-Smith, 2006). On the whole, cognitive functioning (assessed by the British Ability Scales (BAS); verbal and non-verbal reasoning, short-term memory, processing speed and retrieval of knowledge) was within the normal range and there were no significant differences between scores at both 1 year and 3 years. However, as there was only 1 person with CF in the sample, scores cannot be generalised to the rest of the CF population.

7.1.3.2 Cognitive function in adults with CF who have undergone lung transplantation

In a prospective, cross-sectional study, Hoffman et al., (2012) compared cognitive function scores before and 6 months following lung transplantation in 49 adults patients aged 49.6±12.9 years (range 20-65 years); 12 had CF. Before transplantation, verbal memory composite scores were within the normal range, and improvement was observed post-transplant; only for contextual verbal memory. Executive function composite scores were within the normal range before transplantation and were similar at post-transplant. After controlling for pre-transplant composite scores, lower scores post-transplant were predicted by older age. Furthermore, when people with CF were excluded from the analysis (n=37), the effect of age became more pronounced which suggests younger people show improvement, and older people show a decline in executive function. Additionally, significant cognitive decline (>1SD on at least 2 tests) was observed (pre vs post-transplant) in 29% of people. Participants tended to be older (mean age 57 years) and have fewer years of education (mean=12 years).

A further prospective study assessed the effect of lung transplantation on cognitive function. Cognitive function was assessed (within 1 month) before transplant, 1-2 days prior to hospital discharge, and 3 months after discharge in 47 adult transplant recipients (mean age 53.5±17.2 years) using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), TMT and the MoCA (Smith, Rivelli, et al., 2014). People with CF (n=8, mean age 24±6.1 years) were significantly younger than people without CF (n=9, mean age 59.2±11.5 years). Based on composite scores, people with CF and more educated people had better cognitive function across all 3 time points. When people with CF were analysed separately, there was a slight improvement on the RBANS after transplantation, but a significant improvement on TMT (part

B; cognitive flexibility) from discharge to follow-up. In contrast, after transplantation, those without CF showed deterioration in performance, particularly people who were younger, but generally improved to above pre-transplant levels at follow-up. The authors suggested that cognitive function is immediately improved after transplantation in people with CF due to improved hypoxia and reduced fatigue.

In a retrospective study, mild cognitive impairment defined using the MoCA was common amongst 42 adult lung transplant recipients (mean age 60 years; range 57-64) at a median time of 8 months post-operation compared to 14 separate patients (mean age 60 years; range 57-64) on the waiting list (D. G. Cohen et al., 2014). Prolonged total graft ischemia time was the most significant risk factor for impaired cognition, followed by bilateral transplant (i.e. type of lung) and use of cardiopulmonary bypass. In contrast, functional physical gain (i.e. an increase in distance at the end of physical rehabilitation on the 6 minute walk test) was associated with improved cognitive function.

Pre-transplant cognitive function has also been shown to be a predictor for morbidity and more importantly mortality post-transplant (Smith et al., 2015; Smith, Blumenthal, et al., 2014). Lower executive function and memory scores were independently associated with greater mortality in 201 adult lung transplant recipients (mean age 49.1±13.2 years; CF n=39, mean age 30.2±8.0 years) who were followed up for a mean of 9.2 (range 4-12) years (Smith, Blumenthal, et al., 2014). Although people with CF had the longest average survival (5.4 years), these results have implications for people who may exhibit poor cognitive functioning in the period just after transplantation. More recently, Smith and colleagues found that delirium was lower in adults with CF (mean age 52.7 years, SD ±16.8) following lung transplantation compared to other respiratory disorders (COPD, IPF, other), but poor cognitive functioning pre-transplant (measured 4 weeks prior to transplantation) was a risk factor for delirium (Smith et al., 2015). Thus, people with CF with poor cognitive function pre-transplant may develop delirium, and also have greater mortality post-transplant.

In summary, transplantation is associated with improved cognitive function in people with CF. Improvements have been observed seen on tasks of verbal memory and executive function. Table 7.1 below summarises the studies which have investigated cognitive function in both post transplanted children and adolescents, and adults with CF.

Table 7.1 Summary of studies examining cognitive function in people with CF who have undergone transplantation

Authors (year)	People with CF	Control Group	Type of Transplant	Study design	Cognitive assessment	Results	Comments
Wray et al. (2001)	81 children and adolescents (mean age 10.2 yrs, range 5-17 yrs; CF n=13)	Healthy controls (n=44, matched on age, gender and SES),	Heart (n=47) or heart-lung (n=34).	Cross- sectional, Longitudinal; post transplant at 6 mths, 1, 3, and 5 yrs	BAS; short-term memory verbal and nonverbal reasoning, retrieval of knowledge skills, speed of information processing	Compared to controls, overall IQ and academic attainment were significantly lower, but still within the normal range at all time points. Those with CF performed better than those with other initial diseases.	Longitudinal examination of cognitive function is hindered as some patients at 3 and 5 yrs were either above the age range which the test was appropriate for, they were transplanted close to the end of the study period, or had died.
Wray and Radley-Smith (2006)	34 children and adolescents; 1 had CF (mean age at 12mth assessment = 7.9yrs, range 1.3 - 15.3 yrs)	N/A	Heart (n=24) or heart-lung (n=10)	Longitudinal; 1 and 3 yrs post transplant	Children 0-3.5 yrs of age: Ruth Griffiths Development Scales Children 3.6 to 17.3 yrs of age: BAS	Cognitive functioning was within the normal range and there were no significant differences between scores at both 1 yr and 3 yrs.	As there was only 1 person with CF in the sample, scores cannot be generalised to the rest of the CF population. 8 children completed the Ruth Griffiths Developmental Scales at 12 mths but were in the age range for completion of the BAS at 3 yrs.

Authors (year)	People with CF	Control Group	Type of Transplant	Study design	Cognitive assessment	Results	Comments
Hoffman et al. (2012)	49 adults patients, mean age 49.6 yrs (SD 12.9 yrs; range 20-65 yrs); 12 had CF	N/A	Lung	Prospective, cross-sectional; before and 6 mths following lung transplant Patients were a subset who participated in a RCT: *Investigational Study of Psychological Intervention in Recipients of Lung Transplant (INSPIRE)*	Stroop, COWA, Animal Naming Test, TMT (A,B), Ruff 2 and 7 Selective Attention Test, WMS-R (Logical memory, Verbal paired associates), WAIS-R (digit span)	Before transplantation, verbal memory and executive composite scores were within the normal limits. Improvement was observed post-transplant; only for contextual verbal memory. Executive function scores were similar at post-transplant. After controlling for pre-transplant composite scores, lower scores post-transplant were predicted by older age. Significant cognitive decline (>1SD on at least 2 tests) was observed (pre vs post-transplant) in 29% of people; people tended to be older (mean age 57 yrs) and have fewer years of education (mean 12 yrs).	When people with CF were excluded from the analysis (n=37), the effect of age became more pronounced which suggests that post transplant, younger people show improvement, and older people show a decline in executive function. Average time between baseline and 6-month post transplant testing was 1.3 yrs (SD 45 wks)

Authors (year)	People with CF	Control Group	Type of Transplant	Study design	Cognitive assessment	Results	Comments
Smith et al. (2014)	47 adult transplant recipients (mean age 53.5 yrs (SD 17.2 yrs). People with CF (n=8, mean age 24 yrs (SD 6.1 yrs). People without CF (COPD, IPF, Other; mean age 59.2 yrs (SD 11.5 yrs).	N/A	Lung	Prospective; (within 1 mth) before transplant, at hospital discharge (1-2 days prior), and 3 mths after discharge	RBANS, TMT, MoCA	Based on composite scores, people with CF and more educated people had better cognitive function across all 3 time points. When people with CF were analysed separately, there was a slight improvement on the RBANS after transplantation, but a significantly improvement on TMT (B) from discharge to follow-up. In contrast, after transplantation, those without CF showed deterioration in performance, particularly people who were younger, but generally improved to above pre-transplant levels at follow-up.	Cognitive function is immediately improved after transplantation in people with CF due to improved hypoxia and reduced fatigue.
Cohen et al. (2014)	42 adult lung transplant recipients (mean age 60 yrs; range 57-64 yrs) CF n=2	14 patients (mean age 60 yrs; range 57-64 yrs) on the transplant waiting list CF n=1	Lung	*Cognitive Outcomes after Lung Transplantation (COLT);* retrospective; median time 8mths post transplant	MoCA	MCI was common amongst transplant recipients. Prolong total graft ischemia time was the most significant risk factor for impaired cognition, followed by bilateral transplant (i.e. type of lung) and use of cardiopulmonary bypass.	Functional physical gain (i.e. an increase in distance at the end of physical rehabilitation on the 6 minute walk test) was associated with improved cognitive function.

Authors (year)	People with CF	Control Group	Type of Transplant	Study design	Cognitive assessment	Results	Comments
Smith et al. (2014)	201 adult lung transplant recipients (mean age 49.1 yrs (SD 13.2 yrs). CF n=39, (mean age 30.2 yrs (SD 8.0 yrs).	N/A	Lung	*INSPIRE study*, Prospective, Longitudinal; followed up for a mean of 9.2 (4-12) yrs	TMT (A,B), Ruff 2 and 7 Selective Attention Test, Stroop, COWA, Animal Naming Test, WMS-R (Logical memory, verbal paired associates), WAIS-R (digit span)	Lower executive function and memory scores were independently associated with greater mortality.	Pre-transplant cognitive function has also been shown to be a predictor for mortality. Although people with CF had the longest average survival (5.4 yrs), these results have implications for people who may exhibit poor cognitive functioning in the period just after transplantation.
Smith et al. (2015)	Transplant recipients: Adults with CF (n=11; mean age 52.7 yrs, SD 16.8 yrs). Other respiratory disorders (COPD, IPF, other) n=52.	N/A	Lung	Prospective. Pre-transplant (cognition was measured 4 wks prior to transplant)	RBANS, TMT (A,B)	Delirium was lower in adults with CF following lung transplantation compared to other respiratory disorders but poor cognitive functioning was a risk factor for delirium. Demographic and medical predictors were not risk factors.	Pre-transplant cognitive function is a predictor for morbidity. People with CF with poor cognitive function pre-transplant may develop delirium, and also have greater mortality post-transplant.

KEY: BAS, British Ability Scales; COPD, Chronic Obstructive Pulmonary Disease; COWA, Controlled Oral Word Association; IPF, Idiopathic Pulmonary Fibrosis; MoCA, Montreal Objective Cognitive Assessment; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SD, standard deviation; TMT (A,B), Trail Making Test (part A, part B); WAIS-R, Wechsler Adult Intelligence Scale-revised; WMS –R, Wechsler Memory Scale- Revised

7.1.4   Aims of Study 3

Section 7.1.2.1 and 7.1.2.2 showed that diabetes is common comorbidity in post transplantation recipients with CF. No studies have investigated whether the profile of cognitive function in people with CFRD following transplantation occurs as a result of improved glycaemic control in conjunction with improved respiratory health. Study 1 (Chapter 5) showed that people with CFRD who have not undergone transplantation have some degree of cognitive impairment compared to healthy controls. The study also found CANTAB to be sensitive in detecting subtle differences between people with CFRD and CFND. It was therefore proposed that the same cognitive battery would be sensitive in detecting subtle differences between post transplant people with CFRD and people with CFRD who have not undergone transplantation. Hence, the first aim of the study reported in this chapter was to investigate cognitive function in people with CFRD who have undergone transplantation (for clarity and conciseness referred to as CFRDTx) compared to people with CFRD who have not undergone transplantation (CFRD) and healthy controls. This study is cross-sectional due to time limitations of the PhD and the small number of patients registered to the Leeds Adult CF Unit undergoing successful transplantation per year. Of the 399 patients registered to this Unit, there are 45 people with CFRDTx. Furthermore, this study did not solely focus on the effect of lung transplantation due to the progressive nature of CF disease. It is likely people would have received more than one transplant, or experienced end stage disease in another organ, e.g. the liver, before end stage lung disease occurs. To reduce practice effects on the cognitive tests, the present study contained a subsample of people with CFRD from study 1. A subsample of healthy controls was also appropriate to use from study 1 given people with CFRDTx tend to be older. The second aim was to investigate whether people with CFRDTx report subjective cognitive impairments compared people with CFRD and a healthy control group. Factors associated with cognitive functioning such as sleep quality, stress and mood may be improved following transplantation, due to reduced fatigue and better quality of life. Hence, the third aim was to investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness) between people with CFRDTx, people with CFRD and healthy controls.

7.2   Method

7.2.1   Design

A between subjects design with three groups; (i) people with CFRD who have undergone transplantation (CFRDTx), (ii) people with CFRD who have not undergone transplantation (CFRD) and (iii) healthy controls.

7.2.2   Participants

18 PI people with insulin treated CFRDTx were recruited from the regional adult CF Unit in Leeds. Participants were recruited according to the inclusion and exclusion criteria below

(section 7.2.2.1 and 7.2.2.2; table 7.2 and 7.3). Data from a sub sample of people with CFRD and healthy controls who had participated in study 1 were used to act as comparison groups. People with CF were matched as closely as possible on at least one genotype. Across the three groups, participants were matched as closely as possible on gender, age and education level (defined by highest level of qualification achieved).

7.2.2.1 Participant inclusion criteria

Table 7.2 Study 3. Inclusion criteria for people with CFRDTx, people with CFRD and healthy control group

People with CFRDTx	People with CFRD	Healthy control group
Recipient of an organ transplant	Aged over 16 years of age	Aged over 16 years of age
Aged over 16 years of age	PI	In good health and not taking any regular medication (excl. contraceptive preparations)
PI	Diabetes/ positive OGTT screen and treated with insulin	Adequate comprehension of English (written and verbal)
Insulin treated CFRD/ post transplant diabetes	Adequate comprehension of English (written and verbal)	Able to provide Informed Consent
Adequate comprehension of English (written and verbal)	Able to provide Informed Consent	
Able to provide Informed Consent		

These inclusion criteria were required for the following reasons. Research which has investigated the effect of cognitive function in pre and post transplant adults with CF has solely focused on lung or heart-lung transplant. Due to the small number of people with CFRDTx registered to Leeds Adult CF Unit, it was decided type of transplantation would not be restricted, particularly as people may have had more than one transplant due to different stages of CF disease in organs. Transplant history was recorded. As mentioned in Chapter 1 (section 1.2) and section 7.1.2.2, people with CF who are PI are more likely to have gene mutations from class I, II or III, a more severe disease phenotype and develop diabetes. OGTT's were not performed in people with CFRDTx due to the interaction with immunosuppressive medication. CFRDTx participants either had a confirmed diabetes diagnosis (home blood glucose monitoring to confirm the OGTT diabetic result) pre transplant, or presence of post transplant diabetes confirmed with CGM, and basal and bolus insulin therapy had commenced. People with CFRD had received a confirmed diabetes diagnosis and had commenced insulin therapy as reported in Study 1 (section 5.2.2). As mentioned in Study 1, the cognitive tests required participants to understand verbal instructions and one test required them to learn a list of English words, therefore adequate comprehension of English was required.

7.2.2.2 Participant exclusion criteria

Table 7.3 below shows the exclusion criteria for people with CFRDTx, people with CFRD and healthy controls. The reasons for the exclusion criteria have already been outlined in Chapter 5, section 5.2.2.2.

Table 7.3 Study 3. Exclusion criteria for people with CF (CFRD and CFRDTx) and healthy control group

People with CFRDTx	People with CFRD	Healthy control group
Pregnant or been within the past 6 months	Pregnant or been within the past 6 months	Pregnant or been within the past 6 months
Continuous oxygen therapy	Continuous oxygen therapy	Diabetic or known impaired glucose tolerance
Overnight oxygen therapy	Overnight oxygen therapy	Been the recipient of a transplant
	Been the recipient of a transplant	Not a match to people with CF based on gender, age, and education level

7.2.3 Cognitive Tests

The CANTAB cognitive test battery and the same test versions used in Study 1 were used in this study. Details of these tests and outcome measures can be found in Chapter 5 (section 5.2.3).

7.2.4 Questionnaires

The following self report measures were administered and recorded using pencil and paper. Details of these can be found in Chapter 5.

- The Leeds Sleep Evaluation Questionnaire (LSEQ) - modified (previous night and last week; see section 5.2.4.1)
- The Perceived Stress Scale (PSS) – modified (previous week and month; see section 5.2.4.2)
- Hospital Anxiety and Depression Scale (HADS; see section 5.2.4.3)
- Ratings of Mood and Mental Alertness (see section 5.2.4.4)
- Cognitive Test Evaluation Questionnaire (CTEQ; see section 5.2.4.5)
- Cognitive Failures questionnaire (see section 5.2.4.6)
- Debriefing questionnaire (see section 5.2.4.7)

7.2.5 Physiological Measures

7.2.5.1 Blood glucose

Participants were asked to fast for two hours before the testing session and a single blood glucose measurement was taken using the same procedure as study 1 (see Chapter 5, section 5.2.5.1). Post transplant medication can also affect blood glucose levels in addition

to factors associated with CF. Therefore people with CFRDTx were required to have blood glucose levels between 4 and 15mmol/L and where possible euglycaemic. Blood glucose levels for people with CFRD and healthy controls are reported in 5.2.5.1.

7.2.5.2 Carbon monoxide

Carbon monoxide levels were monitored using the same procedure as in Study 1 (Chapter 5, section 5.2.5.2).

7.2.6 Screening and testing procedure

Screening and testing sessions followed the same procedures as Study 1 (see Chapter 5, section 5.2.6.1 and 5.2.6.2). Figure 7.1 below summarises the procedure.
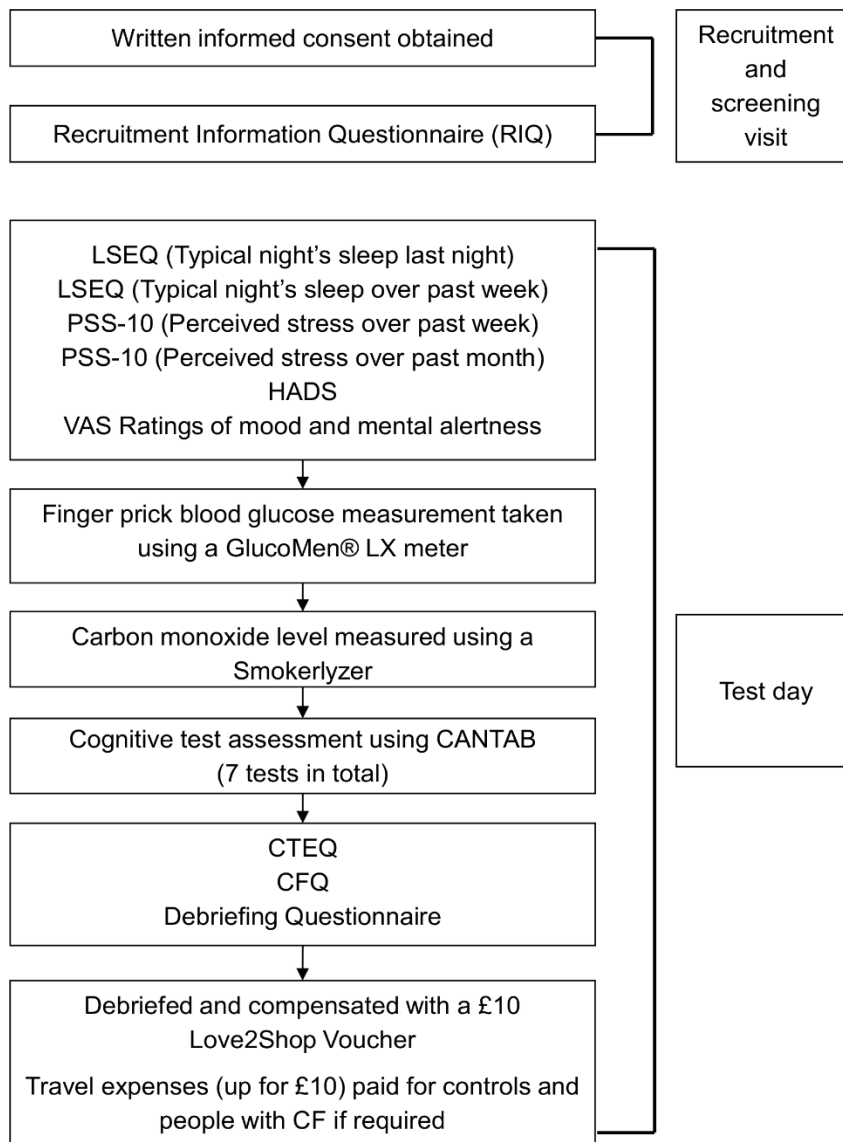
Figure 7.1 Study 3 flow diagram to indicate the order of screening and test day procedures

7.2.7 NHS Ethical Approval

This study was approved by the Leeds West REC (REF: 13/YH/0219, amendment 1; 6th October 2014) and Leeds Teaching Hospitals NHS Trust R&D (27th October 2014). This study was also added to the NIHR CRN Portfolio database and received CRN support.

The informed consent of each participant was obtained in writing prior to commencement of the study. At screening, participants were given written and verbal information about the purpose of the study, and all procedures involved, and what was required of them during participation. Participants received a £10 Love2Shop voucher for completing the testing session. Travel expenses were also reimbursed (up to the value of £10) for controls, and for people with CF if testing was completed on the Unit outside of their allocated appointment and testing at their home was not feasible.

7.2.8 Analysis

7.2.8.1 Method of analysis

The same statistical analysis approached used in Study 1 was employed for Study 2 (See Chapter 5.2.8.2). Participant characteristics relevant to this study were also compared e.g. diabetes duration of CFRD and CFRDTx. However, as age was not significantly different between the groups, it was not included as a covariate in the cognitive or subjective data analysis.

7.3 Results

7.3.1 Participant Characteristics

Table 7.4 shows the participant characteristics for the three groups (people with CFRDTx, people with CFRD and healthy control group).

Table 7.4 Study 3. Participant characteristics (CFRDTx, CFRD and healthy controls) at screening

	People with CFRDTx n=18 Mean (SE)	People with CFRD n=18 Mean (SE)	Healthy control group n=18 Mean (SE)	F (2,51)	*p* value	η_p^2
Gender (n=male)	8	8	8			
Age (years)	40.06 (2.05)	36.22 (1.52)	37.44 (2.17)	1.03	.37	.039
Education (n=degree or higher)	5	5	5	4.08	.998[69]	
Occupation (n=employed full time)	7	3	11	21.75	.003[70]	
Townsend Score	-1.54 (0.54)	-1.33 (0.63)	0.20 (0.75)	2.13	.13[71]	.077
Height (cm)	167.02 (2.68)	167.09 (2.39)	169.32 (2.43)	0.27	.76	.011
Weight (kg)	62.07 (3.97)	65.34 (3.05)	70.66 (3.54)	1.50	.23	.056
BMI (kg/m^2)	21.86 (0.77)	23.30 (0.87)	24.39 (0.79)	2.44	.097	.087
Health Rating (1-10)	8.22 (0.38)	6.72 (0.34)	7.39 (0.32)	5.42	.007[71]	.175
Blood Glucose (mmol/L)	9.60 (0.68)	8.26 (0.50)	5.63 (0.15)	29.19	<.001[72]	.413
Carbon Monoxide (ppm)	3.94 (0.46)	3.28 (0.17)	3.61 (0.41)	0.36	.70[73]	.013
Carbon monoxide (%COHb)	1.28 (0.07)	1.17 (.03)	1.23 (0.07)	0.44	.65	.017
Anxiety (HADS)	5.72 (0.81)	6.94 (1.04)	5.50 (0.65)	0.84	.44	.032
Depression (HADS)	2.67 (0.52)	5.28 (1.03)	2.50 (0.61)	3.16	.051[74]	.110

Table 7.4 shows groups were adequately matched on gender, age, education, Townsend score, height, weight, carbon monoxide readings (ppm and %COHb) and anxiety score. The age range is highest in the CFRDTx group (see Figure 7.2).

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[69] Fishers Exact test, χ^2(12, N=54) = 4.08, *p* = .998
[70] Fishers Exact test, χ^2(10, N=54) = 21.75, *p* = .003
[71] Data were logarithm transformed due to substantial positive skew
[72] Data were logarithm transformed due to substantial positive skew. Assumption of homogeneity of variance was violated; the Welch F-ratio is reported.
F(2, 28.24) = 29.19, *p* < .001
[73] An inverse transformation was applied to data due to severe positive skew. Assumption of homogeneity of variance was violated; the Welch F-ratio is reported. *F*(2, 31.59) = 0.36, *p* = .70
[74] Data were logarithm transformed due to substantial positive skew
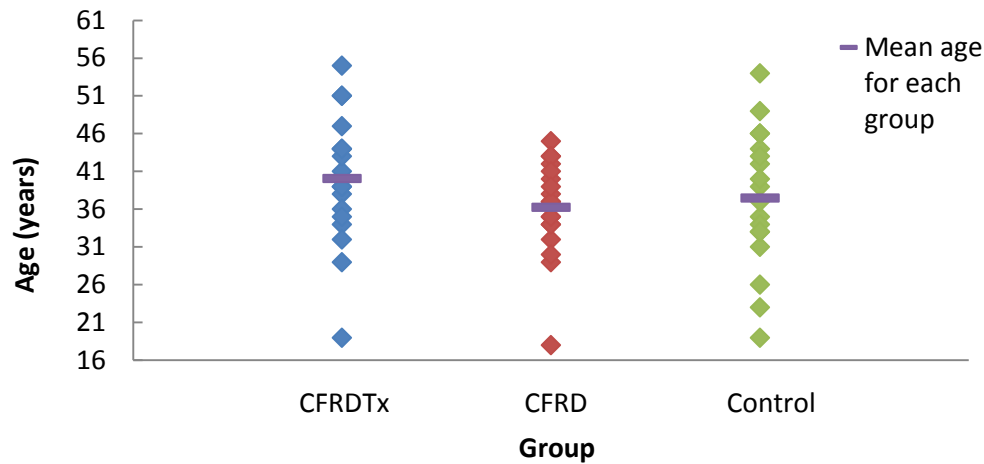
Figure 7.2 Study 3. Distribution of participants' ages for each experimental group (CFRDTx, CFRD and healthy control)

Figures 7.3 and 7.4 show the frequency of educational qualification achieved, and the types of occupation in each group. More people with CFRDTx had achieved GCSE or GCE O level qualifications, whereas more of the controls and people with CFRD had achieved Diplomas. There was no difference between groups who had achieved Degree level or above qualifications. People with CFRDTx and controls were more likely to be in employment than people with CFRD.
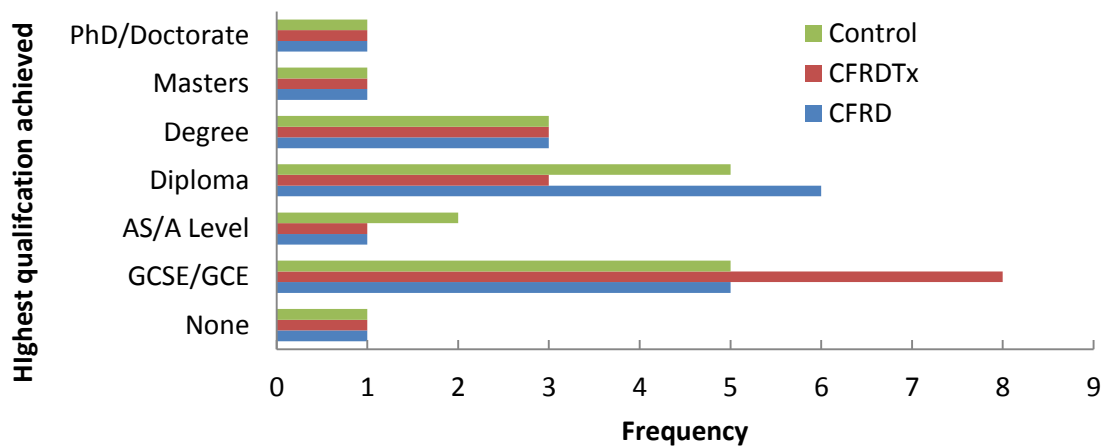
Figure 7.3 Study 3. Frequency of educational qualifications in each experimental group (CFRDTx, CFRD and healthy control)
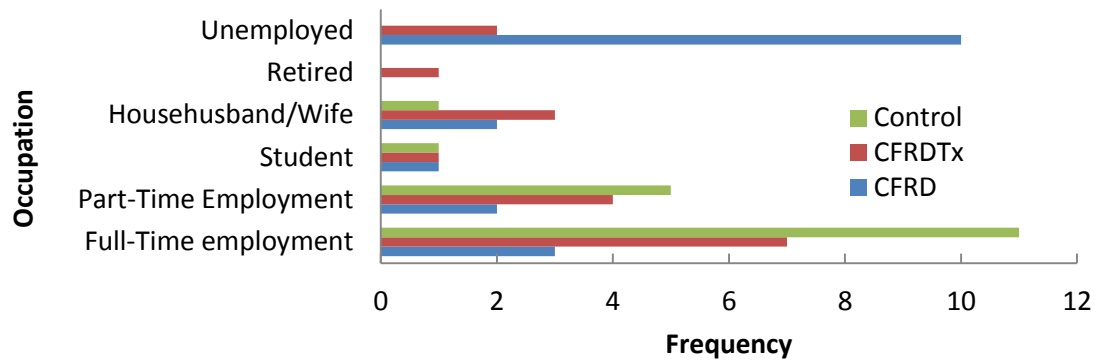
Figure 7.4 Study 3. Frequency of type of occupation in each experimental group (CFRDTx, CFRD and healthy control)

There was a significant difference between groups for fasted blood glucose levels, ratings of health and depression scores and a trend for BMI. People in the CFRDTx group rated their health as significantly better than people with CFRD ($p = .007$) and there was a trend for the CFRDTx group to rate their health as better than controls ($p = .097$). As expected, the control group had significantly lower blood glucose scores than people with CFRD ($p < .001$) and people with CFRDTx ($p < .001$; see Figure 7.5).
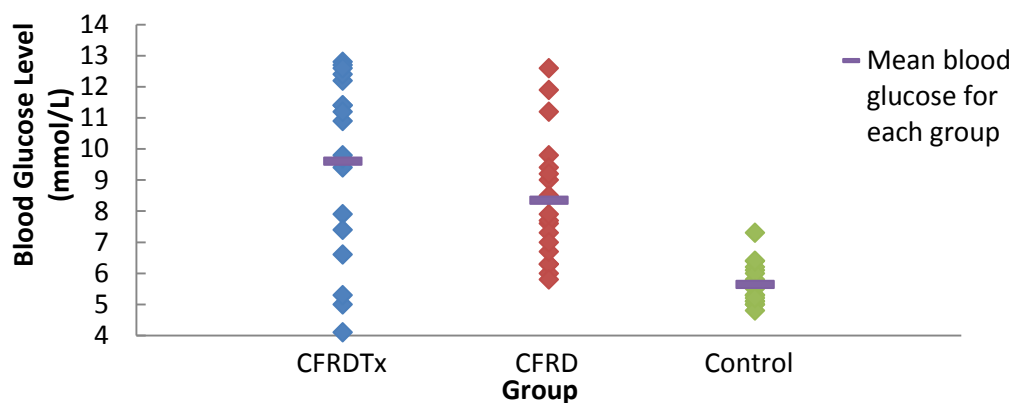
Figure 7.5 Study 3. Distribution of (capillary) blood glucose measurements in each experimental group (CFRDTx, CFRD and healthy control)

There was a trend for people with CFRD to score higher on the depression scale than people with CFRDTx ($p = .06$; see Figure 7.6). People with CFRDTx and controls scored within the normal range, while people with CFRD had up to moderate scores of depression.
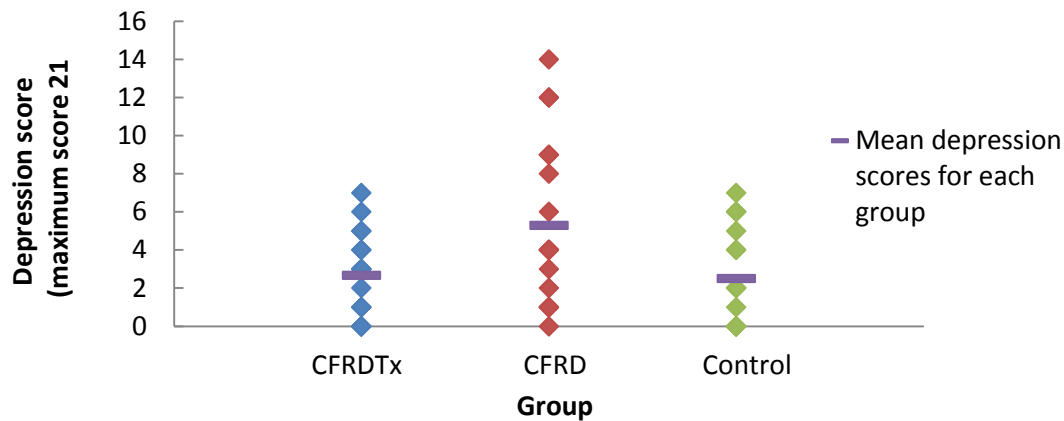
Figure 7.6 Study 3. Distribution of depression scores (measured using the HADS) for each experimental group (CFRDTx, CFRD and healthy control)

There was a trend for people in the CFRDTx to have a lower BMI than control group ($p = .097$; see Figure 7.7).
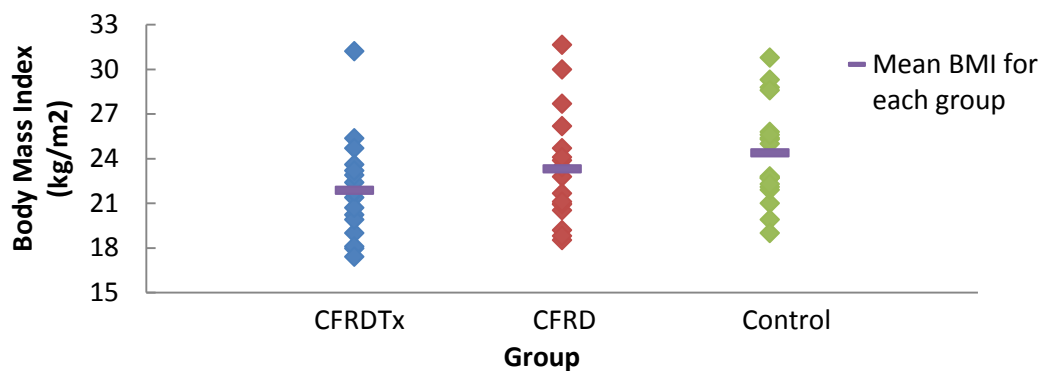
Figure 7.7 Study 3. Distribution of BMI for each experimental group (CFRDTx, CFRD and healthy control)

Table 7.5 shows the type of transplantation people in the CFRDTx group have received, and Table 7.6 shows the clinical characteristics of the CFRD and CFRDTx participants.

Table 7.5 Study 3. Frequency of transplant type in the CFRDTx group

Type of transplant	Frequency
Bilateral lung	13
Heart and double lung	2
Double lung and kidney	2
Liver	1

Table 7.5 shows that most of the CFRDTx group had received a lung transplant. Transplantation of more than one type of organ was present in 4 participants which reflects CF affecting many organs in the body, not just the lungs. Progression of CF disease was

evident in the two people who had received both lung and kidney transplants. The kidney transplant was performed after 10.5 and 12.5 years respectively following lung transplantation.

Table 7.6 Study 3. Clinical Characteristics of people with CFRD (i.e. CFRDTx and CFRD)

	CFRDTx (n=18) Mean (SE)	CFRD (n=18) Mean (SE)	F (1,27)	p value	η_p^2
Heterozygous F508del (n)	16	18	1.99	.49[75]	
P. aeruginosa infection (n)	7	14	10.61	.009[76]	
Age at CF diagnosis (yrs)	3.28 (1.32)	1.43 (0.47)	0.006	.94[77]	<.001
Duration since (first) transplantation	9.32 (1.53)	-			
Duration of diabetes (yrs)	11.92 (1.54)	13.83 (1.76)	0.67	.42	.019
FEV$_1$	2.38 (0.21)	1.69 (0.20)	5.56	.024	.141
FEV$_1$%predicted	74.39 (5.97)	50.28 (5.76)	8.46	.006	.199
FVC	3.30 (0.23)	2.77 (0.26)	2.33	.14	.064
FVC % predicted	85.50 (3.56)	70.44 (5.94)	5.16	.03[78]	.132
Oxygen saturation (%)	97.56 (0.32)	96.44 (0.48)	3.74	.061	.099
HbA1c (mmol/mol; IFCC)	59.67 (4.85)	58.33 (4.09)	0.03	.87[79]	.001
Plasma blood glucose	8.11 (1.11)	8.09 (0.95)	.01	.91[79]	<.001
Patients with microvascular complications	0	0			
SBP (mmHg)	124.33 (3.08)	130.89 (3.97)	1.70	.20	.048
DBP (mmHg)	78.94 (2.14)	78.83 (2.03)	.001	.98[79]	<.001
Pulse (bpm)	96.00 (3.37)	91.67 (3.95)	.78	.39[79]	.022
Receiving IV's (n)	1	5	3.20	.089[80]	
CRP (mg/L)	14.47 (4.69)	12.86 (2.87)	.012	.91[81]	<.001
Vitamin A (ng/mL)	2.33 (0.21)	1.64 (0.11)	8.48	.006	.200
Vitamin D (ng/mL)	62.36 (5.30)	81.92 (5.77)	6.24	.018	.155
Vitamin E (ng/mL)	32.23 (2.44)	30.41 (1.88)	0.35	.56	.010
Serum creatinine (µmol/L)	119.33 (13.30)	65.78 (5.67)	21.38	<.001[82]	.386
Serum urea (mmol/L)	9.34 (0.87)	5.32 (0.49)	22.00	<.001	.393
Albumin (g/L)	41.17 (0.80)	42.44 (1.05)	0.94	.34	.027

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[75] Mutation 1, χ^2(2, N= 36) = 1.99, p = .049. Mutation 2, χ^2(12, N=36) = 13.99, p = .024.
[76] Fishers Exact Test χ^2(4, N = 36) = 10.51, p = .009.
[77] Data were logarithm transformed due to substantial positive skewness
[78] Data were square root transformed (but not reflected) due to moderate negative skewness.
[79] Data were square root transformed due to moderate positive skewness
[80] Chi Square test, χ^2(1, N=18) = 3.20, p = .089.
[81] Data were reflected and an inverse transformation applied due to severe positive skewness
[82] Dara were logarithm transformed due to substantial positive skewness

Table 7.6 shows there were no significant differences between the two CF groups (CFRD, CFRDTx) for gene mutation, age at CF diagnosis, duration of CFRD, HbA1c, plasma blood glucose, FVC, SBP, DBP, pulse, CRP, Vitamin E, Albumin and the presence of (no) microvascular complications. There were, however, significant differences between groups for pulmonary infection, FEV1, FEV1% predicted, FVC % predicted, Vitamin A and D, serum creatinine and urea. There was also a trend for higher frequency of people with CFRD receiving IV treatment at the time of testing and lower oxygen saturation levels relative to those in the CFRDTx group. Most of these differences are to be expected due to the majority of the CFRDTx group having undergone lung transplantation. The lower number of CFRDTx group being on IVs at the time of testing, the trend for higher oxygen saturations levels, and the lower frequency of pulmonary infection is reflective of improved lung health. The person with CFRDTx was at the end of IV treatment, while in the CFRD group, 2 people were mid IV treatment and 3 at the end of treatment. Figure 7.8 shows the various lung function measures with higher scores in the CFRDTx as a function of having undergone transplantation.
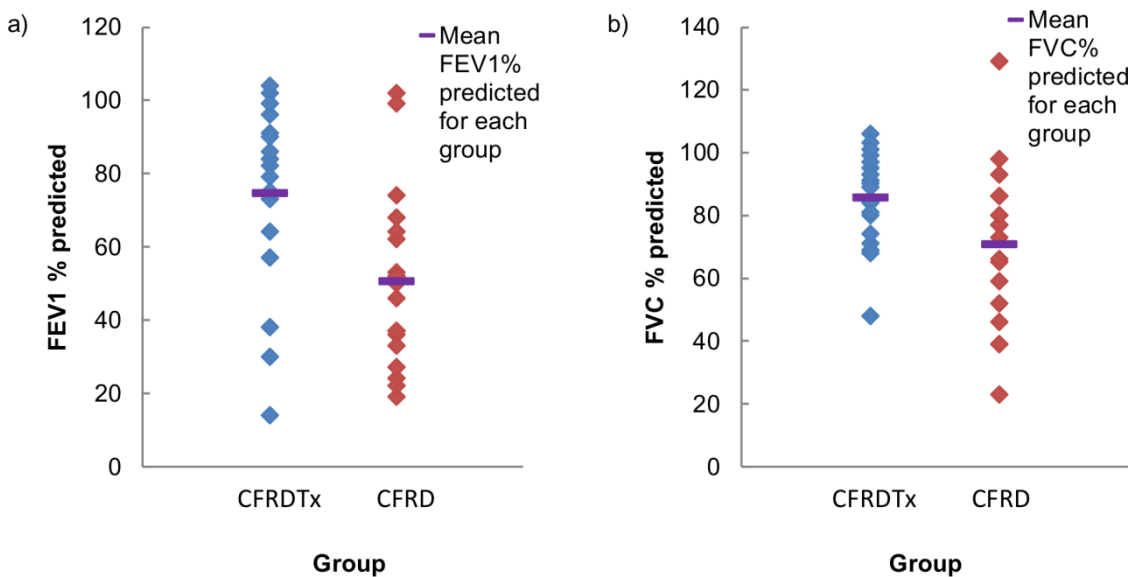
Figure 7.8 Study 3. Lung function scores (a) FEV1%, and (b) FVC% predicted) in people with CFRD and CFRDTx

The significantly higher levels of serum creatinine and urea in the people with CFRDTx are likely to be the result of nephrotoxic post transplant medication in addition to CF disease (see Figure 7.9).
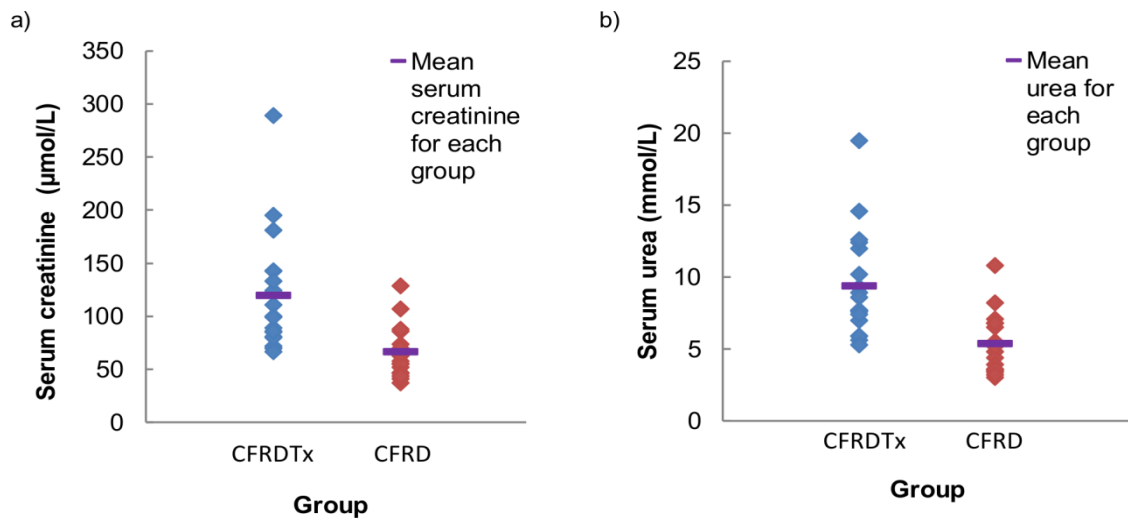
Figure 7.9 Study 3. Distribution of serum creatinine (a) and urea (b) in people with CFRD

7.3.2 Questionnaires

7.3.2.1 Leeds Sleep Evaluation Questionnaire (LSEQ)

7.3.2.1.1 Ease of getting to sleep

Data showed a bimodal distribution with a slight positive skew for both previous night and last week. Therefore, a square root transformation was applied to the data. There was no significant main effect of time, $F(1, 51) = 1.08$, $p = .30$, $\eta_p^2 = .021$, therefore there was no difference in how easy it was to get to sleep the night before the testing session compared to the previous week (see Figure 7.10). There was no effect of group, $F(2, 51) = 2.06$, p $= .14$, $\eta_p^2 = .075$, or time*group interaction, $F(2, 51) = 0.22$, $p = .98$, $\eta_p^2 = .001$.
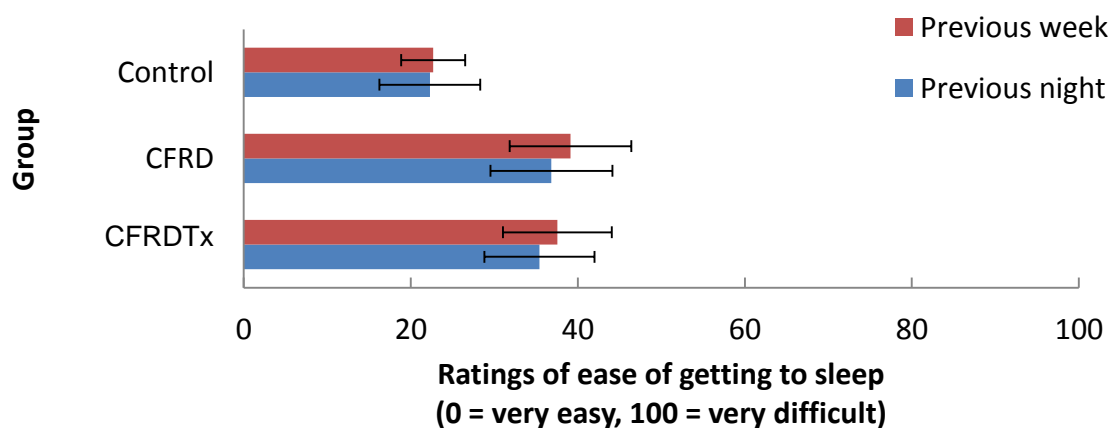
Figure 7.10 Study 3. Mean ratings of ease of getting to sleep (±SE) for the night before the testing session and previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.2 Time to get to sleep

Data showed a moderate positive skew for both previous night and last week. Therefore, a square root transformation was applied to the data. There was a significant main effect of time, $F(1, 51) = 5.64$, $p = .02$, $\eta_p^2 = .100$, such that participants were quicker to get to sleep the night before the testing session compared to the previous week (see Figure 7.11). There was a trend for a main effect of group, $F(2, 51) = 2.43$, p $= .099$, $\eta_p^2 = .087$, but there were no differences between groups on the post hoc tests. There was no significant time*group interaction, $F(2, 51) = 0.29$, $p = .75$, $\eta_p^2 = .011$.
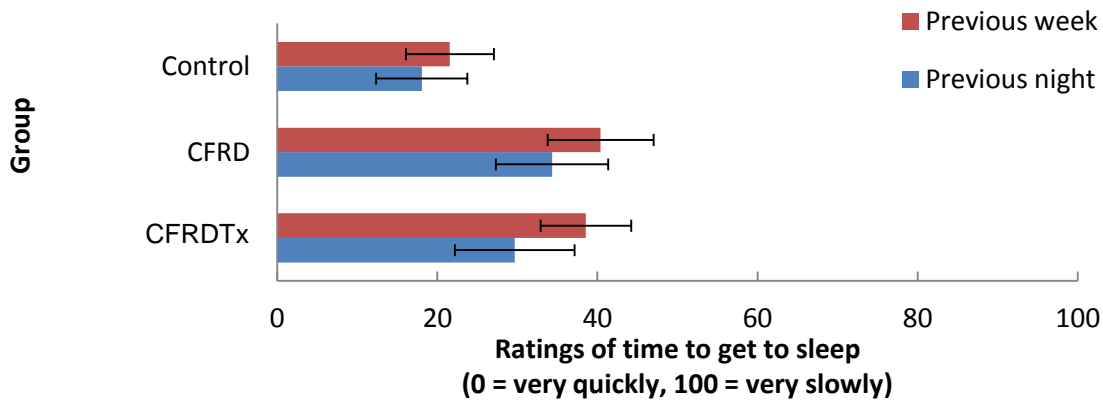
Figure 7.11 Study 3. Mean ratings of time to get to sleep (±SE) for the night before the testing session and previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.3 Restfulness of sleep

There was no significant main effect of time, $F(1, 51) = 0.89$, $p = .35$, $\eta_p^2 = .017$, such that there was no difference between how restful sleep was the night before the testing session compared to the previous week (see Figure 7.12). There was a trend for a main effect of group, $F(2, 51) = 2.60$, p $= .084$, $\eta_p^2 = .087$, but no time*group interaction, $F(2, 51) = 0.71$, $p = .50$, $\eta_p^2 = .027$. There was a trend for people in the CFRD group to have more restless sleep than the control group ($p = .087$).
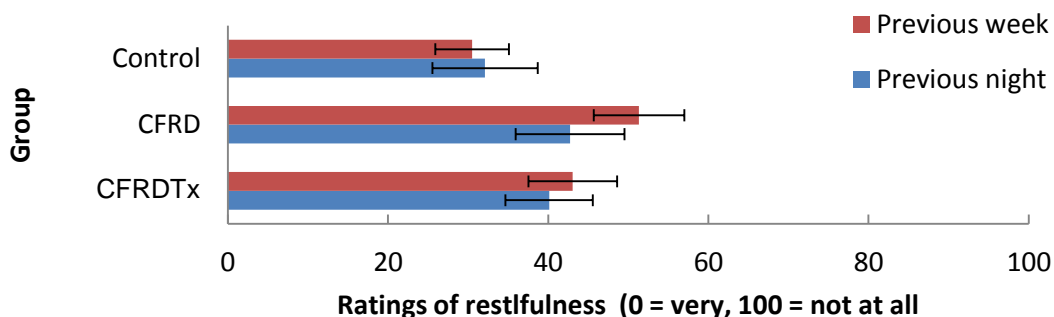
Figure 7.12 Study 3. Mean ratings of restfulness (±SE) during sleeping for the night before the testing session and previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.4 Wakefulness

Data showed a moderate positive skew for both previous night and last week. Therefore, a square root transformation was applied to the data. There was a significant main effect of time, $F(1, 50) = 6.84$, $p = .012$, $\eta_p^2 = .120$, such that participants had less periods of wakefulness the night before the testing session compared to the previous week (see Figure 7.13). There was a significant main effect of group, $F(2, 50) = 3.30$, p = .045, $\eta_p^2 = .117$, but no time*group interaction, $F(2, 50) = 0.54$, $p = .58$, $\eta_p^2 = .021$. Post hoc tests showed that there was a trend for people in the control group to report less periods of wakefulness than people with CFRD ($p = .071$).
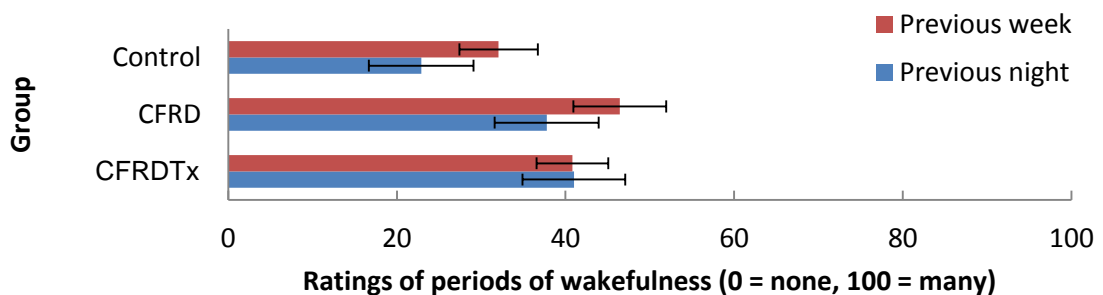
Figure 7.13 Study 3. Mean ratings of periods of wakefulness (±SE) during sleeping for the night before the testing session and previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.5 Ease of waking

Data showed a moderate positive skew for both previous night and last week. Therefore, a square root transformation was applied to the data. There was no significant main effect of time, $F(1, 51) = 0.05$, $p = .83$, $\eta_p^2 = .001$, such that participants' ease of waking was not different night before the testing session compared to the previous week (see Figure 7.14). There was no time*group interaction, $F(2, 51) = 0.64$, $p = .53$, $\eta_p^2 = .025$. There was a trend for a significant main effect of group, $F(2, 51) = 2.46$, p = .095, $\eta_p^2 = .088$. Post hoc tests showed that there was a trend for people in the control group to wake up easier than people with CFRD ($p = .093$).
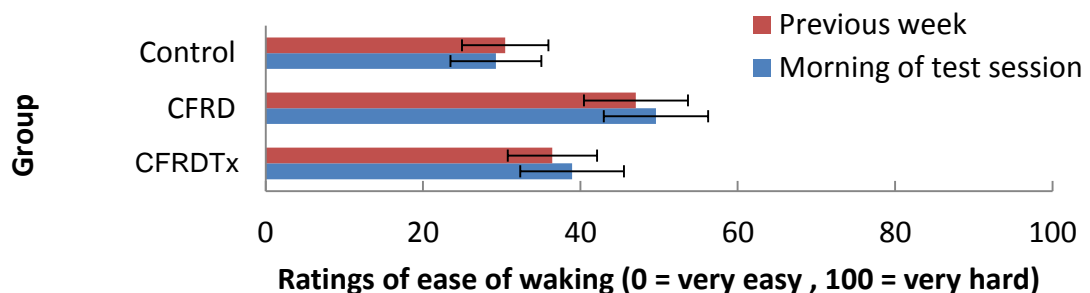
Figure 7.14 Study 3. Mean ratings of ease of waking (±SE) for the morning of the testing session and previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.6 Waking duration

Data showed a moderate negative skew for last week. Therefore, a square root transformation was applied to the data. There was no significant main effect of time, $F(1, 51) = 0.40$, $p = .53$, $\eta_p^2 = .008$, such that participants' duration of waking was not different night before the testing session compared to the previous week (see Figure 7.15). There was no time*group interaction, $F(2, 51) = 0.20$, $p = .82$, $\eta_p^2 = .008$, and no significant main effect of group, $F(2, 51) = 2.37$, p = .10, $\eta_p^2 = .085$.
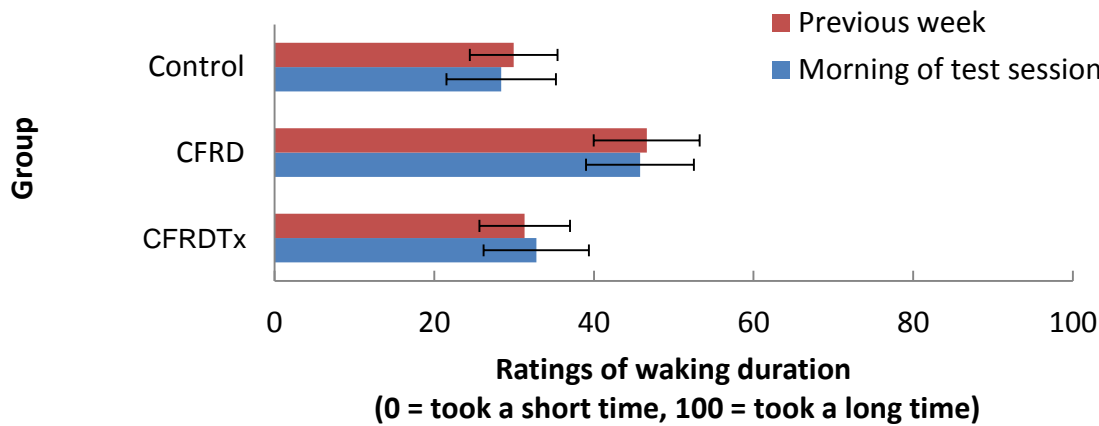
Figure 7.15 Study 3. Mean ratings of waking duration (±SE) on the morning of the testing session and for the previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.7 Alertness on waking

Data showed a moderate positive skew for both previous night and last week. Therefore, a square root transformation was applied to the data. There was no significant main effect of time, $F(1, 51) = 2.10$, $p = .15$, $\eta_p^2 = .040$, such that participants' alertness on waking was not different on the morning of the testing session compared to the previous week (see Figure 7.16). There was no time*group interaction, $F(2, 51) = 0.82$, $p = .62$, $\eta_p^2 = .019$, but a significant main effect of group, $F(2, 51) = 5.51$, p = .007, $\eta_p^2 = .178$, such that people in the control group were significantly more awake than people in the CFRD group ($p = .005$).
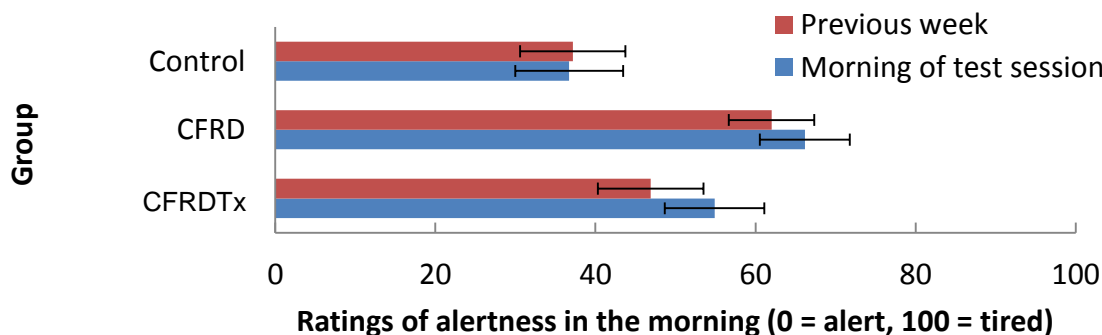
Figure 7.16 Study 3. Mean ratings of alertness (±SE) on the morning of the testing session and for the previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.1.8 Alertness 1hour after waking

Data showed a substantial positive skew for both previous night and last week. Therefore, a logarithm transformation was applied to the data. There was a significant main effect of time, $F(1, 51) = 4.49$, $p = .039$, $\eta_p^2 = .081$, such that participants' were more alert one hour after on waking on the morning of the testing session compared to the previous week (see Figure 7.17). There was a trend for a time*group interaction, $F(2, 51) = 2.45$, $p = .097$, $\eta_p^2 = .088$, but no significant main effect of group, $F(2, 51) = 1.83$, p = .17, $\eta_p^2 = .067$.
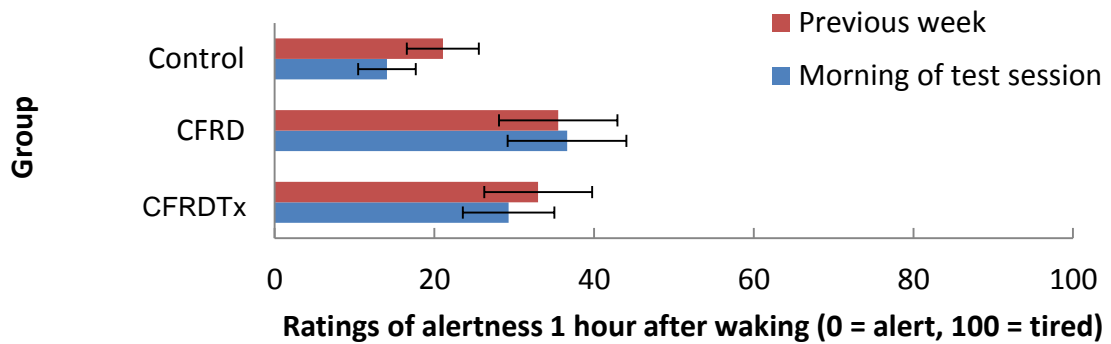
Figure 7.17 Study 3. Mean ratings of alertness 1 hour after waking (±SE) on the morning of the testing session and for the previous week, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.2 Perceived stress (PSS)

Data showed a moderate positive skew for both previous week and last month. Therefore, a logarithm transformation was applied to the data. There was a significant main effect of time, $F(1, 51) = 7.94$, $p = .007$, $\eta_p^2 = .135$, such that participants' were less stressed the week before the testing session compared to the previous month (see Figure 7.18). There was no time*group interaction, $F(2, 51) = 0.41$, $p = .67$, $\eta_p^2 = .016$, but a significant main effect of group, $F(2, 51) = 4.64$, p = .014, $\eta_p^2 = .154$, such that people in the control group were significantly less stressed than people in the CFRD group.
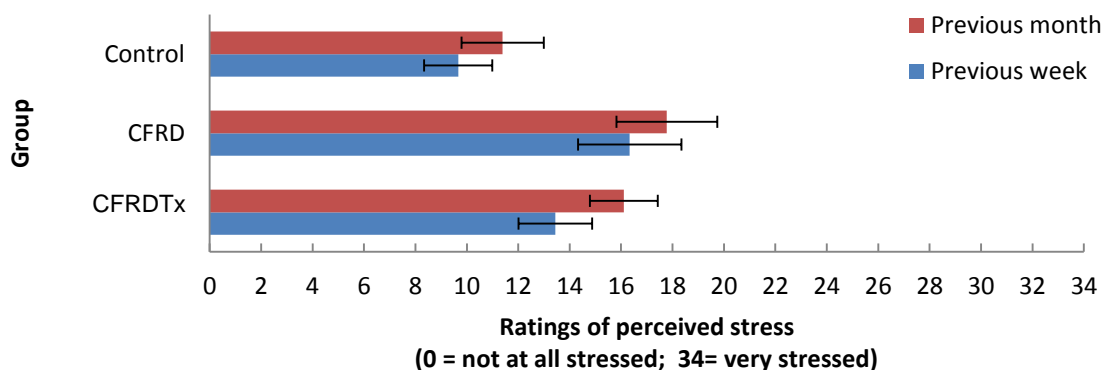
Figure 7.18 Study 3. Perceived stress ratings for the previous month and week before the test session, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3 **VAS Ratings of mood and mental alertness**

7.3.2.3.1 Contentedness

Data were reflected and square root transformed due to moderate negative skewness. There was a significant main effect of group for contentedness, $F(2, 51) = 5.76$, $p = .006$, $\eta_p^2 = .184$ such that those in the control group were significantly more contented than those in the CFRD group ($p = .012$) and the CFRDTx group ($p = .019$; see Figure 7.19).
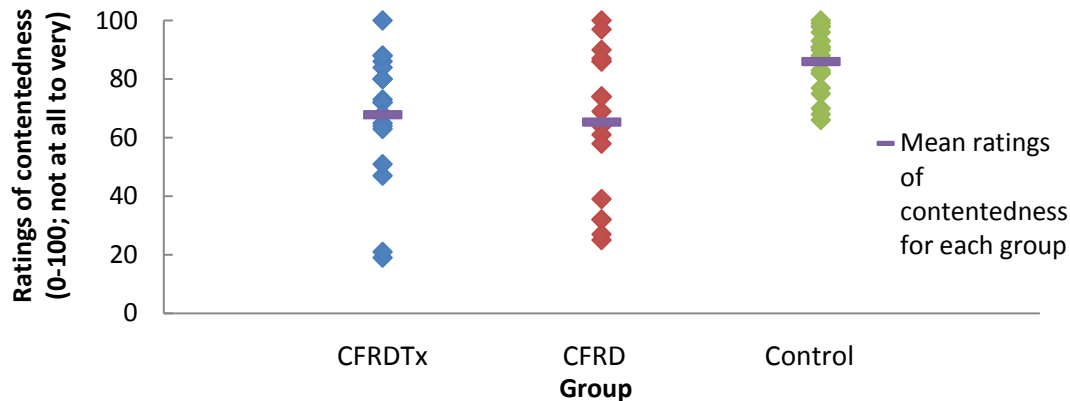
Figure 7.19 Study 3. VAS ratings of contentedness for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3.2 Irritability

Data on irritability were log transformed to correct for negative skewness. There was no effect of group on irritability, $F(2, 51) = 2.10$, $p = .13$, $\eta_p^2 = .076$ (see Figure 7.20).
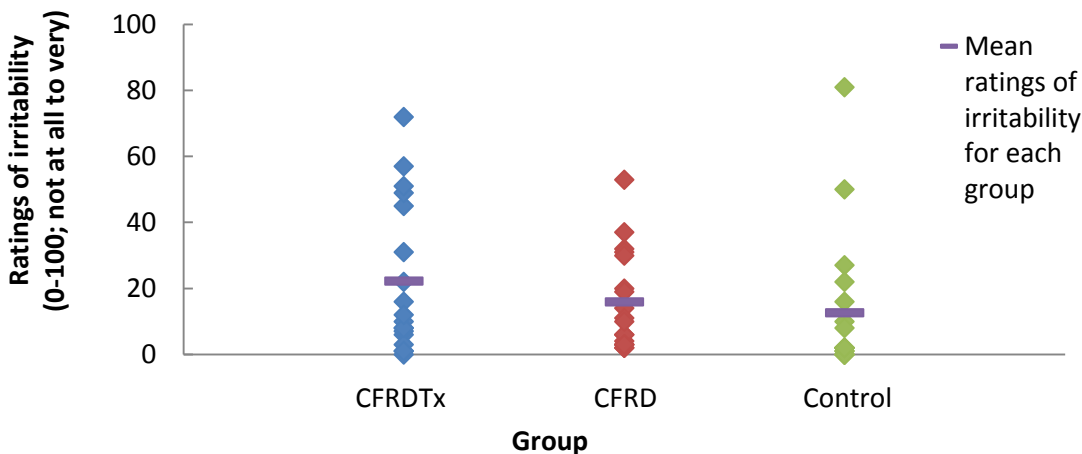
Figure 7.20 Study 3. VAS ratings of irritability for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3.3 Sleepiness

Data were logarithm transformed due to moderate positive skewness. There was a significant main effect of group on sleepiness, $F(2, 51) = 10.41$, $p < .001$, $\eta_p^2 = .290$, such that controls were significantly less sleepy than those with CFRD ($p < .001$) and CFRDTx ($p = .001$; see Figure 7.21).
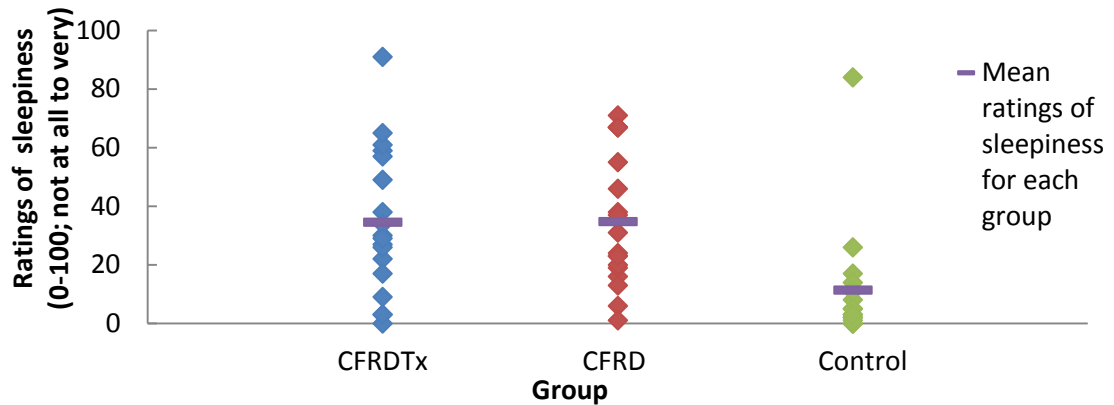
Figure 7.21 Study 3. VAS ratings of sleepiness for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3.4 Mental alertness

Data were reflected and logarithm transformed due to moderate negative skewness. There was for a main effect of group on mental alertness, $F(1, 51) = 4.41$, $p = .017$, $\eta_p^2 = .147$, such that controls reported being more mentally alert than those in the CFRD group ($p = .019$; see Figure 7.22).
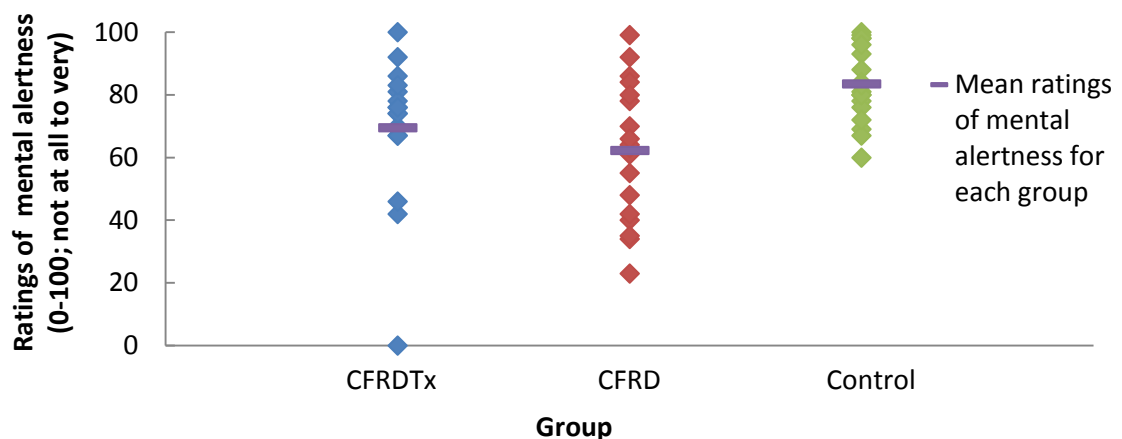
Figure 7.22 Study 3. VAS ratings of mental alertness for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3.5 Ability to concentrate

Data were reflected and square root transformed due to moderate negative skewness. There was a significant main effect of ability to concentrate, $F(2, 51) = 9.26$, $p < .001$, η_p^2

= .266 such that people with CFRD reported a significantly lower ability to concentrate relative to the controls ($p < .001$) and there was a trend for people with CFRDTx to report a lower ability to concentrate relative to the controls ($p = .076$; see Figure 7.23).
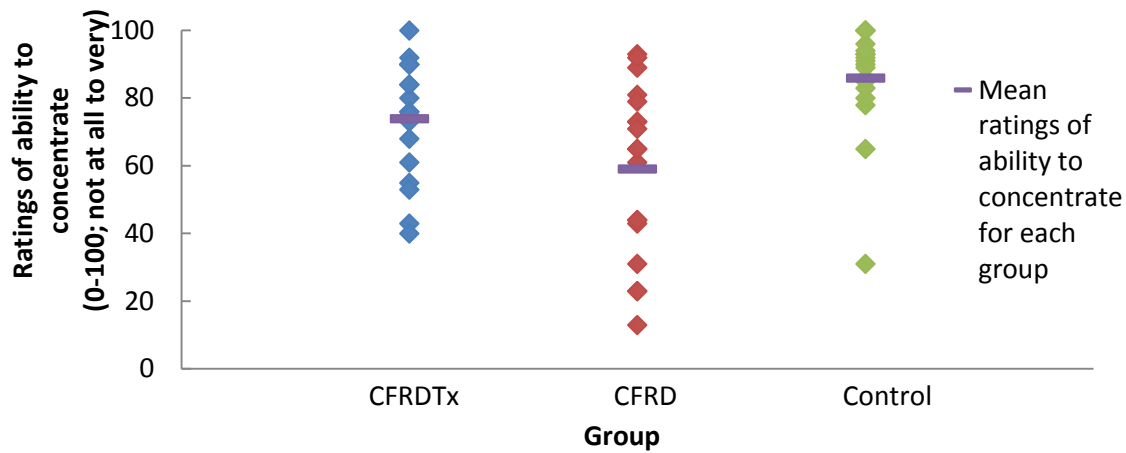
Figure 7.23 Study 3. VAS ratings of ability to concentrate for each experimental group (CFRDTx, CFRD and healthy control)

7.3.2.3.6 Feeling energetic

Data were square root transformed due to slight positive skewness. There was a significant main effect of group for feeling energetic, $F(2, 51) = 3.45$, $p = .039$, $\eta_p^2 = .119$, such that those in the control group reported feeling significantly more energetic than those with CFRD ($p = .050$; see Figure 7.24).
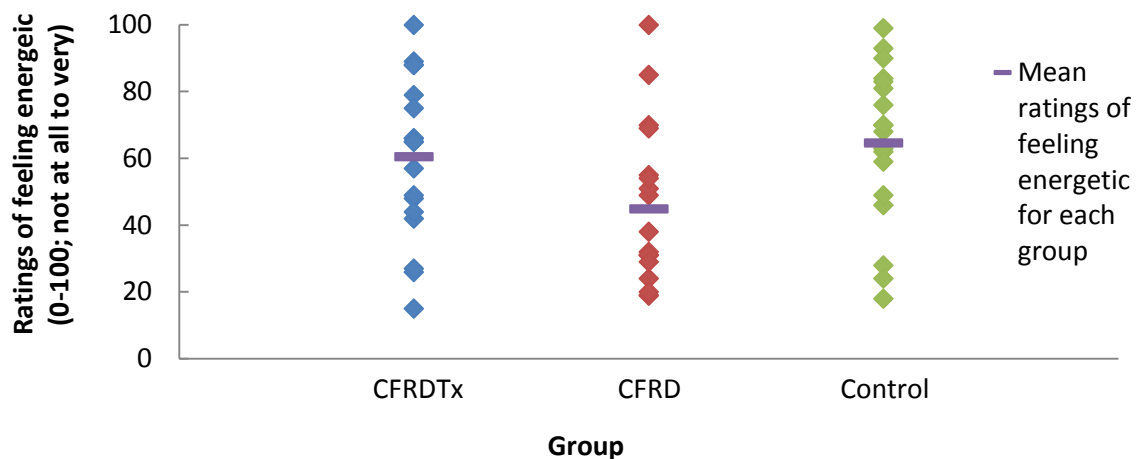
Figure 7.24 Study 3. VAS ratings of feeling energetic for each experimental group (CFRDTx, CFRD and healthy control)

7.3.3 Subjective occurrences of minor daily cognitive errors

Figure 7.25 shows the mean number of subjective occurrences of minor daily cognitive errors which occurred in the previous 6 months reported on the CFQ by each group. There was no significant main effect of group, $F(2, 51) = 1.58$, $p = .22$, $\eta_p^2 = .058$.
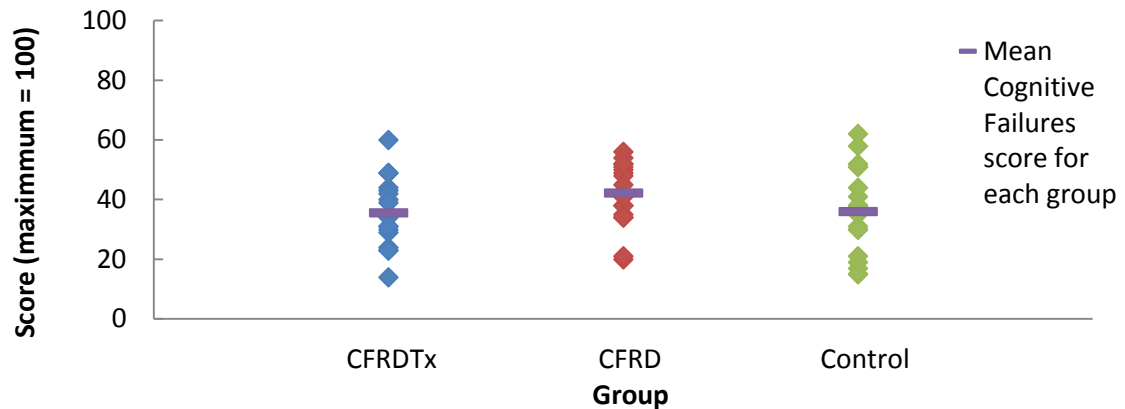
Figure 7.25 Study 3. Cognitive Failures Questionnaire scores for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4 Cognitive Tests

Figure 7.26 shows that the time of day at which testing was completed did not differ between groups, $\chi2(2, N = 54) = 1.04$, $p = .60$. More people with CFRD completed the testing in the afternoon, while more people in the CFRDTx group completed testing in the morning.
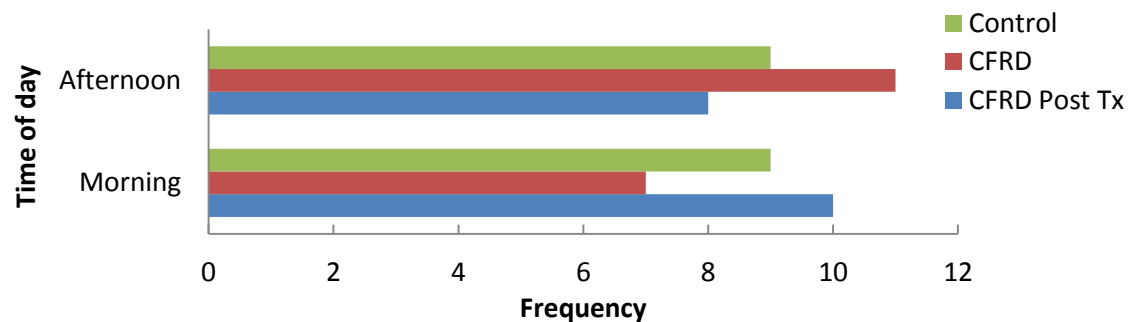
Figure 7.26 Study 3. Frequency of time of day testing was completed for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.1 Motor Screening Test

7.3.4.1.1 Total correct

This outcome measure suffered from ceiling effects and a logarithm transformation was applied to the data. People with CFRD correctly responded to all 10 crosses while the CFRDTx group and control group correctly responded to 9 crosses. There was no significant main effect of group, $F(1,51) = 0.50$, $p = .61$, $\eta_p^2 = .019$.

7.3.4.1.2 Mean error

Mean error is a measurement of accuracy (see Chapter 5, Table 5.4). Data for were logarithm transformed due to substantial positive skewness. There was no main effect of group, $F(2, 51) = 0.25$, $p = .78$, $\eta_p^2 = .010$, ($R^2 = .010$; see Figure 7. 27).
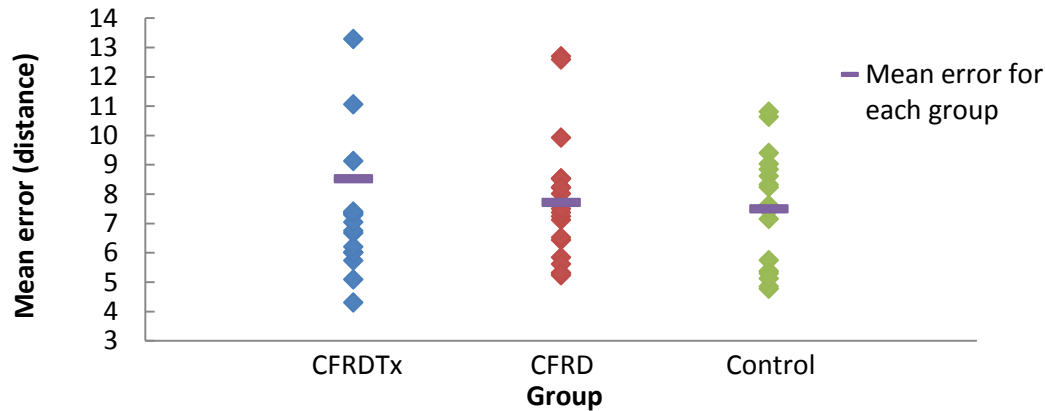
Figure 7.27 Study 3. Mean error (distance; measurement of accuracy) on the MOT, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.1.3 Reaction time for correct responses

Data were square root transformed due to moderate positive skewness. There was no significant main effect of group, $F(2, 51) = 1.27$, $p = .29$, $\eta_p^2 = .047$, ($R^2 = .047$; see Figure 7. 28).
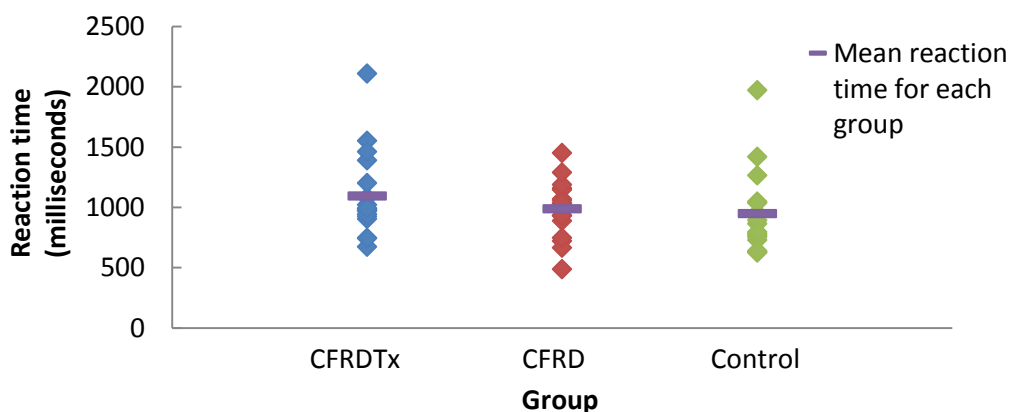
Figure 7.28 Study 3. Reaction time (milliseconds) for correct responses on the MOT, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2 **Paired Associates Learning**

The outcome measures for the PAL test are the same as Study 1 (Chapter 5, section 5.3.4.2; Table 5.4 for a definition of each outcome variable). As the degree of test completion varied

as a function of individual performance, the outcome measure of stages completed was included as a covariate where applicable.

7.3.4.2.1 Stages completed

Data were reflected and an inverse transformation applied due to severe negative skewness. There was no significant main effect of group, $F(2, 51) = 1.00$, $p = .38$, $\eta_p^2 = .038$ ($R^2 = .038$; see Figure 7.29).
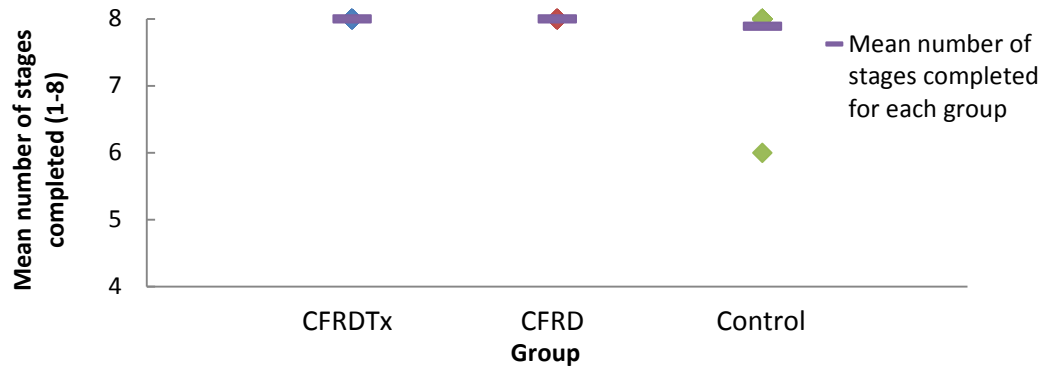
Figure 7.29 Study 3. Number of stages completed on the PAL test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.2 Stages completed on first trial

Stages completed was not a significant covariate, $F(1, 50) = 2.19$, $p = .15$, $\eta_p^2 = .042$. There was no significant main effect of group, $F(2, 50) = 0.47$, $p = .63$, $\eta_p^2 = .018$ ($R^2 = .051$; see Figure 7.30).
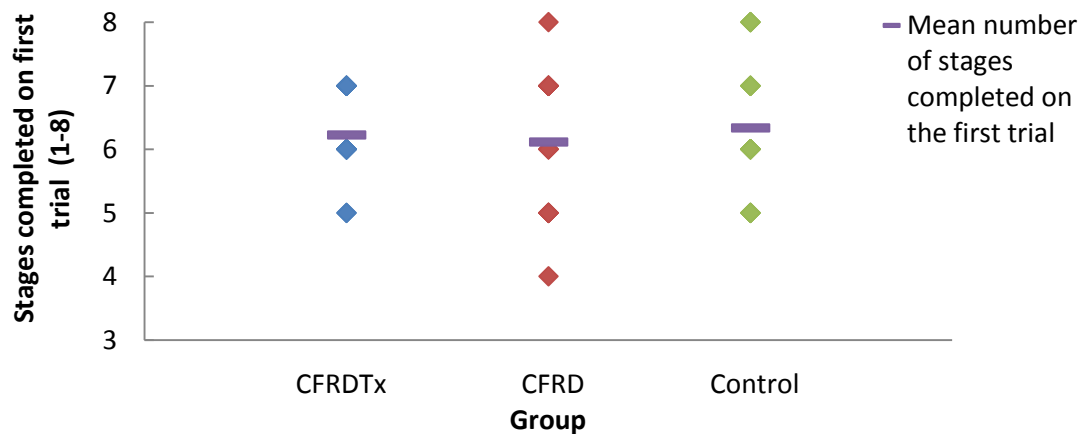
Figure 7.30 Study 3. Number of stages completed on the first trial on the PAL test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.3 First trial memory score

Stages completed was a significant covariate, $F(1, 50) = 11.75$, $p = .001$, $\eta_p^2 = .190$. There was no significant main effect of group, $F(2, 50) = 0.46$, $p = .63$, $\eta_p^2 = .018$ ($R^2 = .192$; see Figure 7.31).
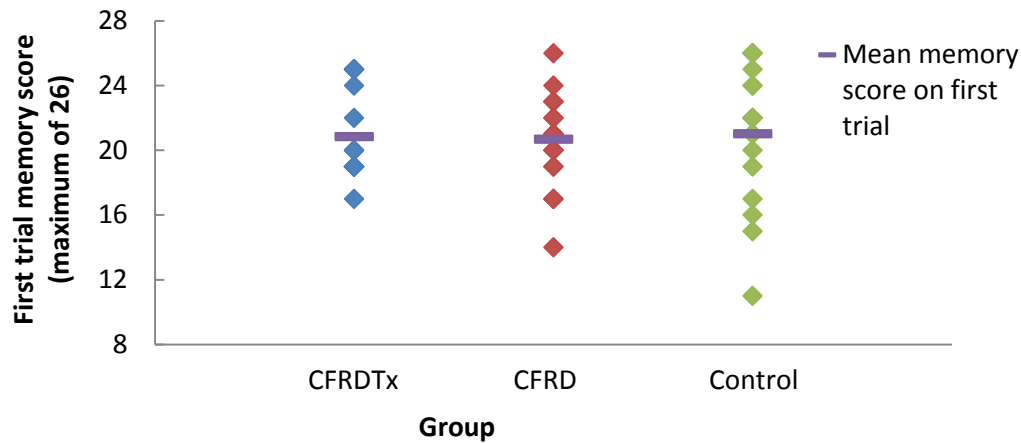
Figure 7.31 Study 3. First trial memory score on the PAL test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.4 Total trials

Data were logarithm transformed due to substantial positive skewness. Stages completed was a significant covariate, $F(1, 50) = 6.35$, $p = .015$, $\eta_p^2 = .113$. There was no significant main effect of group, $F(2, 50) = 1.93$, $p = .16$, $\eta_p^2 = .072$ ($R^2 = .147$; see Figure 7.32).
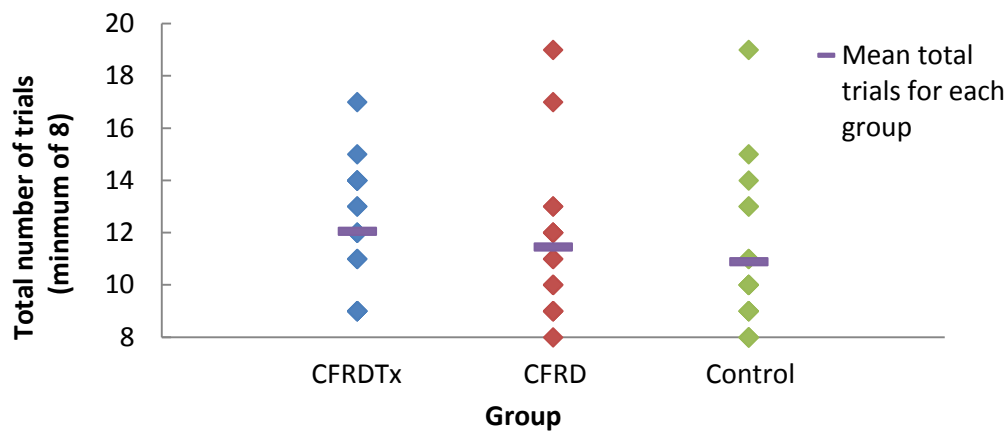
Figure 7.32 Study 3. Total trials on the PAL test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.5 Total trials at n-patterns

4 data points were excluded as outliers. Age was a significant covariate, $F(1, 50) = 5.18$, $p = .027$, which indicated that younger participants performed better than older participants. There was no group*level interaction $F(8, 199) = 1.42$, $p = .19$. There was no significant main effect of group, $F(2, 50) = 0.93$, $p = .40$ (AICC = 610.4). As expected, there was a significant main effect of level, $F(4, 201) = 33.02$, $p < .0001$ (see Figure 7.33).
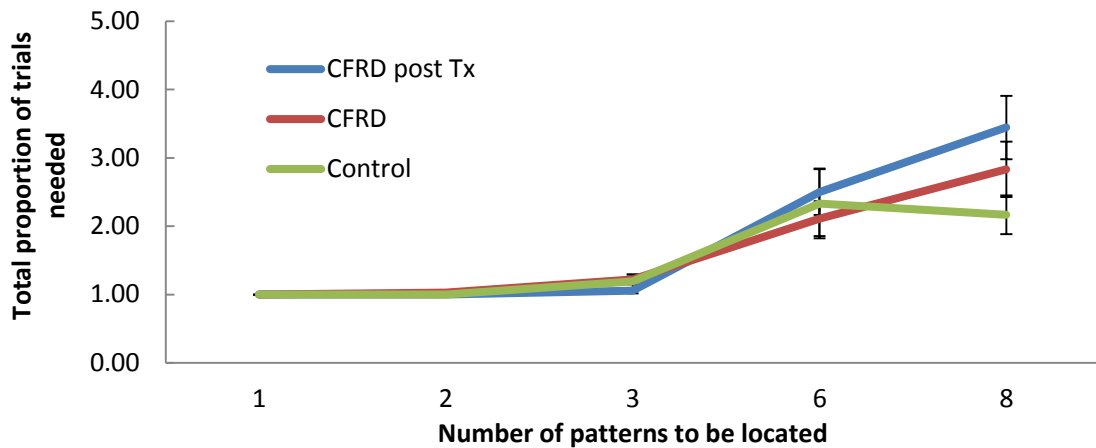
Figure 7.33 Study 3. Total proportion number of trials at each at n-pattern on the PAL test (1,2,3,6,8; four outliers excluded) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.6 Total errors

Data were square root transformed due to moderate positive skewness. Stages completed was a significant covariate, $F(1, 50) = 9.69$, $p = .003$, $\eta_p^2 = .162$. There was no significant main effect of group, $F(2, 50) = 2.06$, $p = .14$, $\eta_p^2 = .076$ ($R^2 = .193$; see Figure 7.34).
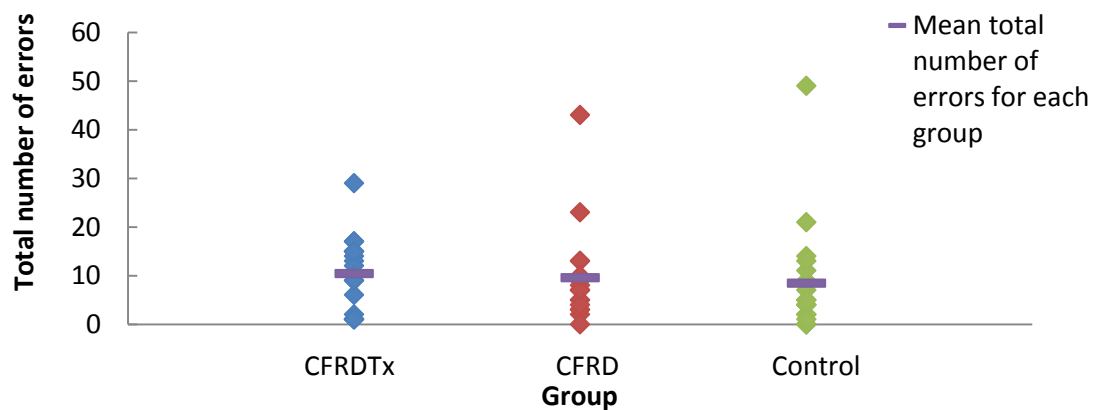
Figure 7.34 Study 3. Total number of errors produced on the PAL test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.2.7 Total errors at n-patterns

Age was a significant covariate, $F(1, 50) = 6.88$, $p = .01$, which indicated that younger participants performed better than older participants. There was no group*level interaction $F(8, 201) = 1.44$, $p = .18$. There was no significant main effect of group, $F(2, 50) = 1.06$, $p = .35$ (AICC = -896.2). As expected, there was a significant main effect of level, $F(4, 201) = 33.02$, $p < .0001$ (see Figure 7.35).
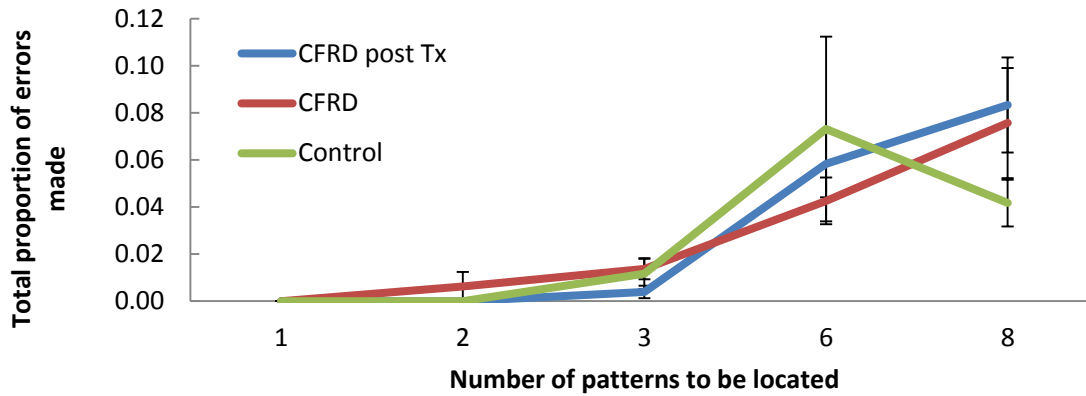
Figure 7.35 Study 3. Proportion number of errors produced at each n-pattern (1,2,3,6,8) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3 Verbal Recognition Memory

7.3.4.3.1 Immediate verbal memory

7.3.4.3.1.1 Number of correctly recalled words at immediate recall

Data were square root transformed due to moderate positive skewness. There was no significant main effect of group, $F(2, 51) = 1.16$, $p = .32$, $\eta_p^2 = .043$ ($R^2 = .043$; see Figure 7.36).
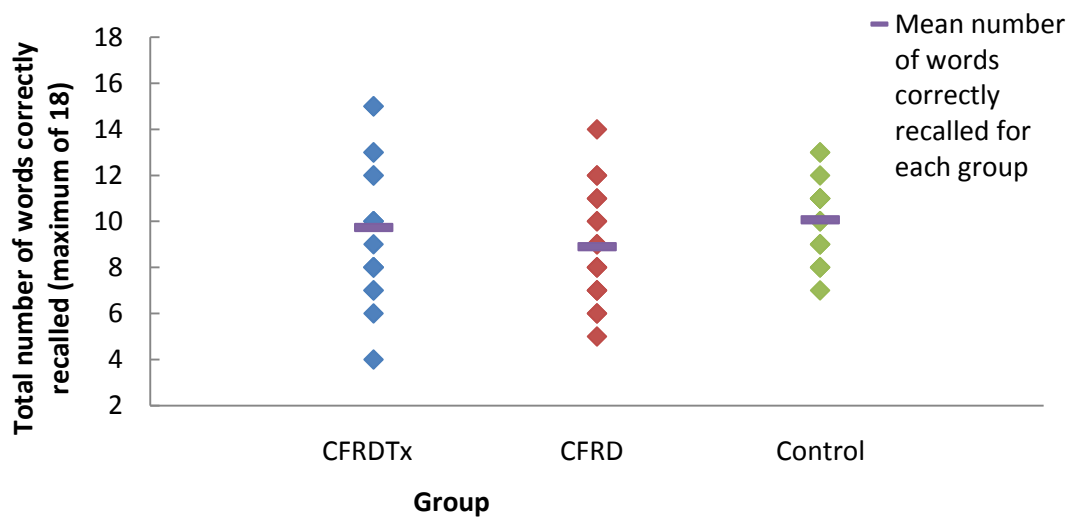
Figure 7.36 Study 3. Number of correctly recalled words at immediate free recall on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.1.2 Number of novel words produced at immediate recall

There were too few data points to perform analysis for novel words produced at immediate recall. This showed that participants did not, on the whole, generate words which were not in the word list.

7.3.4.3.1.3 Number of perseverations produced at immediate recall

Data were logarithm transformed due to substantial positive skewness. There was a significant main effect of group, Wadj$F(2,30.20) = 3.43$ $p = .045$, $\eta_p^2 = .120$ ($R^2 = .120$), such that the people in the control group produced significantly less repetitions of correctly recalled words at immediate recall compared people in the CFRDTx group ($p = 0.29$; see figure 7.37).
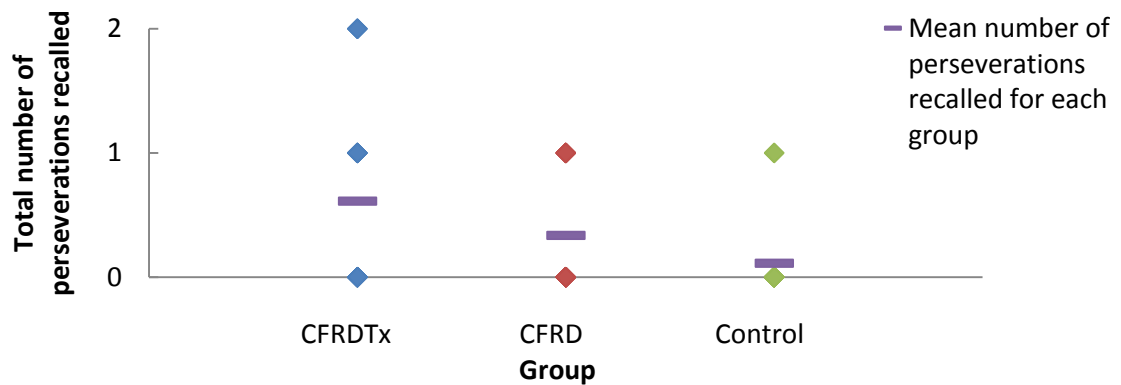
Figure 7.37 Study 3. Number of perseverations at immediate free recall on the VRM test, for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.1.4 Total number of correctly recognised target words (recognition task)

Data were reflected and an inverse transformation applied due to severe negative skewness. There was no significant main effect of group, $F(2, 51) = 0.082$, $p = .92$, $\eta_p^2 = .003$ ($R^2 = .003$; see Figure 7.38).
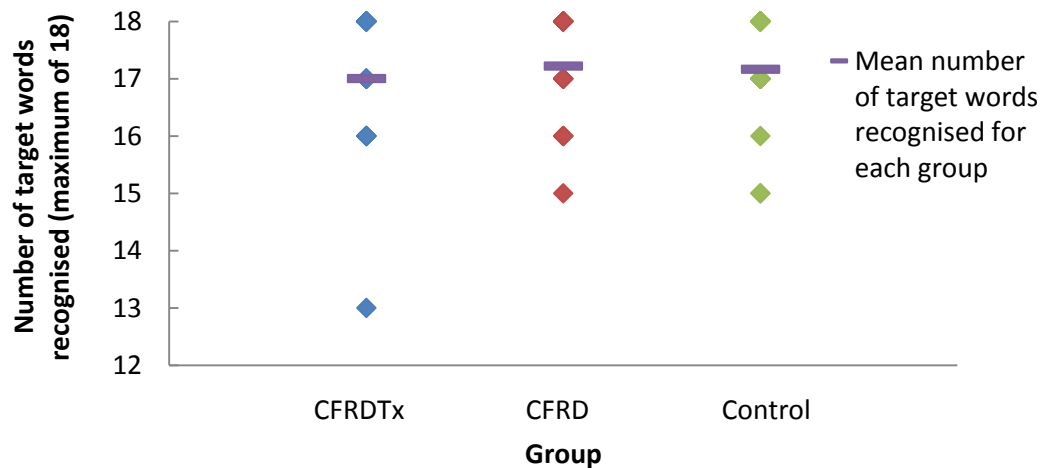
Figure 7.38 Study 3. Total number of correctly recognised target words at delayed recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.1.5 Total number of false positives (recognition task)

Data were logarithm transformed due to substantial positive skewness. Data for one participant was excluded as an outlier. There was no significant main effect of group, Wadj$F(2,30.70) = 0.15$, $p = .86$, $\eta_p^2 = .120$ ($R^2 = .012$; see Figure 7.39).
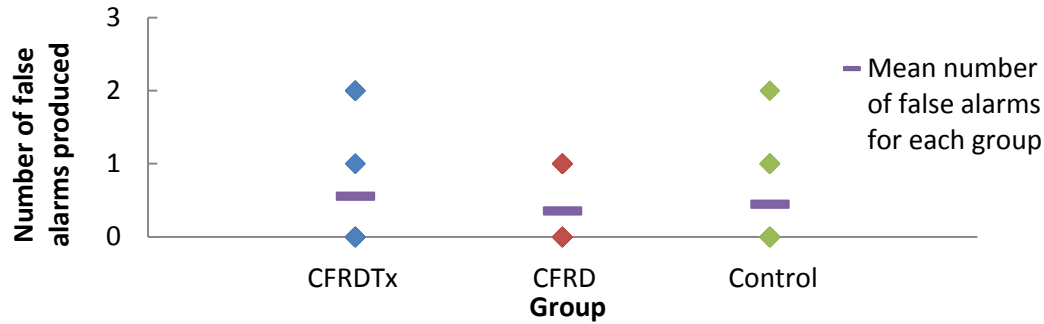
Figure 7.39 Study 3. Total number of false positives produced at delayed recognition (excluding one outlier) on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.2 Delayed verbal memory

7.3.4.3.2.1 Number of correctly recalled words at delayed recall

Data were square root transformed due to moderate positive skewness. Figure 7.40 shows there was no significant main effect of group, $F(2, 51) = 1.45$, $p = .24$, $\eta_p^2 = .05$ ($R^2 = .054$).
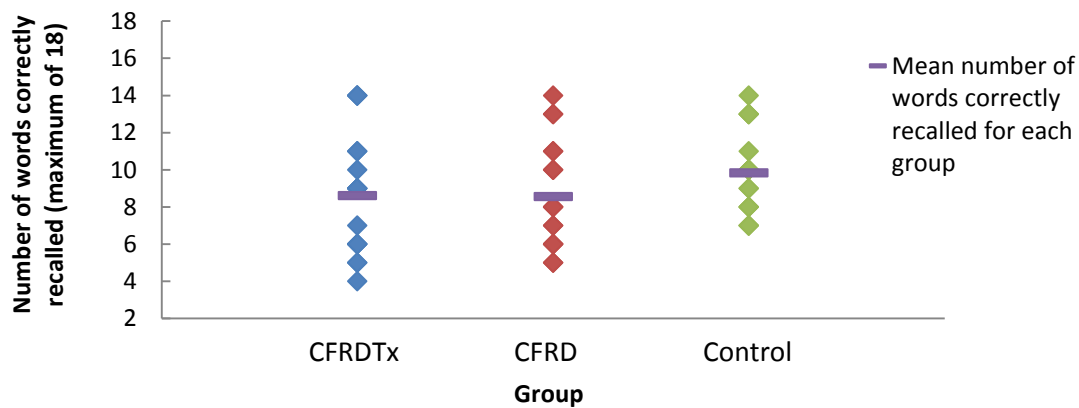
Figure 7.40 Study 3. Total number of correctly recalled words at delayed recall on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.2.2 Number of novel words produced at delayed recall

Data were logarithm transformed due to substantial positive skewness. There was a trend for a significant main effect of group, Wadj$F(2,31.28) = 2.69$ $p = .083$, $\eta_p^2 = .120$ ($R^2 = .134$),

such that there was a trend for the control group to generate less novel words than people in the CFRD group ($p = .059$; see figure 7.41).
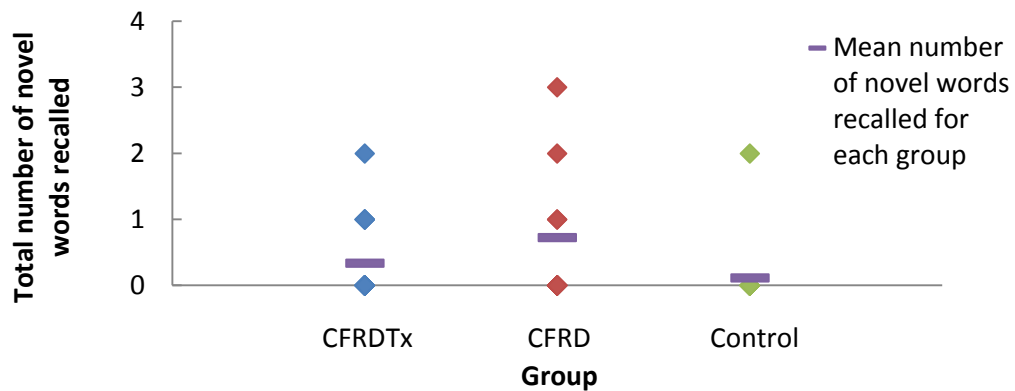
Figure 7.41 Study 3. Number of novel words produced at delayed free recall on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.2.3   Number of perseverations produced at delayed recall

Data were logarithm transformed due to substantial positive skewness. Figure 7.42 shows there was no significant main effect of group, $F(2, 51) = 2.34$, $p = .106$, $\eta_p^2 = .084$ ($R^2 = .084$).
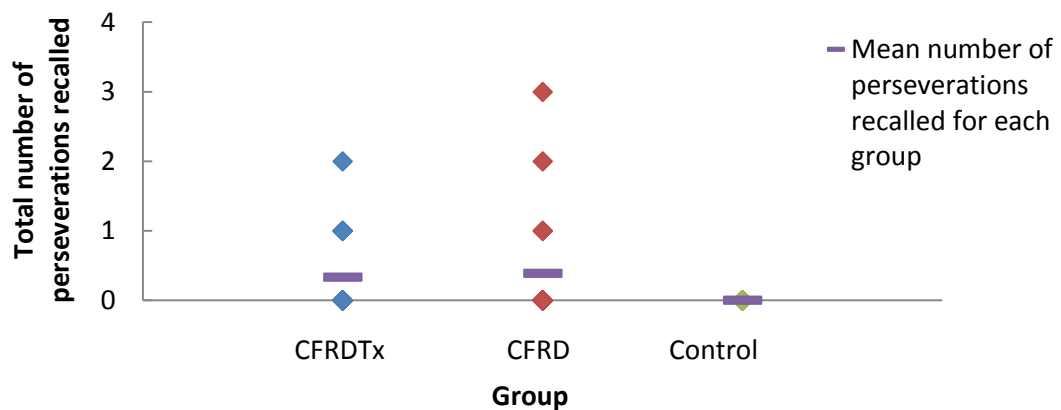
Figure 7.42 Study 3. Number of perseverations at delayed free recall on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.2.4   Total number of correctly recognised target words (recognition task)

Data were reflected and an inverse transformation applied due to severe negative skewness. There was no a significant main effect of group, $F(2, 51) = 0.38$, $p = .68$, $\eta_p^2 = .015$ ($R^2 = .015$; see Figure 7.43).
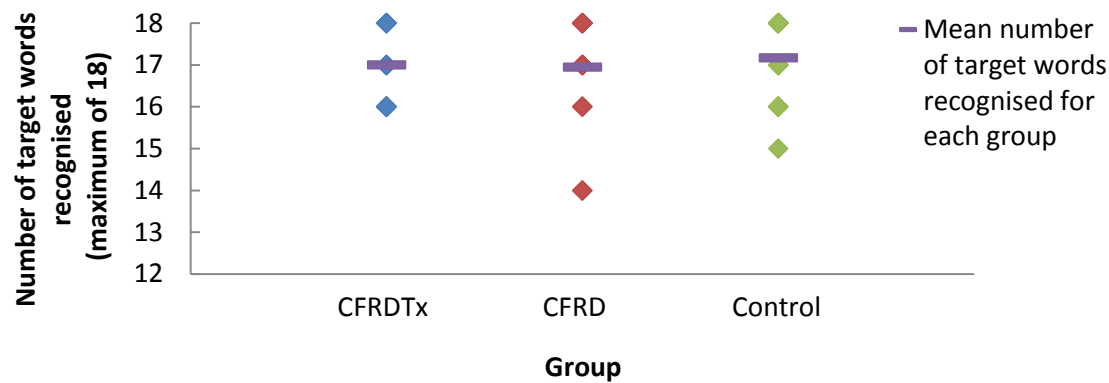
Figure 7.43 Study 3. Total number of correctly recognised target words at delayed recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.3.2.5 Total number of false positives (recognition task)

Data were logarithm transformed due to substantially positive skewness. Data for one participant was excluded as an outlier. There was no significant main effect of group, $F(2, 50) = 0.24$, $p = .79$, $\eta_p^2 = .010$ ($R^2 = .035$; see Figure 7.44).
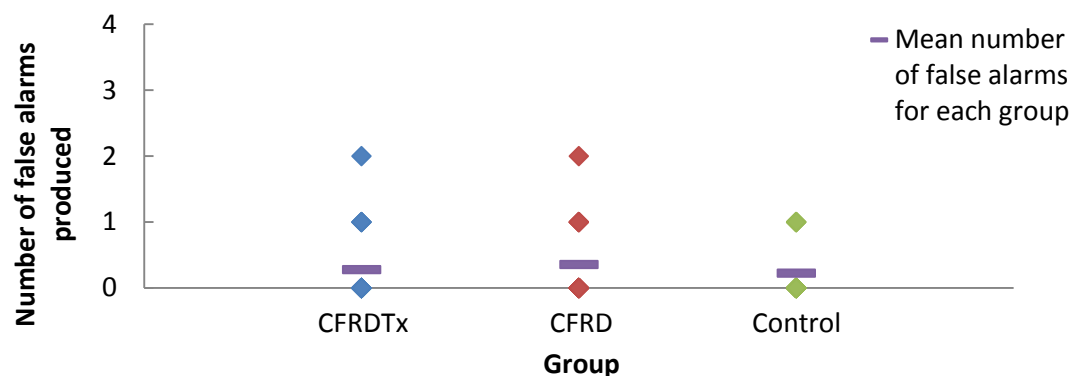
Figure 7.44 Study 3. Total number of false positives produced at delayed recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.4 **Pattern Recognition Memory**

7.3.4.4.1 Immediate pattern recognition

7.3.4.4.1.1 Number of correctly recognised patterns

Data were reflected and inverse transformed due to severe negative skewness. There was no significant main effect of group, $F(2, 51) = 0.01$, $p = .99$, $\eta_p^2 = .001$ ($R^2 = .001$; see Figure 7.45).
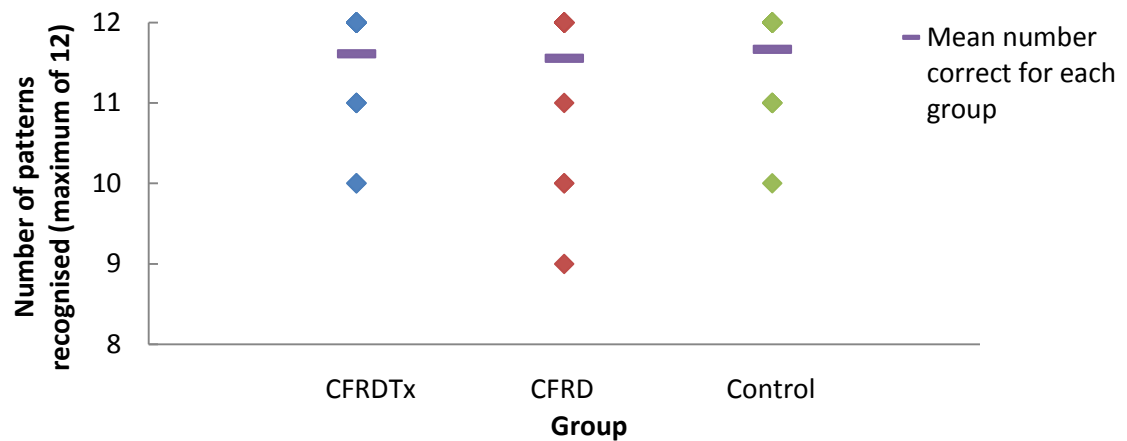
Figure 7.45 Study 3. Number of correctly recognised patterns at immediate recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.4.1.2 Reaction time for correctly recognised patterns

Data were substantially positively skewed and therefore a logarithm transformation was applied. There was no significant main effect of group, $F(2, 51) =1.04$, $p = .36$, $\eta_p^2 = .039$ ($R^2 = .039$; see Figure 7.46).
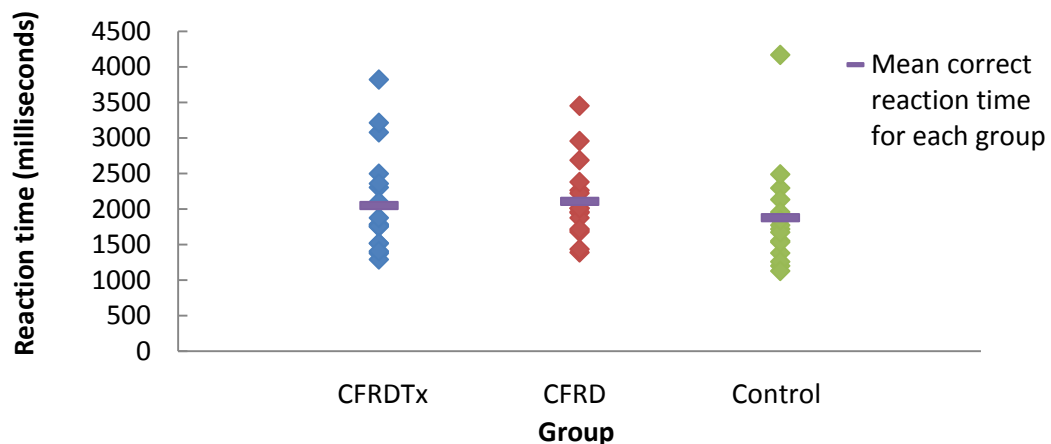
Figure 7.46 Study 3. Reaction time for correctly recognised patterns at immediate recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.4.2 Delayed pattern recognition

7.3.4.4.2.1 Number of correctly recognised patterns

Data were substantially positively skewed and therefore a logarithm transformation was applied. There was no significant main effect of group, $F(2, 50) =1.39$, $p = .26$, $\eta_p^2 = .053$ ($R^2 = .053$; see Figure 7.47).
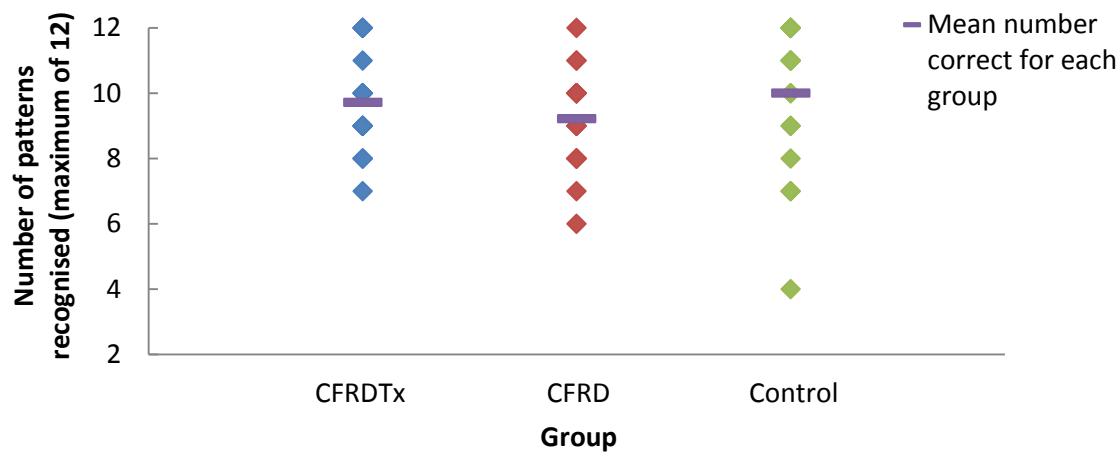
Figure 7.47 Study 3. Number of correctly recognised patterns at delayed recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.4.2.2   Reaction time for correctly recognised patterns

Data were substantially positively skewed and therefore a logarithm transformation was applied. Data for one participant was excluded as an outlier. There was no significant main effect of group, $F(2, 51) =1.87$, $p = .17$, $\eta_p^2 = .068$ ($R^2 = .068$; see Figure 7.48).
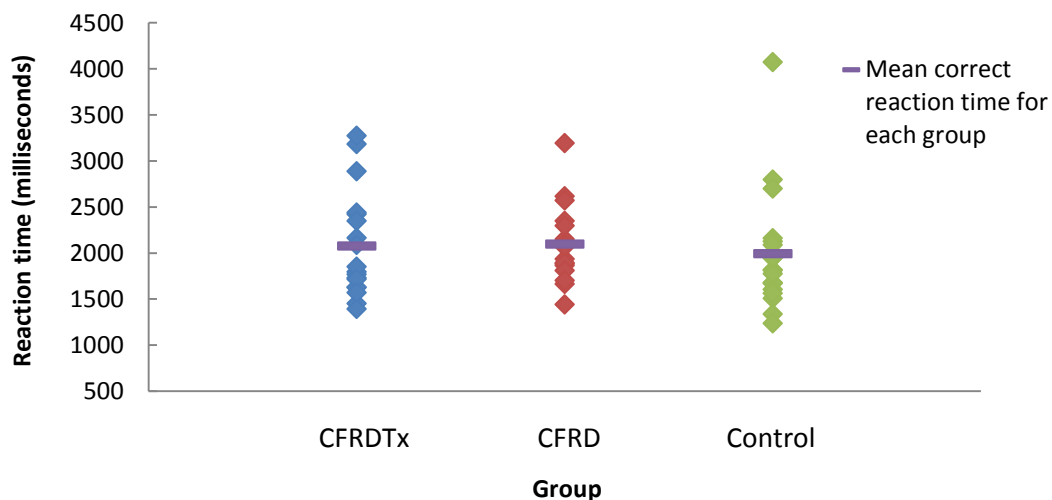
Figure 7.48 Study 3. Reaction time for correctly recognised patterns at delayed recognition on the VRM test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5   **Rapid Visual Processing**

There are a total of 36 target sequences to detect on the four minute task (9 per minute). The outcome measures for the RVP test are the same as Study 1 (see section Chapter 5.2.3.3.5, and Table 5.4 for a definition of each outcome variable).

7.3.4.5.1   Total hits (correct detections of target sequences)

Data were reflected and square root transformed due to moderate negative skewness. There was a significant main effect of group, $F(2, 51) = 14.20$, $p < .001$, $\eta_p^2 = .358$ ($R^2 = .352$), such that people in the control group detected more targets than people with CFRD ($p < .001$) and people with CFRDTx ($p < .001$; see Figure 7.49).
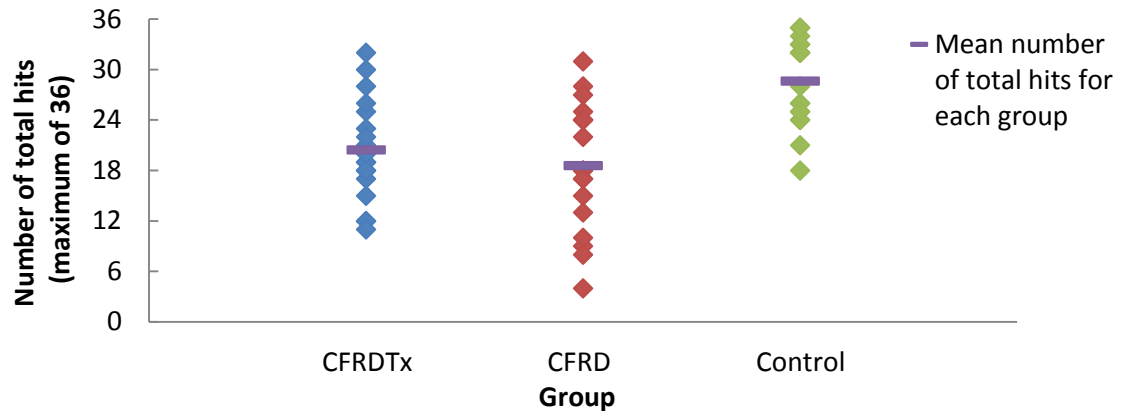
Figure 7.49 Study 3. Total hits (correct detections) on the RVP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.2   Total hits at each minute

Age was not a significant covariate, $F(1, 50) = 1.02$, $p = .32$. There was no group*level interaction $F(6, 153) = 0.95$, $p = .46$. There was a significant main effect of group, $F(2, 50) = 12.93$, $p < .0001$ (AICC = 847.8) such that controls performed significantly better than people with CFRD ($p < .0001$) and CFRDTx ($p = .0002$). There was no significant main effect of level, $F(3, 153) = 0.30$, $p = .82$ (see Figure 7.50).
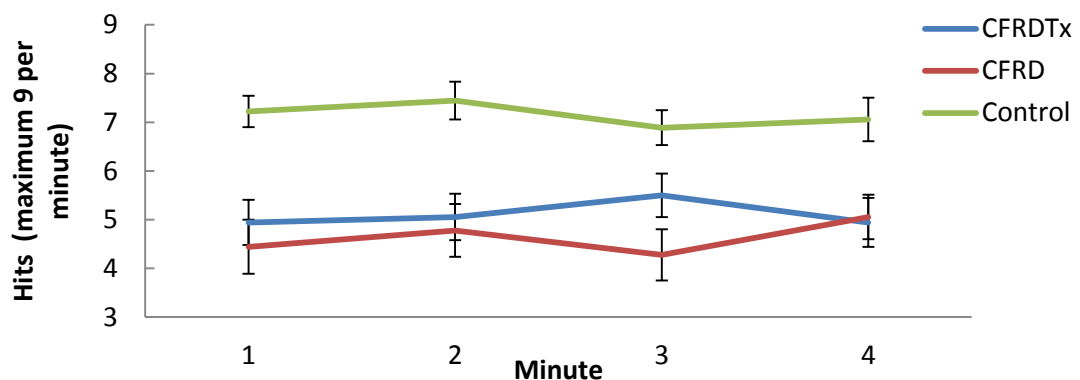
Figure 7.50 Study 3. Mean (±SE) number of hits at each minute of the RVP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.3 Total false alarms

Data were square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 3.20$, $p = .049$, $\eta_p^2 = .112$ ($R^2 = .112$), such that people in the control group made less false alarms than people with CFRD ($p = .089$; see Figure 7.51).
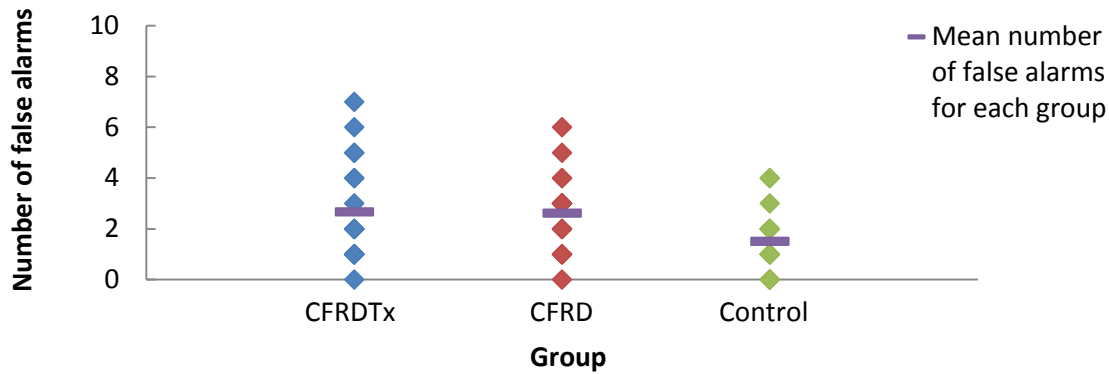
Figure 7.51 Study 3. Total number of false alarms produced on the RVP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.4 Mean reaction time for hits

Data for one participant was excluded as an outlier. There was a trend for a significant main effect of group, $F(2, 51) = 3.06$, $p = .056$, $\eta_p^2 = .109$ ($R^2 = .109$), such that there was a trend for people in the control group to respond faster to the detection of targets than people with CFRDTx ($p = .068$; see Figure 7.52).
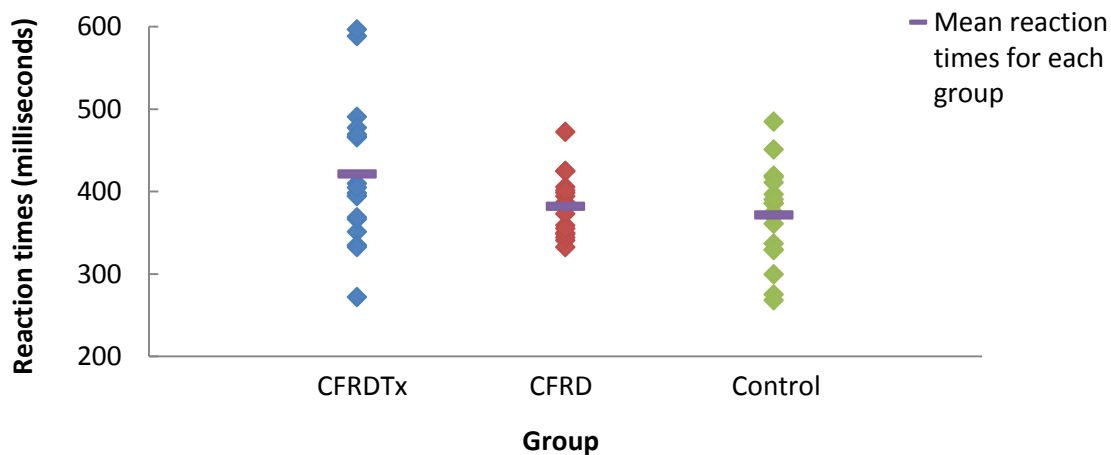
Figure 7.52 Study 3. Mean reaction time for hits on the RVP test (excluding one outlier) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.5 Reaction time for hits at each minute

7 data points were excluded as outliers. Age was not a significant covariate, $F(1, 50) = 1.65$, $p = .20$. There was no group*level interaction $F(6, 146) = 1.22$, $p = .30$. There was no significant main effect of group, $F(2, 50) = 2.19$, $p = .12$ (AICC = 2343.2). There was no significant main effect of level, $F(3, 146) = 0.65$, $p = .59$ (see Figure 7.53).
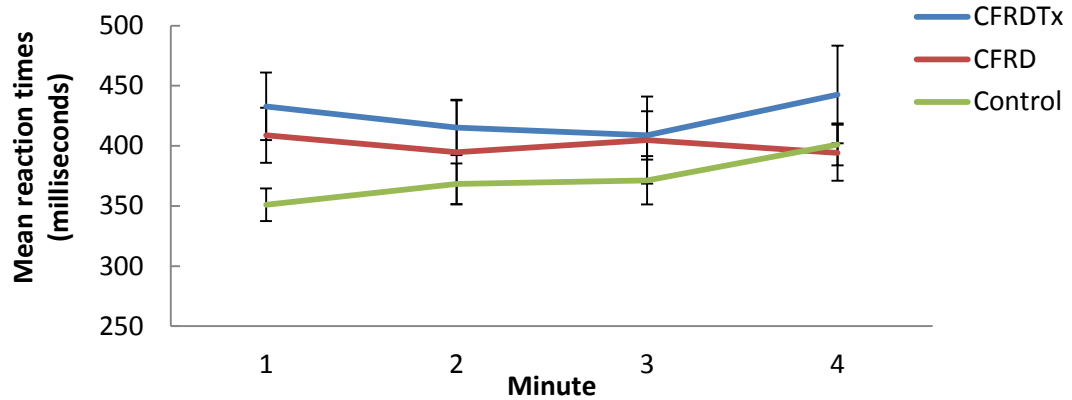
Figure 7.53 Study 3. Mean (±SE) reaction time for hits at each minute of the RVP (7 outliers excluded) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.6 A' Prime

Data were logarithm transformed due to substantial negative skewness. There was a significant main effect of group, $F(2, 51) = 13.50$, $p < .001$, $\eta_p^2 = .346$ ($R^2 = .346$), such that the control group had a significantly better sensitivity to detecting target sequences compared to those in the CFRD ($p < .001$) and CFRDTx group ($p = .001$; see Figure 7.54).
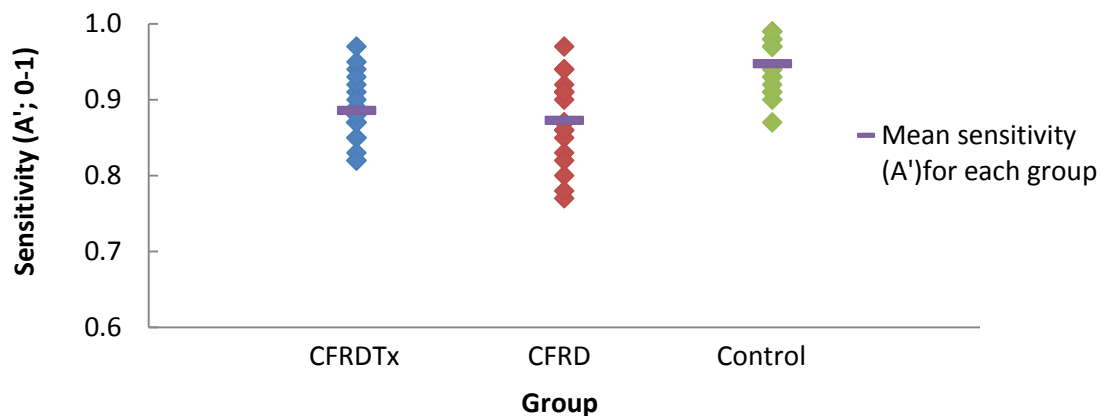
Figure 7.54 Study 3. A' prime (Sensitivity to the target, regardless of response tendency) on the RVP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.5.7 B' Prime

Data were reflected and an inverse transformation applied due to severe negative skewness. There was no significant main effect of group, $F(2, 51) = 0.39$, $p = .68$, $\eta_p^2 = .015$ ($R^2 = .015$; see Figure 7.55).
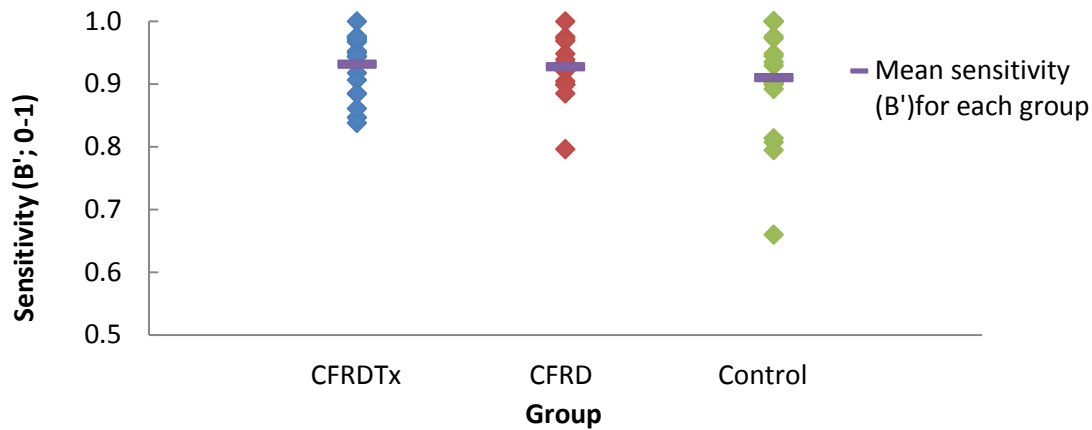
Figure 7.55 Study 3. B' prime (tendency to respond regardless of whether the target sequence is present) on the RVP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6 **Spatial Span**

7.3.4.6.1 Span length (longest number sequence successfully recalled)

Data were reflected and square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 9.45$, $p < .001$, $\eta_p^2 = .270$ ($R^2 = .270$), such that the control group reached a higher span length compared to those in the CFRD ($p = .005$) and CFRDTx group ($p < .001$; see Figure 7.56).
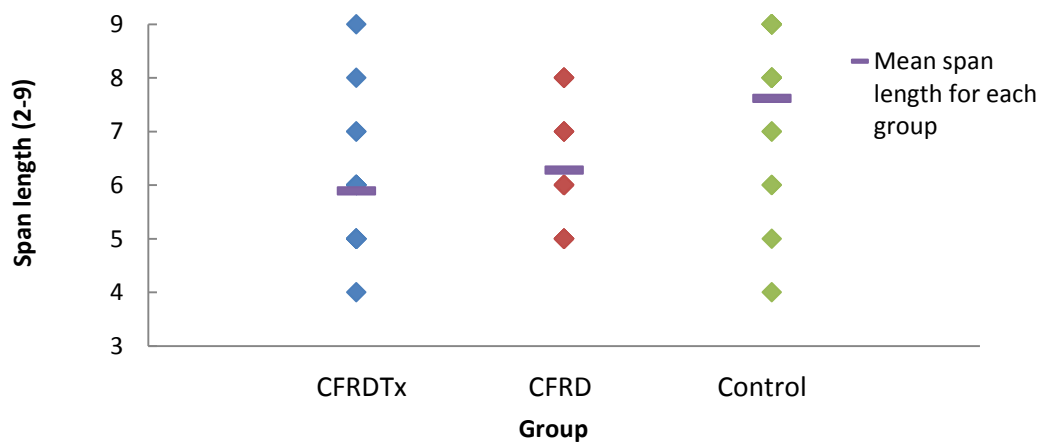
Figure 7.56 Study 3. Span length (longest number sequence successfully recalled; 2-9) on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6.2   Total number of attempts

Data were square root transformed due to moderate positive skewness. Span level was a significant covariate, $F(1, 51) = 57.20$, $p < .001$, $\eta_p^2 = .534$. More attempts were required on the higher span levels compared to the lower levels. There was a no main effect of group, $F(2, 51) = 0.18$, $p = .84$, $\eta_p^2 = .007$ ($R^2 = .534$; see Figure 7.57). The higher number of attempts in the control group is a function of better overall performance on this test i.e. they reached higher span levels, and therefore as task difficulty increased, so did the number of attempts. Figure 7.57 illustrates that the control group required less attempts at each level, although the number of attempts at span 9 is confounded by there being only 2 people with CFRDTx, compared to 12 controls.
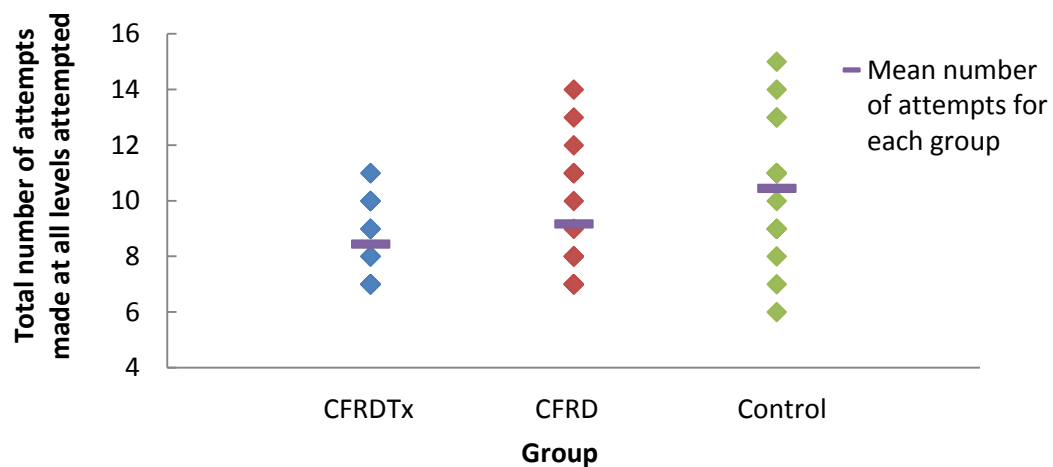
Figure 7.57 Study 3. Total number of attempts made at all levels reached on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)
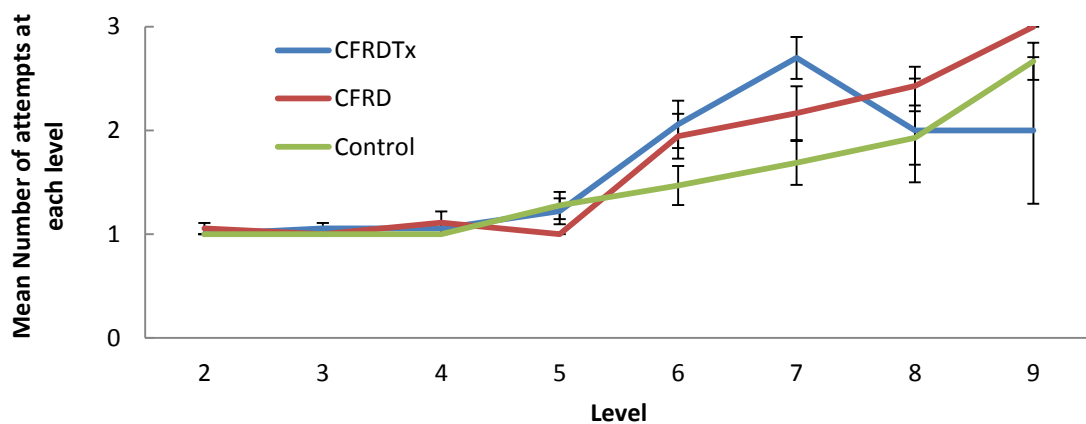
Figure 7.58 Study 3. Mean (± SE) number of attempts made at each level on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6.3 Reaction time outcome measures on the SSP test

7.3.4.6.3.1 Mean time to first response

Data were square root transformed due to moderate positive skewness. Span level was a significant covariate, $F(1, 51) = 9.14$, $p = .004$, $\eta_p^2 = .155$. There was a significant main effect of group, $F(2, 51) = 7.97$, $p = .001$, $\eta_p^2 = .242$ ($R^2 = .260$), such that people in the control group responded faster to initiate recalling a sequence compared to those in the CFRD ($p = .002$) and CFRDTx group ($p = .003$; see Figure 7.59).
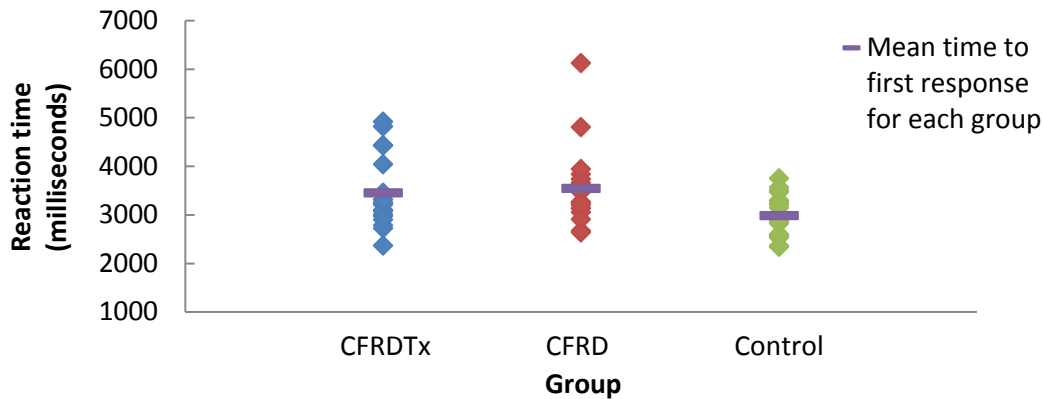
Figure 7.59 Study 3. Mean time to first response (milliseconds) on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6.3.2 Mean time to last response

Data were logarithm transformed due to substantial positive skewness. Span level was a significant covariate, $F(1, 51) = 25.04$, $p < .001$, $\eta_p^2 = .334$. There was a significant main effect of group, $F(2, 51) = 5.87$, $p = .005$, $\eta_p^2 = .190$ ($R^2 = .359$), such that people in the control group were faster to finish recalling a sequence compared to those in the CFRD ($p = .004$) and CFRDTx group ($p = .050$; see Figure 7.60).
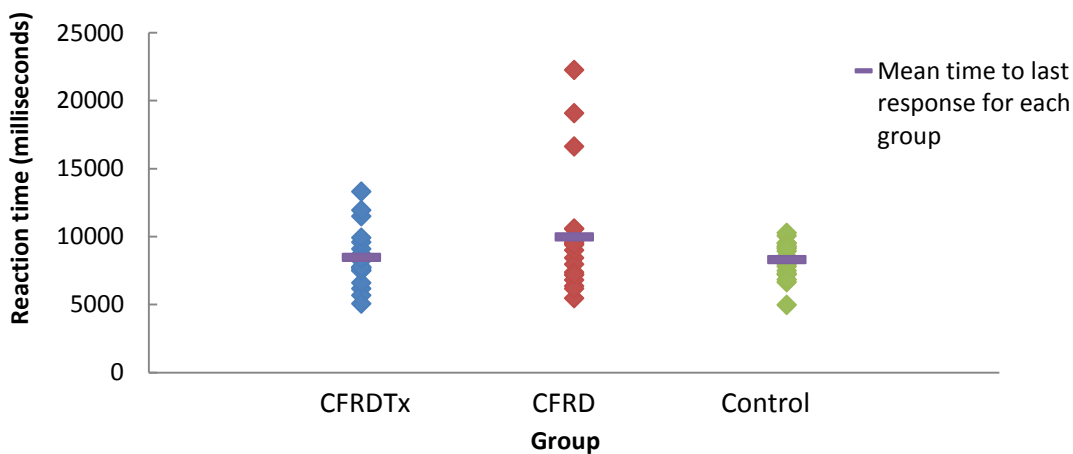
Figure 7.60 Study 3. Mean time to last response (milliseconds) on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6.4   Errors

7.3.4.6.4.1   Total errors

Data were square root transformed due to moderate positive skewness. Data for one participant was an outlier and excluded from the analysis. Span level was a significant covariate, $F(1, 49) = 9.86$, $p = .003$, $\eta_p^2 = .167$. There was no significant main effect of group, $F(2, 49) = 0.37$, $p = .70$, $\eta_p^2 = .015$ ($R^2 = .183$; see Figure 7.61).
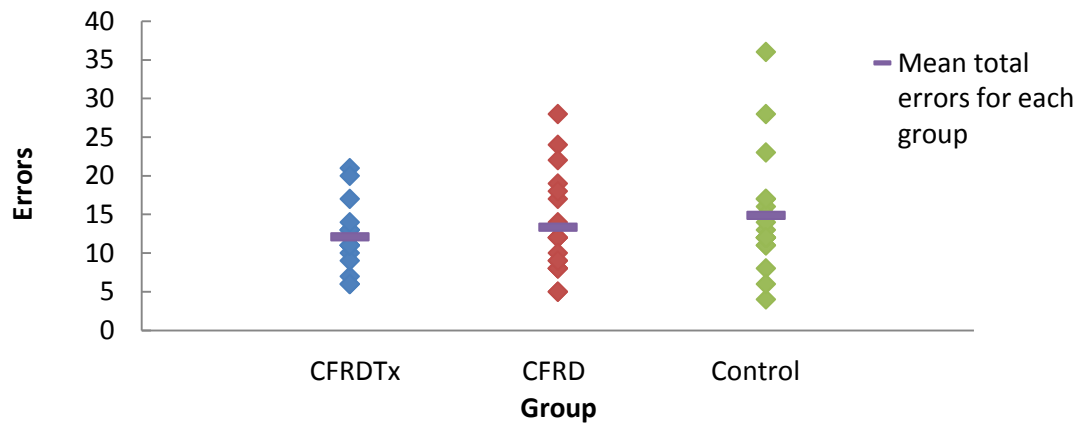
Figure 7.61 Study 3. Total number of errors produced whilst recalling sequences on the SSP test (one outlier removed) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.6.4.2   Total usage errors

Data were square root transformed due to moderate positive skewness. Span level was a significant covariate, $F(1, 50) = 9.92$, $p = .003$, $\eta_p^2 = .166$. There was no significant main effect of group, $F(2, 49) = 1.40$, $p = .26$, $\eta_p^2 = .053$ ($R^2 = .307$; see Figure 7.62).
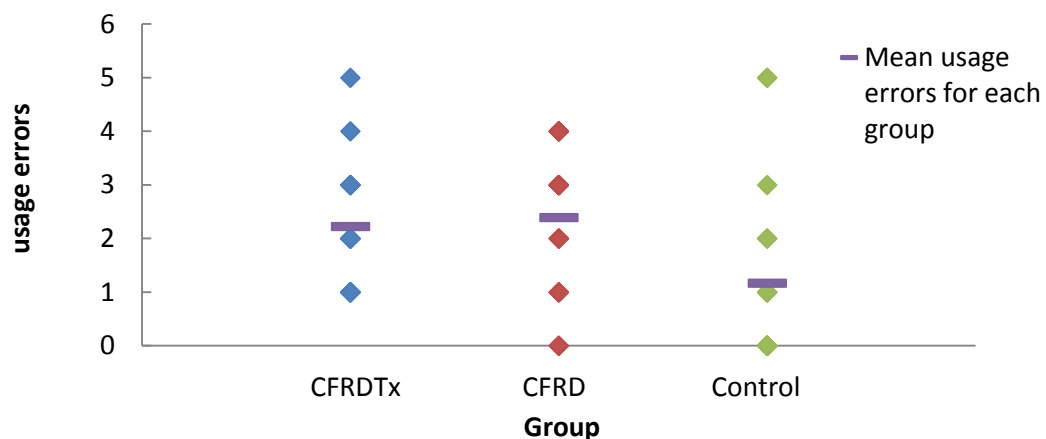
Figure 7.62 Study 3. Total number of usage errors produced on the SSP test for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7 **Attention Switching Task**

A total of 160 responses were required per test administration. The outcome measures for AST are accuracy (correct trials), reaction time for correct trials, errors (omission and commission), congruency cost, and switch cost (see section 5.2.3.3.7, and Table 5.4 for a definition of each outcome variable). As there were an unequal number of switched and non-switched trials, reaction time for switched and non-switched trials and switch cost should be treated with some degree of caution.

7.3.4.7.1 Total correct trials

7.3.4.7.1.1 Total correct trials (overall accuracy)

Data were reflected and logarithm transformed due to substantial negative skewness. There was no significant main effect of group, $F(2, 51) = 0.60$, $p = .55$, $\eta_p^2 = .023$ ($R^2 = .023$; see Figure 7.63).
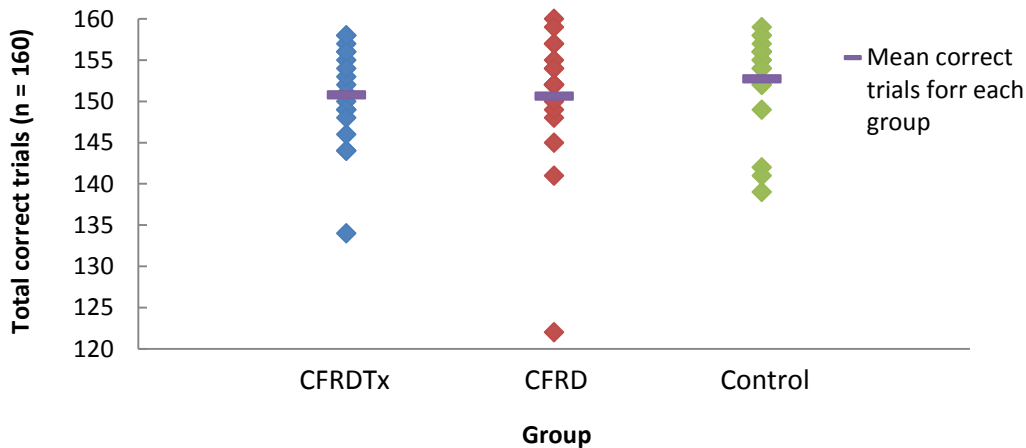
Figure 7.63 Study 3. Total number of correct trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.1.2 Mean reaction time for total correct trials

Data were square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 3.75$, $p = .030$, $\eta_p^2 = .128$ ($R^2 = .128$; see Figure 7.64). Post hoc tests showed there was a trend for the control group to respond faster to correct trials compared to the CFRD group ($p = .056$), and CFRDTx group ($p = .074$).
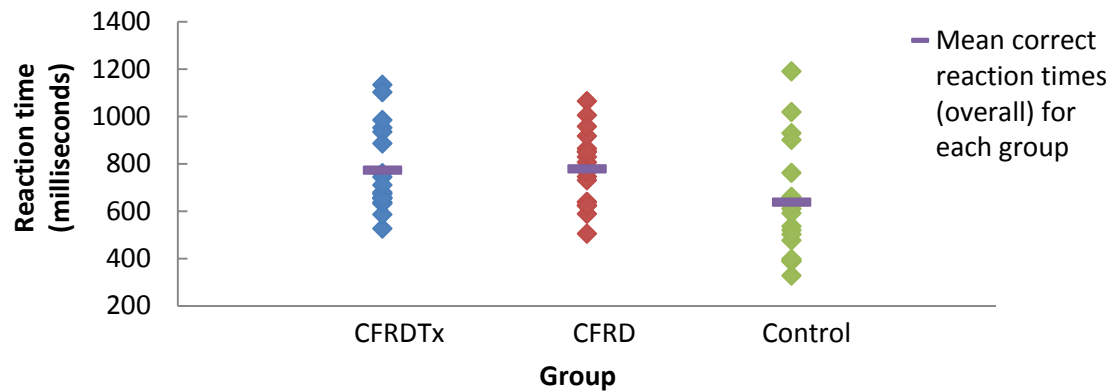
Figure 7.64 Study 3. Reaction time for correct trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.2 Direction trials

7.3.4.7.2.1 Total correct trials with direction as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. There was no significant main effect of group, $F(2, 51) = 0.71$, $p = .93$, $\eta_p^2 = .143$ ($R^2 = .003$; see Figure 7.65).
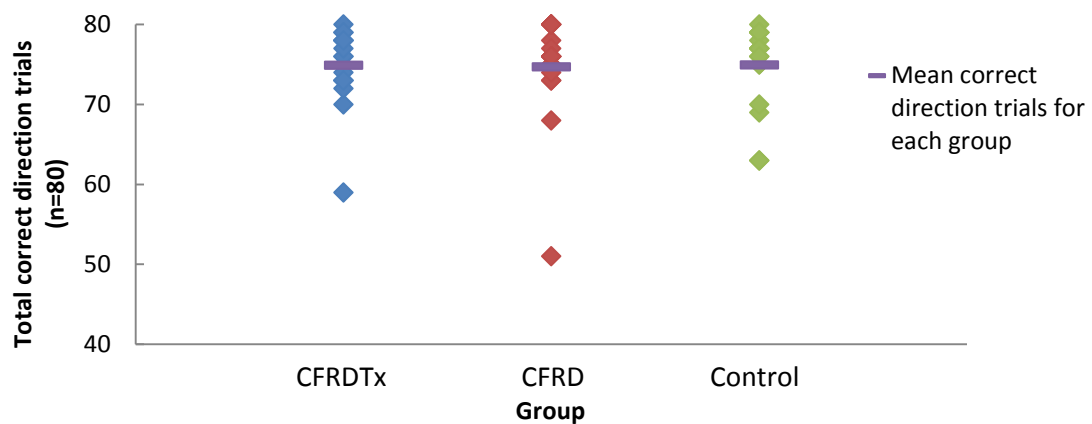
Figure 7.65 Study 3. Number of correct direction trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.2.2 Reaction time for correct trials with direction as the rule

Data were square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 4.10$, $p = .022$, $\eta_p^2 = .138$ ($R^2 = .138$), such that the control group responded significantly faster to correct direction trials compared to the CFRD group ($p = .035$). There was also a trend for controls to respond faster than people with CFRDTx ($p = .075$; see Figure 7.66).
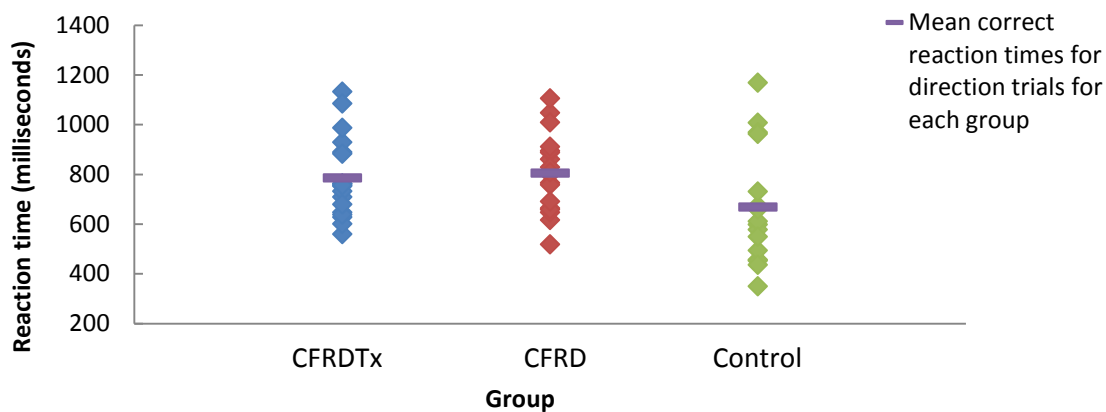
Figure 7.66 Study 3. Reaction time for correct direction trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.3 Side trials

7.3.4.7.3.1 Total correct trials with side as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. There was a significant main effect of group, $F(2, 51) = 4.97$, $p = .011$, $\eta_p^2 .163$ ($R^2 = .95$; see Figure 7.67). Post hoc tests showed that the control group correctly responded to significantly more trials with side as the rule than the CFRD group ($p = .045$) and CFRDTx group ($p = .017$).
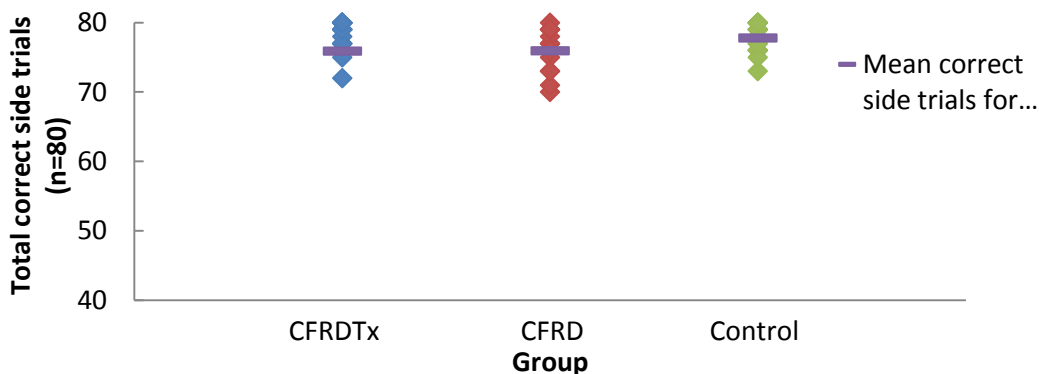
Figure 7.67 Study 3. Number of correct side trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.3.2 Reaction time for correct trials with side as the rule

Data were square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 3.87$, $p = .027$, $\eta_p^2 = .132$ ($R^2 = .132$), such that there was a trend for the control group to respond faster to correct side trials compared to the CFRDTx ($p = .055$) and CFRD group ($p = .063$; see Figure 7.68).
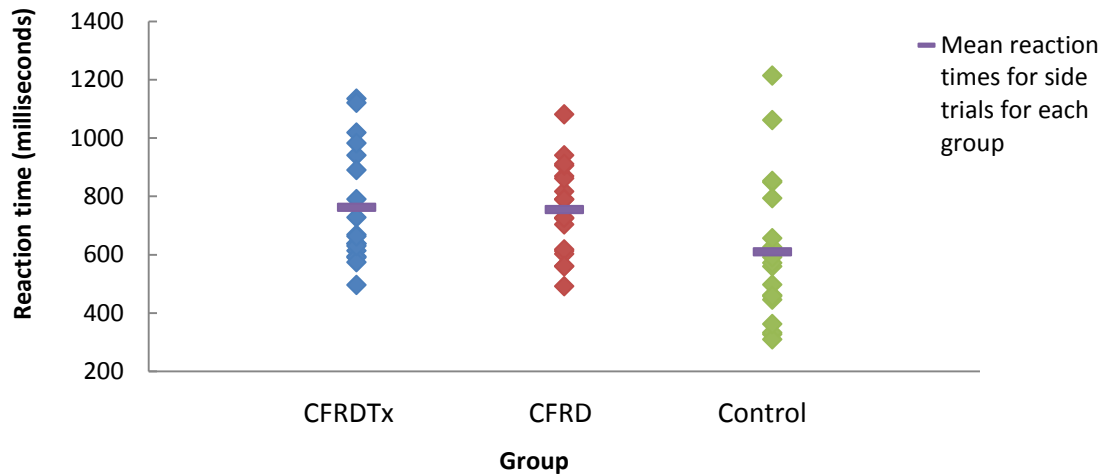
Figure 7.68 Study 3. Reaction time for correct side trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.4   Congruent trials

7.3.4.7.4.1   Total correct congruent trials

Data were reflected and inversely transformed due to severe negative skewness. There was no significant main effect of group, $F(2, 51) = 1.11$, $p = .34$, $\eta_p^2 = .042$ ($R^2 = .042$; see Figure 7.69).
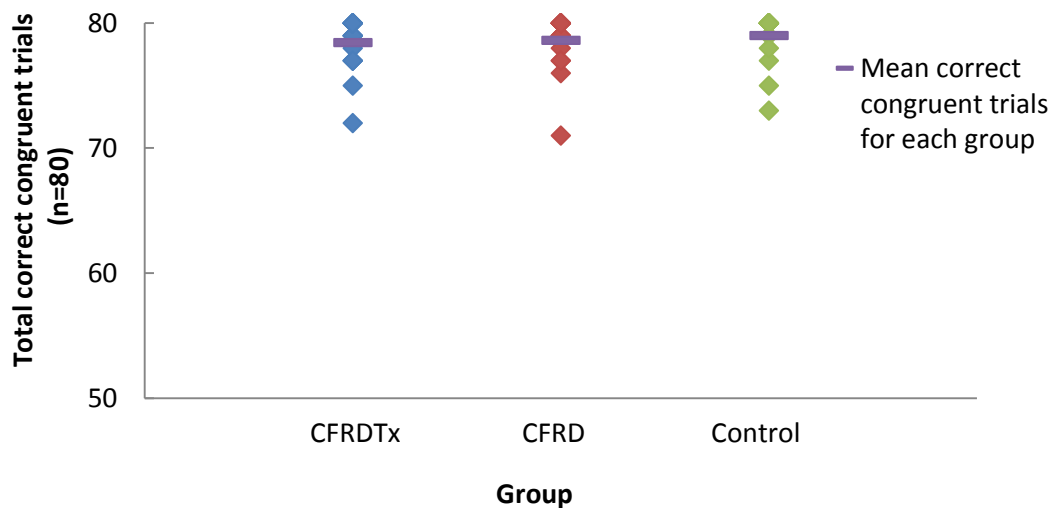
Figure 7.69 Study 3. Number of correct congruent trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.4.2   Reaction time for correct congruent trials

Data were square root transformed due to moderate positive skewness. There was a significant main effect of group, $F(2, 51) = 3.78$, $p = .030$, $\eta_p^2 = .129$ ($R^2 = .129$), such that

there was a trend for the control group to respond faster to correct congruent trials compared to the CFRDTx ($p = .063$) and CFRD ($p = .064$; see Figure 7.70).
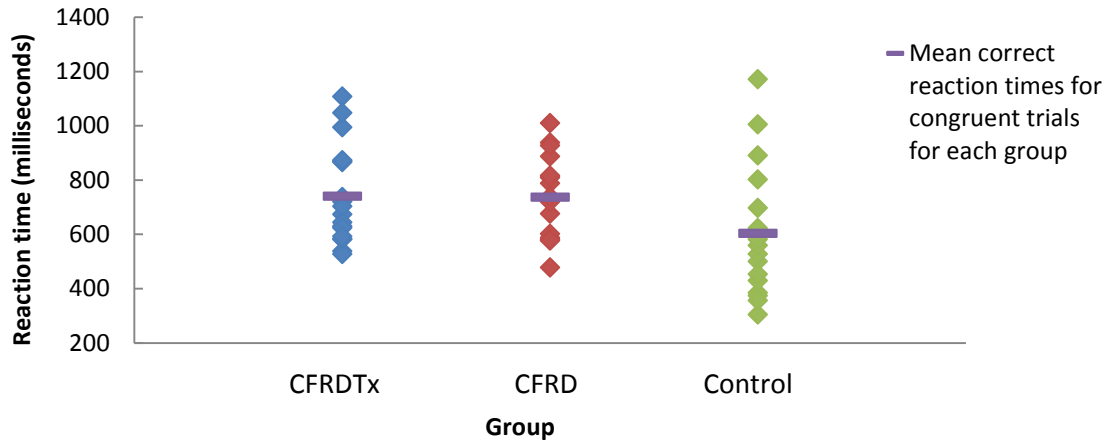
Figure 7.70 Study 3. Reaction time for correct congruent trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.5 Incongruent trials

7.3.4.7.5.1 Total correct incongruent trials

Data were reflected and an inverse transformation applied due to severe negative skewness. There was no significant main effect of group, $F(1, 51) = 0.47$, $p = .63$, $\eta_p^2 = .018$ ($R^2 = .018$; see Figure 7.71).
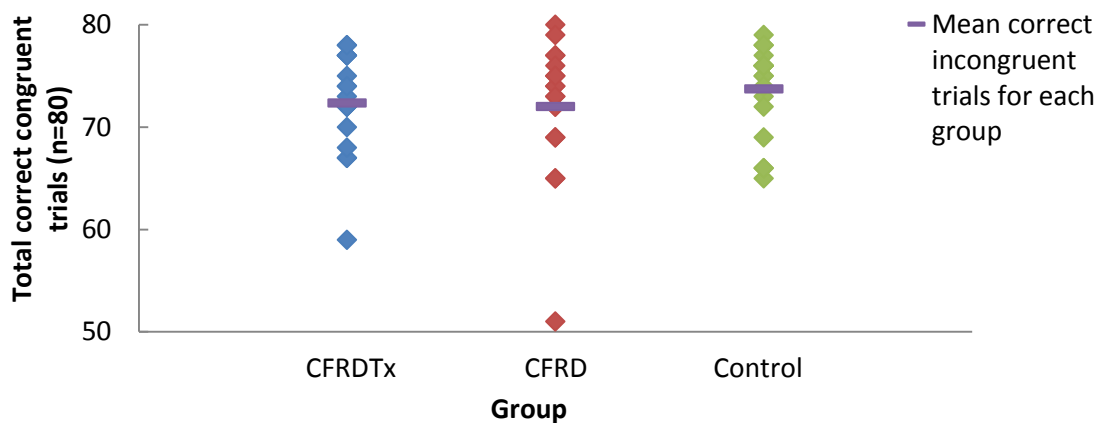
Figure 7.71 Study 3. Number of correct incongruent trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.5.2 Reaction time for correct incongruent trials

There was a trend for a significant main effect of group, $F(2, 51) = 2.96$, $p = .061$, $\eta_p^2 = .104$ ($R^2 = .104$), such that there was a trend for the control group to respond to correct incongruent trials faster compared to the CFRD group ($p = .094$; see Figure 7.72).
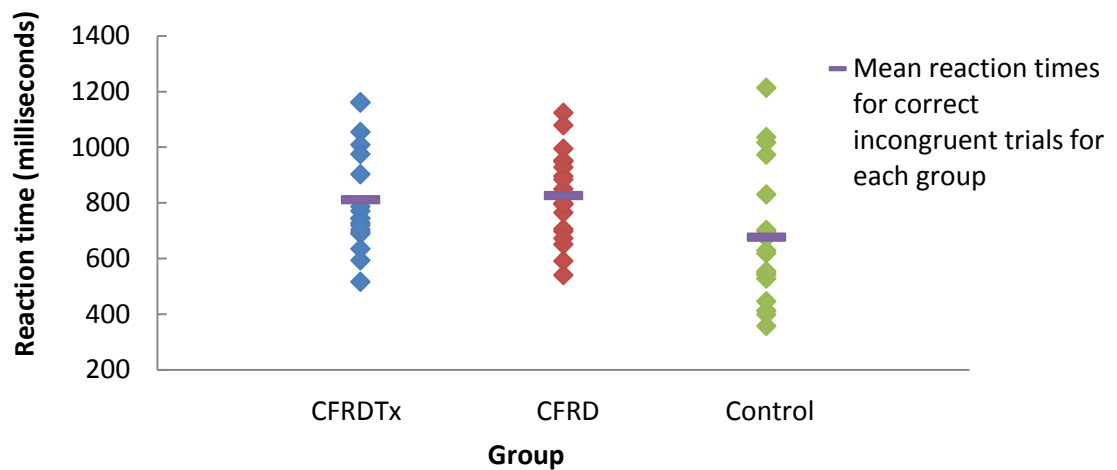
Figure 7.72 Study 3. Mean reaction time for correct incongruent trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.6 Switched trials

7.3.4.7.6.1 Proportion of correct switched trials

Data were reflected and inversely transformed due to severe negative skewness. Data for one participant was an outlier and excluded from the analysis. There was no significant main effect of group, $F(2, 50) = 1.12$, $p = .33$, $\eta_p^2 = .043$ ($R^2 = .043$; see Figure 7.73).
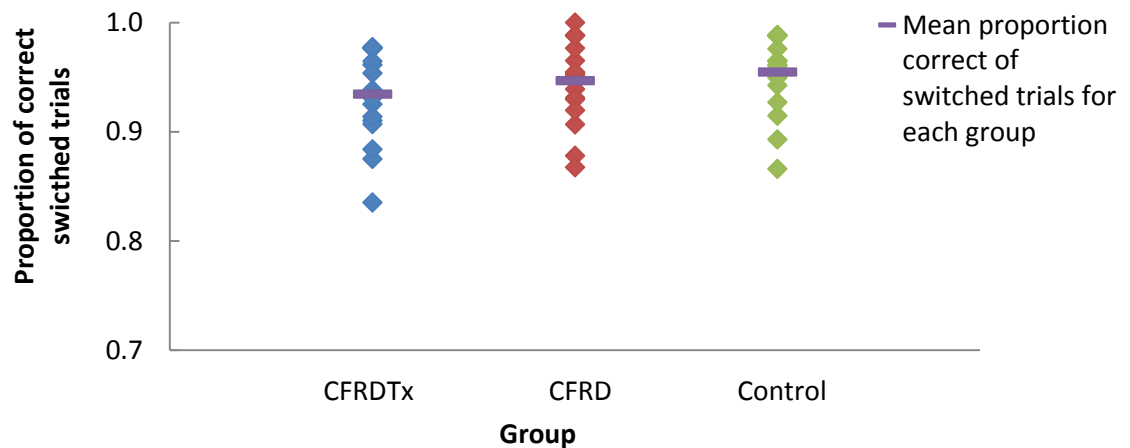
Figure 7.73 Study 3. Number of correct switched trials on the AST (excluding one outlier) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.6.2 Reaction time for correct switched trials

Data were logarithm transformed due to substantial positive skewness. There was a significant main effect of group, $F(2, 51) = 3.66$, $p = .033$, $\eta_p^2 = .126$ ($R^2 = .126$), such that

the control group were significantly faster to respond to correct switched trials compared to the CFRD group ($p = .050$; see Figure 7.74).
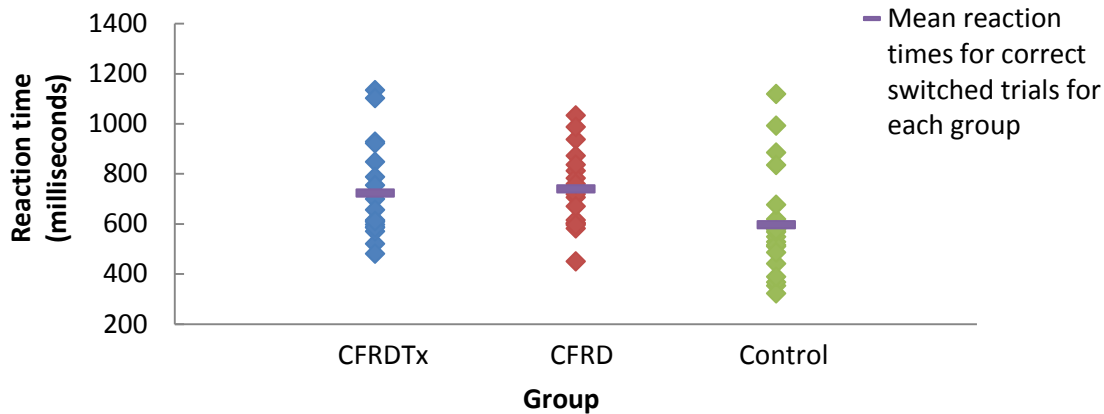
Figure 7.74 Study 3. Reaction time for correct switched trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.7   Non switched trials

7.3.4.7.7.1   Proportion of correct non switched trials

Data were reflected and an inverse transformation applied due to severe negative skewness. Data for one participant was excluded as an outlier. There was no significant main effect of group, $F(2, 51) = 0.14$, $p = .87$, $\eta_p^2 = .006$ ($R^2 = .006$; see Figure 7.75).
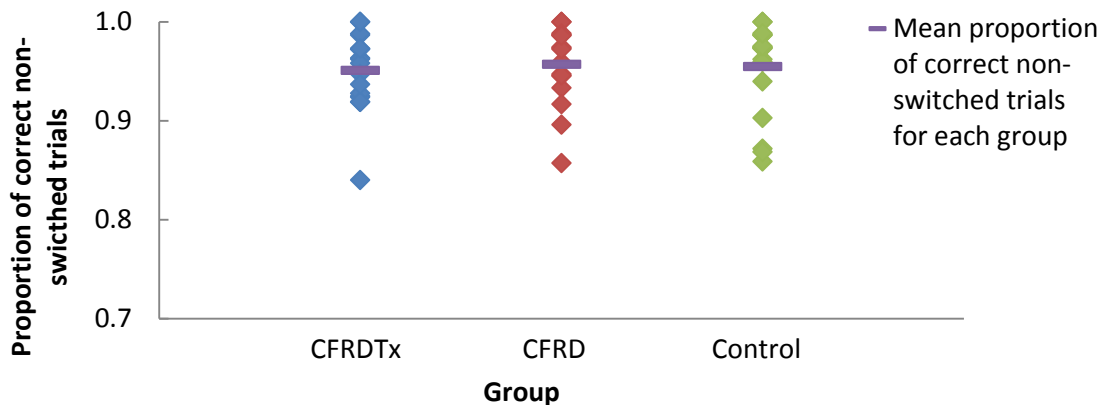
Figure 7.75 Study 3. Number of correct non-switched trials on the AST (excluding one outlier) for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.7.2   Reaction time for correct non switched trials

There was a trend for a significant main effect of group, $F(2, 51) = 2.93$, $p = .063$, $\eta_p^2 = .103$ ($R^2 = .103$), but the post hoc tests revealed no significant differences between the groups (see Figure 7.76).
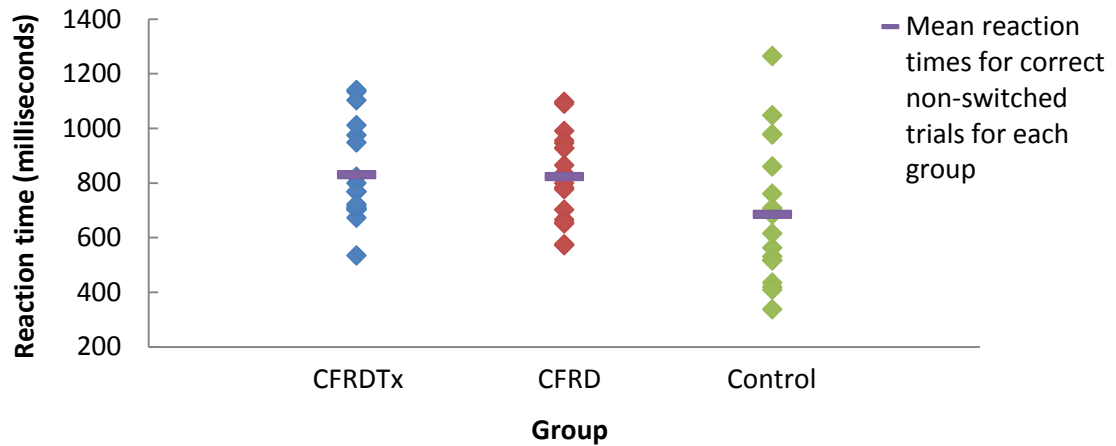
Figure 7.76 Study 3. Reaction time for correct non switched trials on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.8 Omission errors

Data were inverse transformed due to severe positive skewness. There was no significant main effect of group, $F(2, 51) = 1.64$, $p = .20$, $\eta_p^2 = .060$ ($R^2 = .060$; see Figure 7.77).
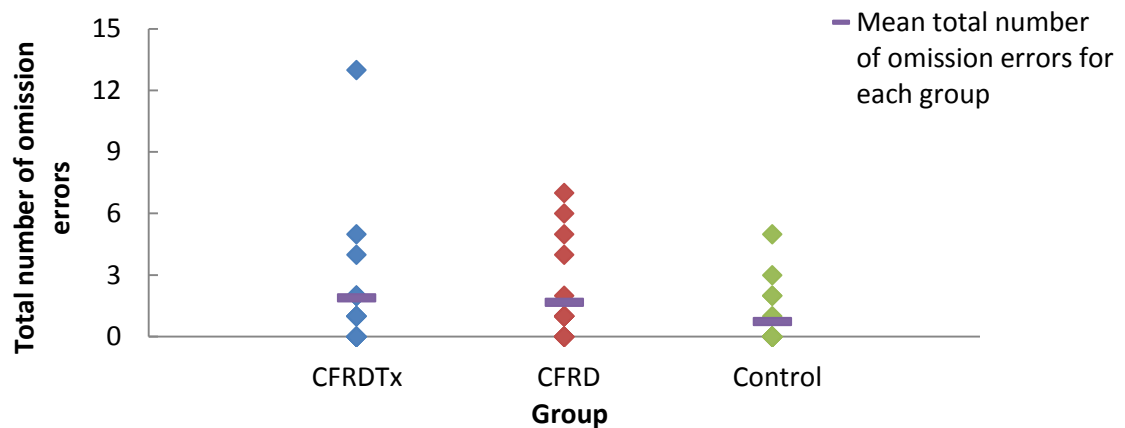
Figure 7.77 Study 3. Total number of omission errors produced on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.9 Commission errors

There were too few data points to perform analysis for commission errors (4 occurrences; CFRDTx = 2, CFRD = 2). This showed that participants did not, on the whole, respond too soon, either prior to the end of the pre-empt window or prior to the stimulus being shown.

7.3.4.7.10 Congruency cost

Data were logarithm transformed due to substantial positive skewness. There was no significant main effect of group, $F(2, 51) = 0.81$, $p = .45$, $\eta_p^2 = .031$ ($R^2 = .031$). Figure 7.78

shows that on average, participants in all three groups responded faster to congruent trials than incongruent trials.
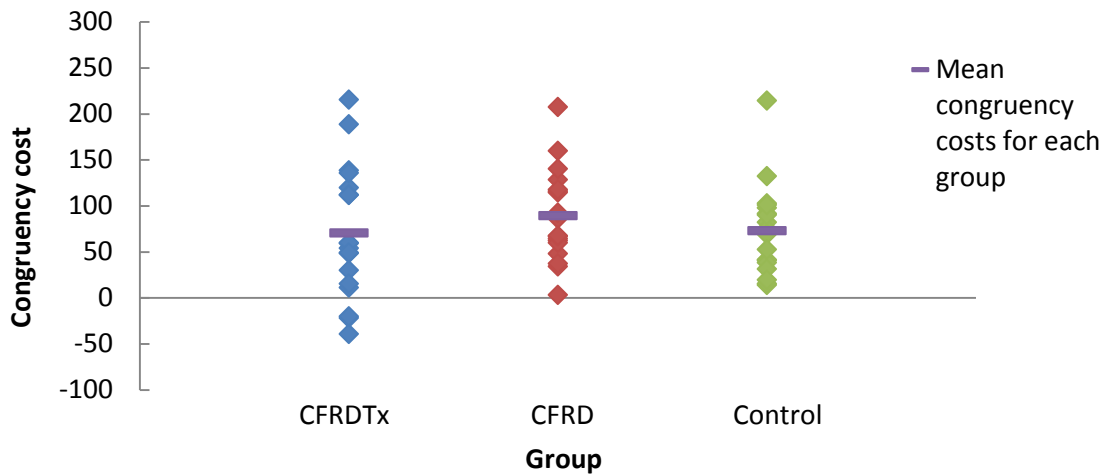
Figure 7.78 Study 3. Congruency cost for correct trials (subtraction of congruent from incongruent reaction times for correct trials) on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.4.7.11 Switch cost

Data were reflected and a square root transformation applied due to moderate negative skewness. There was no significant main effect of group, $F(2, 51) = 0.40$, $p = .67$, $\eta_p^2 = .015$ ($R^2 = .015$; see Figure 7.79). On average, participants in all three groups were faster at responding to non switched trials than switched trials as expected.
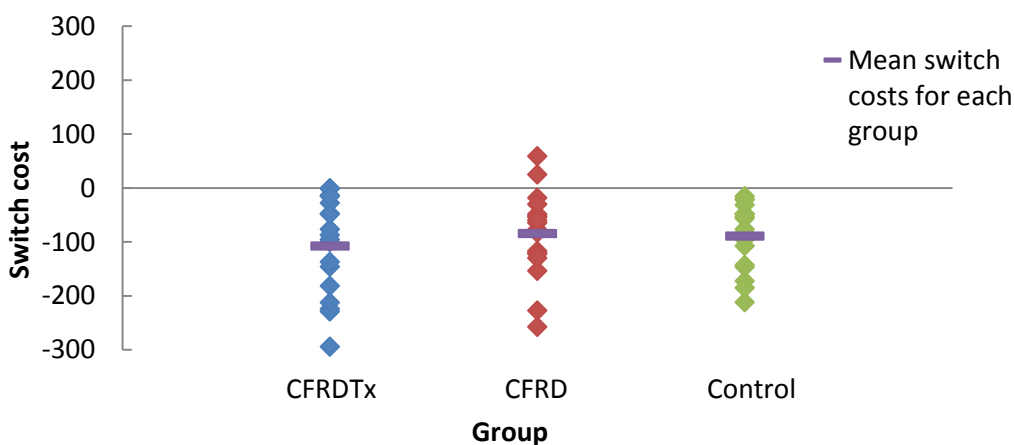
Figure 7.79 Study 3. Switch cost for correct trials (subtraction of switched from non switched reaction times) on the AST for each experimental group (CFRDTx, CFRD and healthy control)

7.3.5 Cognitive test evaluation questionnaire (CTEQ)

Table 7.7 shows there were no differences in scores on any of the cognitive workload measures between the three groups on the CTEQ.

Table 7.7 Study 3. Subjective experience of completing the cognitive test battery in people with CFRDTx, CFND and controls

	CFRDTx group n=18 Mean (SE)	CFRD group n=18 Mean (SE)	Healthy control group n=18 Mean (SE)	F (2,51)	*p* value	η_p^2
Time pressure	30.28 (6.39)	33.28 (5.88)	44.44 (8.00)	0.91	.41	.034
Test difficulty	40.67 (4.19)	46.89 (5.24)	50.89 (5.57)	0.85	.43	.032
Ability to concentrate	78.61 (3.62)	87.11 (2.95)	84.61 (4.92)	2.09	.14	0.76
Effort	86.50 (2.92)	88.94 (2.14)	94.33 (1.47)	2.42	.10	.087
Performance	56.00 (4.16)	58.06 (3.20)	62.00 (3.70)	0.68	.51	.026
Frustration	40.72 (5.32)	41.83 (5.20)	40.83 (6.57)	0.01	.99	<.001

Figures 7.80 and 7.81 show the frequency of participants' ratings regarding which test within the battery was the hardest and easiest, respectively. The CFRD group was more likely to rate the RVP as the hardest cognitive test while the controls and CFRDTx group were more likely to rate the SSP the hardest. Ratings of which test participants found the easiest were more variable across tests. The PRM test was rated as easiest by more of the CFRDTx and control groups, while the VRM was rated as easiest by more of the CFRD group.
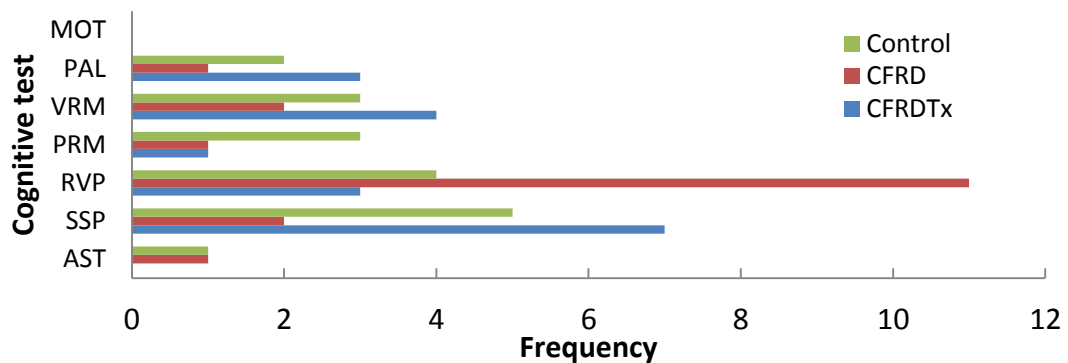
Figure 7.80 Study 3. Distribution of the frequency with which participants in each group identified each test within the battery as the hardest
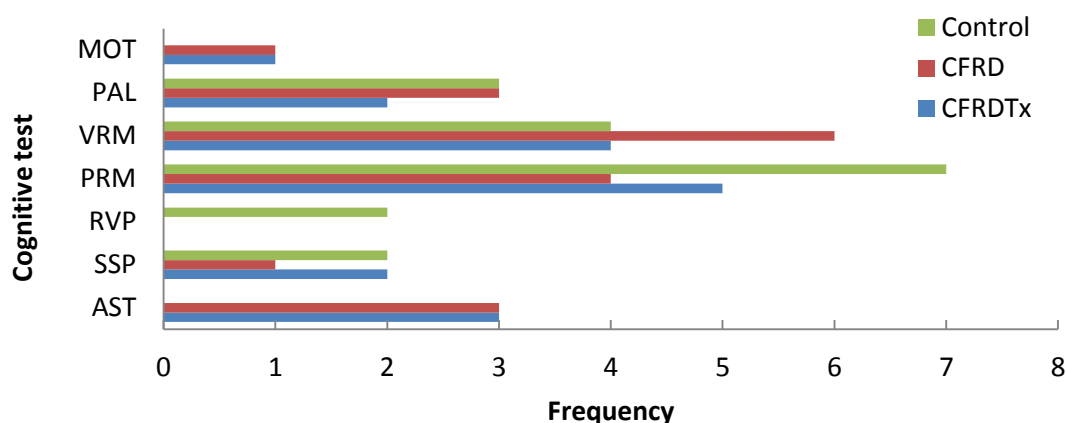
Figure 7.81 Study 3. Distribution of the frequency with which participants in each group identified each test within the battery as the easiest

7.4 Summary of findings from Study 3

7.4.1 Participant characteristics

- In the CFRDTx group, 17 people had received a lung transplant, and 1 person had received a liver transplant. Of the 17 lung transplant recipients, 2 were heart and lung, and 2 people had subsequently received a kidney transplant after an average period of 11.5 years.

- The three groups were matched on age, gender and education level achieved.

- There were no significant differences between groups for the time of day testing was completed, SES, weight, CO (COppm and %COHb), anxiety score on the HADS or the number of subjective minor daily cognitive errors.

- More participants in the control and CFRDTx group were in employment compared to people in the CFRD group.

- There was a trend for people with CFRDTx to have a lower BMI than controls.

- Blood glucose levels were significantly lower in the control group relative to the two groups of people with CFRD (with and without transplant).

- The CFRDTx and control groups subjectively rated their health as significantly better and there was a trend for lower scores on the depression scale of the HADS than for those in the CFRD group. There was a trend for the CFRDTx to rate their health as higher than the control group.

- There were no significant differences between the two CF groups for clinical characteristics except the CFRDTx group had an average higher FEV1, FEV1%predicted, FVC%, vitamin A, serum creatinine and urea level, an average lower vitamin D level and a trend for higher oxygen saturation levels and receiving less IV treatment than CFRD.

7.4.2 Findings from the cognitive tests (Aim 1)

A detailed summary of the outcomes for each tests is presented in Table 7.8. Taken together, the cognitive assessments indicated that:

- People with CFRDTx performed worse than controls tests of on attention and processing speed (RVP, AST), spatial working memory (SSP) and cognitive flexibility (AST) and to a lesser extent verbal memory (VRM).
- People with CFRD performed worse than controls on tests of attention and processing speed (RVP), spatial working memory (SSP) and cognitive flexibility (AST) and to a lesser extent verbal memory (VRM).
- There were no significant differences in cognitive test performance between people with CFRD and CFRDTx.
- Cognitive impairment was not evident for motor function (MOT) or visual memory (PRM) and new pattern learning (PAL)

Table 7.8 Study 3. Summary of cognitive test outcomes for Aim 1: the effect of CFRDTx relative to CFRD and controls, and CFRD relative to controls ('+' better performance, '-' worse performance, '0' no difference)

Test	Outcome measure	Covariate added	The effect of CFRDTx relative to controls	The effect of CFRD relative to controls	Differences between CFRDTx and CFRD
MOT	Mean error	No	0	0	0
	Reaction time	No	0	0	0
PAL	Stages completed	No	0	0	0
	Stages completed on first trial	Yes[83]	0	0	0
	First trial memory score	Yes[84]	0	0	0
	Total trials	Yes[84]	0	0	0
	Total errors at n patterns	No	0	0	0
	Total errors	Yes[84]	0	0	0
	Total errors at n patterns	No	0	0	0
VRM	Immediate free recall	No	0	0	0
	Immediate novel words	No	n/a	n/a	n/a
	Immediate perseverations	No	-	0	0
	Immediate target recognition	No	0	0	0
	Immediate false alarm recognition	No	0	0	0
	Delayed free recall	No	0	0	0
	Delayed novel words	No	0	-(trend)	0

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[83] 'Stages completed' was also added in the model as a covariate, but was not a significant predictor of stages completed on the first trial.

[84] 'Stages completed' was also added in the model as a covariate. There was a trend for stages completed to be a significant predictor of first trial memory score.

Test	Outcome measure	Covariate added	The effect of CFRDTx relative to controls	The effect of CFRD relative to controls	Differences between CFRDTx and CFRD
VRM *continued*	Delayed perseverations	No	0	0	0
	Delayed target recognition	No	0	0	0
	Delayed false alarm recognition	No	0	0	0
PRM	Immediate number correct	No	0	0	0
	Immediate reaction time	No	0	0	0
	Delayed Number correct	No	0	0	0
	Delayed reaction time	No	0	0	0
RVP	Total hits	No	-	-	0
	Total hits at each minute	No	-	-	0
	False Alarms	No	0	-	0
	Mean reaction time for hits	No	-(trend)	0	0
	Reaction time: minute by minute	No	0	0	0
	A' Prime	No	-	-	0
	B' Prime	No	0	0	0
SSP	Span length	No	-	-	0
	Total number of attempts	Yes[85]	0	0	0
	Mean time to first response	Yes[85]	-	-	0
	Mean time to last response	Yes[85]	-	-	0
	Total errors	Yes[85]	0	0	0
	Total usage errors	Yes[85]	0	0	0

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[85] Span length was also included in the model as a covariate and was a significant predictor for total number of attempts, mean time to first and last response and errors (total and usage)

Test	Outcome measure	Covariate added	The effect of CFRDTx relative to controls	The effect of CFRD relative to controls	Differences between CFRDTx and CFRD
AST	Total correct trials	No	0	0	0
	Mean reaction time for correct trials	No	-(trend)	-(trend)	0
	Correct direction trials	No	0	0	0
	Mean reaction time for direction trials	No	-(trend)	-(trend)	0
	Correct side trials	No	-	-	0
	Mean reaction time for side trials	No	- (trend)	- (trend)	0
	Correct congruent trials	No	0	0	0
	Mean reaction time for congruent trials	No	- (trend)	- (trend)	0
	Correct incongruent trials	No	0	0	0
	Mean reaction time for incongruent trials	No	0	-	0
	Correct switched trials	No	0	0	0
	Mean reaction time for switched trials	No	0	-	0
	Correct non-switched trials	No	0	0	0
	Mean reaction time for non-switched trials	No	0	0	0
	Omission errors	No	0	0	0
	Commission errors	No	0	0	0
	Congruency cost	No	0	0	0
	Switch cost	No	0	0	0

7.4.3 Findings from the subjective ratings questionnaires (Aim 2 and 3)

- Overall sleep quality did not differ between the groups in terms of ratings for the previous week and night before the test session. People with CFRD tended to report they had more restless sleep, more periods of wakefulness, it was harder to wake up, and felt less alert on waking compared to controls.

- Participants reported feeling more stressed during the past month compared to the past week. Those in the CFRD group to report greater stress than those in the control group.

- People with CFRD reported feeling less contented, mentally alert and energetic, sleepier and having a lower ability to concentrate than the control group at the time of testing. People with CFRDTx reported feeling sleepier, and a tendency to have a lower ability to concentrate than the control group.

- There were no differences between the three groups on the cognitive workload measures.

- The CFRD group was more likely to rate the RVP as the hardest while the controls and CFRDTx rated the SSP the hardest.

- Ratings of which tests participants found easiest were most widely distributed across tests. The PRM test was rated as easiest by more of the CFRDTx and control groups, while the VRM was rated as easiest by more of the CFRD group.

7.5 Discussion

The first aim of this study was to investigate cognitive function in people with CFRDTx compared to people with CFRD (who have not undergone transplantation) and healthy controls. The second aim was to investigate whether people with CFRDTx report subjective cognitive impairments compared people with CFRD and a healthy control group. The third aim was to investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness) between people with CFRDTx, people with CFRD and healthy controls. Factors associated with cognitive functioning such as sleep quality, stress and mood were also examined since these may be improved following transplantation, due to reduced fatigue and better quality of life.

7.5.1 Aim 1: To investigate cognitive function in people with CFRDTx compared to people with CFRD (who have not undergone transplantation) and healthy controls.

The present cross sectional study demonstrated clear impairment in cognitive function in the two CF patient groups compared with controls in the domains of attention and processing speed, working memory and cognitive flexibility and to a lesser degree verbal memory (see section 7.4.2). Although there were no significant cognitive differences between the CF groups, overall the CFRDTx group performed slightly better on the tests where impairment was apparent.

The cognitive domains found to be impaired in people with CFRDTx are similar to those in which changes occur post transplant. Smith et al. (2014) showed that after lung transplantation, cognitive flexibility improved, and Hoffman et al. (2012) showed that verbal memory improved,

and executive function improved in younger age participants. Although these studies tended to have samples with a higher mean age, which was partly due to not exclusively including people with CF in their sample, they did control for CF in their analysis. In the present study, the mean age of people with CF was approximately 40 years, compared to 24 years in the study by Smith et al. (2014). The lack of improvement in the CFRDTx group compared to CFRD may therefore be an effect of age. Given that 40 years old is considered old age in CF (see Chapter 1, section 1.1.1) it may be that CF induces cognitive changes that are normally associated with ageing.

Hoffman et al. (2012) found that executive function scores improved in younger participants and declined in older participants, and that decline was more evident in people who were older (>57 years) and had fewer years of education (<12 years). This study did not see people with CFRDTx decline significantly on any aspects of cognitive function compared to people with CFRD, and as the present matched participants on age, gender and education, any effect of age and education is likely to have been controlled for.

The time since transplant may have also contributed to the lack of a significant improvement in cognitive function in people with CFRDTx. On average, CFRDTx participants were 9 years post (first) transplant. Therefore any initial significant improvement in verbal memory, executive function, and cognitive flexibility in people with CFRDTx may have diminished with CF disease progression. This is supported by the finding that people with CFRDTx had higher levels of creatinine and urea, indicative of kidney disease, than both other groups. The domains in which cognitive impairment was demonstrated in CFRD and CFRDTx are commonly observed to be impaired in people with T1DM and T2DM (see Chapter 5, section 5.1). Although people with CF are more likely to develop post transplant diabetes (see section 7.1.1), people in the current sample had, on average, been diagnosed with CFRD for 12 years. Hence CFRD was already present for many years pre transplant. In people without CF, it is probable that lung transplantation restores previous good health, while for people with CF, lung transplantation does not cure someone of CF as CFTR is present throughout the body. Therefore, cognitive impairment already induced by diabetes is possibly too advanced to be reversed.

Study 1 (Chapter 5) showed that a deficit in processing speed was more pronounced in people with CFRD compared to controls. A slowing in processing speed was also present in this study in both groups of people with CF, but to a lesser degree in those in people with CFRDTx. However, as in Study 1, this may be explained by a speed –accuracy trade off. On the RVP test, people with CFRDTx were slightly better at detecting target sequences than CFRD, but this was at the expense of tending to respond more slowly. On the SSP task, people with CFRDTx were slightly worse on tests of increased span length than people with CFRD, but this may have been the result of less thinking time before making a response, and responding faster to recall a sequence. On the AST, there was no difference in accuracy between the three groups, except for side trials, but this was at the expense of tending to respond slower for the two CF groups. Together, these findings support the hypothesis that CFRD is associated with a slowing in processing speed as seen in T1DM and T2DM (Brands et al., 2005; Awad et al., 2004), and that transplantation does not alleviate this deficit.

7.5.2 Aim 2: To investigate whether people with CFRDTx report subjective cognitive impairments compared people with CFRD and a healthy control group.

There was no difference in the number of subjective reporting of daily minor cognitive daily errors which had occurred in the past 6 months between people with CFRDTx, CFRD and healthy controls. This supports the conclusion reported in Study 1, that there is a lack of association between objectively and subjectively reported memory impairment in people with CF. The suggestion by Hertzog and Pearman (2013) that depressive symptomology is likely explain the number of subjective cognitive complaints people report is not supported in this study. There was a trend for people with CFRD to have higher depression scores than people with CFRDTx, but this was not mirrored by people with CFRD making significantly more complaints of minor cognitive failures.

7.5.3 Aim 3: To investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness) between people with CFRDTx, people with CFRD and healthy controls

Smith et al. (2014) proposed that the mechanism behind improved performance in people who had received a lung transplant was due to a reduction in fatigue and hypoxia. In the present study, people with CFRDTx had significantly better lung function scores, but this did not translate into significant improvements in objectively measured cognitive function post transplant. This suggests that improvement in lung function does not outweigh the negative impact that diabetes has on cognitive function. Alternatively, the reduction of fatigue and hypoxia may have conferred beneficial effects on cognitive performance, but as mentioned above, people with CFRDTx had higher levels of creatinine and urea indicative of kidney disease. Chronic kidney disease has been shown to be associated with impairments in verbal learning, visual attention, cognitive flexibility and executive functioning (Elias et al., 2009; Schneider et al., 2012). Therefore, the mechanism of cognitive dysfunction in people with CFRDTx may be related to kidney disease, whereas people with CFRD may experience cognitive impairment due to hypoxia.

Fasting blood glucose levels were slightly higher in people with CFRDTx compared to people with CFRD, but both groups of people with CF had significantly higher levels than controls. This was a function of disease and therefore not controlled for in the analysis. The blood glucose cut off level for inclusion in this study (compared to Study 1) had to be relaxed slightly due to the interaction of post transplant medication influencing the ability for people with CFRDTx to achieve good glucose control and achieve blood glucose levels lower than 12mmol/L. There was no difference in HbA1c levels between people with CF, which may explain why performance was similar in both groups compared to controls.

Study 1 (Chapter 5, section 5.5.3) discussed how features of the metabolic syndrome may have contributed to the cognitive impairment seen in people with CF (Gunstad et al., 2007; Meusel et al., 2014). Although there was a trend for people with CFRDTx to have a lower BMI than controls, overall, BMI was in the normal range. Therefore, being overweight or obese did not contribute to the cognitive impairment seen in people with CF in this study. Prehypertension has been

shown to be associated with cognitive impairment in executive function and processing speed, and both groups of people with CF had SBP indicative of prehypertension, which may have contributed to the degree of impairment seen in these domains. CRP levels were also slightly elevated in both CF groups, and this may explain the impairment seen on visual working memory (Noble et al., 2010).

The findings suggest that sleep quality and perceived stress improve post transplant as people with CFRD tended to report they had more restless sleep and it was harder to wake, had significantly more periods of wakefulness, and felt less alert on waking compared to controls. As there were no significant differences in sleep quality or perceived stress between people with CFRDTx and controls, these factors cannot explain the significant impairment in performance demonstrated on verbal memory, attention and processing speed, spatial working memory and cognitive flexibility relative to controls.

Both groups of people with CF reported a lower ability to concentrate and felt sleepier before starting the tests compared to controls. People with CFRD also reported a lower ability to concentrate compared to people with CFRDTx. The lack of ability to concentrate may partially explain worse performance in the domains of attention and processing speed in people with CF. However, as attention and processing were impaired in both CFRD and CFRDTx relative to controls, it is possible that people with CFRD may have expended more effort to match the performance of those with CFRDTx. This is supported as more people in the CFRD group rated RVP as the hardest cognitive test relative to the other groups. Nevertheless, the ratings reported immediately after the cognitive tests did not show there were any differences between groups in how hard people concentrated (CTEQ).

7.6 **Conclusion**

There was consistent evidence that CFRD is associated with cognitive impairment in attention and processing speed, spatial working memory, cognitive flexibility and, to a lesser extent, verbal memory. However, cognitive function does not seem to improve post transplantation in people. The progressive nature of CF disease and nephrotoxic post transplant medication may cause people with CF to develop cognitive impairment due to renal disease despite of improved lung function.

Chapter 8

Changes in cognitive function in post transplanted people with CFRD (CFRDTx) during a 18±6 month period: a follow up study (Study 4)

8.1 Introduction

The study reported in Chapter 7 showed clear differences in cognitive function in people with CFRD and CFRDTx compared with healthy controls in the domains of verbal and working memory, attention and processing speed, and cognitive flexibility (see Chapter 7, section 7.4.2). Furthermore, there were clear differences between CFRD and CFRDTx with significantly worse cognitive function in CFRDTx than CFRD in terms of verbal memory (number of perseverations at immediate verbal recall), attention and processing speed (reaction time for hits on the RVP). In addition, the results of this study suggest that factors associated with the metabolic syndrome (hypertension and inflammation), depression, glycaemic control (blood glucose level during testing), serum creatinine and urea, sleep quality, stress and mood may have contributed to the degree of impairment seen in people with CF.

Chapter 3 (section 3.2.3.3) described how chronic hyperglycaemia, duration of diabetes and the development of microvascular complications have been proposed to contribute to the development of cognitive impairment in people with T1DM and T2DM. Chapter 6 (section 6.1) proposed that poor glycaemic control and duration of diabetes (and the development of microvascular complications) may also be mechanisms for a decline in cognitive function in people with CFRD. It is therefore plausible that over time, people with CFRDTx may also experience a decline in cognitive function, due to longer diabetes duration and the development of microvascular complications. Conversely, people with CFRDTx may have experienced improved glycaemic control which may have beneficial effects on cognitive function. Furthermore, factors which have previously been shown to be associated with cognitive function such as serum creatinine and urea, depression, sleep quality, and mood may have also changed as a function of time and disease.

Chapter 7 investigated cognitive function in people with CFRDTx at one point in time (on average 9 years post transplant). Therefore it is unknown how their profile of cognitive function has changed in the preceding 9 years since transplantation, if at all. Longitudinal studies are needed to examine if people with CFRDTx show evidence of cognitive decline, or if their cognitive functioning is stable. The first aim of the study presented in this chapter was to investigate whether cognitive function had changed over a period of 18 (±6) months in people with CFRDTx. The second aim was to investigate whether the number of subjective cognitive daily errors had changed over this period of time. The third aim was to

investigate whether there were any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period. It is hypothesised that worsening of factors related to glycaemic control may impact on cognitive functioning in people with CFRDTx.

8.2 **Method**

8.2.1 **Design**

A repeated measures design with two levels of time of testing; i) baseline and ii) follow up (18±6 months later).

8.2.2 **Participants**

The 18 PI people with CFRDTx who participated in Study 3 (Chapter 7) were eligible to take part in follow-up testing providing they still met the inclusion criteria outlined in Study 3 (see Chapter 7, section 7.2.2.1) at follow-up. Participants were not approached if they met any of the exclusion criteria outlined in Study 3 at follow-up (see Chapter 7, section 7.2.2.2).

8.2.3 **Cognitive Tests**

The same CANTAB cognitive test battery employed in Study 2 was used for follow-up testing in people with CFRDTx. Details of these tests and outcome measures are described in Chapter 6 (section 6.2.3).

8.2.4 **Questionnaires**

The following self report measures were administered. Details of questionnaires used can be found in Chapters 5 (section 5.2.4) and 6 (6.2.4).

- The Leeds Sleep Evaluation Questionnaire (LSEQ**)** - modified (previous night and last week; see section 5.2.4.1)
- The Perceived Stress Scale (PSS-10) –modified (previous week and month; see section 5.2.4.2)
- Hospital Anxiety and Depression Scale (HADS; see section 5.2.4.3)
- Ratings of mood and mental alertness (see section 5.2.4.4)
- Cognitive Test Evaluation Questionnaire (CTEQ; see section 5.2.4.5)
- Cognitive Failures Questionnaire (CFQ; see section 5.2.4.6)
- Cognitive Failures Questionnaire for others (CFQ for others; see section 6.2.4)
- Cognitive Difficulties Scale (CDS; see section 6.2.4)
- Debriefing questionnaire (see section 6.2.4)

8.2.5 Physiological Measures

8.2.5.1 Blood glucose

Participants were asked to fast for two hours before the testing session and a single blood glucose measurement was taken using the same procedure as in Study 1 (see Chapter 5, section 5.2.5.1).

8.2.5.2 Carbon monoxide

Carbon monoxide levels were monitored using the same procedure as Study 1 (Chapter 5, section 5.2.5.2).

8.2.6 Procedure

8.2.6.1 Screening and testing session

People with CFRDTx who had taken part in Study 3 were checked for eligibility against the inclusion and exclusion criteria described in Chapter 7 (see section 7.2.2.1 and 7.2.2.2) with the assistance of the CF specialist clinical dietitian using EMIS. Screening and testing sessions followed the same procedures as Study 2 (see Chapter 6, section 6.2.6.1 and 6.2.6.2). Figure 8.1 below summarises the procedure.

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┌─────────────────────────────────────────┐      ┌──────────────┐
│   Written informed consent obtained      │──┐   │ Recruitment  │
└─────────────────────────────────────────┘  │   │     and      │
                    │                         ├───│  screening   │
                    ▼                         │   │    visit     │
┌─────────────────────────────────────────┐  │   └──────────────┘
│ Recruitment Information Questionnaire (RIQ)│─┘
└─────────────────────────────────────────┘


┌─────────────────────────────────────────┐──┐
│   LSEQ (Typical night's Sleep last night) │  │
│ LSEQ (Typical night's Sleep over past week)│ │
│   PSS-10 (Perceived stress over past week) │ │
│  PSS-10 (Perceived stress over past month) │ │
│                  HADS                     │  │
│    VAS Ratings of mood and mental alertness│ │
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                    │                         │
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┌─────────────────────────────────────────┐  │
│ Finger prick blood glucose measurement taken │
│      using a GlucoMen® LX meter           │  │
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┌─────────────────────────────────────────┐  │   ┌──────────────┐
│   Carbon monoxide level measured using a  │  │   │              │
│              Smokerlyzer                  │  │   │              │
└─────────────────────────────────────────┘  ├───│   Test day   │
                    │                         │   │              │
                    ▼                         │   │              │
┌─────────────────────────────────────────┐  │   └──────────────┘
│   Cognitive test assessment using CANTAB  │  │
│            (7 tests in total)             │  │
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                    │                         │
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┌─────────────────────────────────────────┐  │
│                  CTEQ                     │  │
│                  CFQ                      │  │
│              CFQ for others               │  │
│                  CDS                      │  │
│          Debriefing Questionnaire         │  │
└─────────────────────────────────────────┘  │
                    │                         │
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┌─────────────────────────────────────────┐  │
│   Debriefed and compensated with a £25    │  │
│          Love2Shop Voucher                │  │
│                                           │  │
│   Car parking charges paid if applicable  │  │
│                                           │  │
│ Travel expenses (up for £20) paid if testing was│
│ completed on the Unit outside of their allocated│
│              appointment                  │──┘
└─────────────────────────────────────────┘
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Figure 8.1 Study 4 flow diagram to indicate the order of screening and test day procedures

8.2.7   NHS Ethical Approval

This study was approved by the Leeds West NHS REC on 12th May 2015 (REF: 13/YH/0219; Substantial amendment 2). Approval from Leeds Teaching Hospitals NHS Trust R&D was gained on 15th May 2015. Following approval from both NHS REC and R&D, the study was added to the NIHR CRN Portfolio database.

At screening, participants were given written and verbal information about the purpose of the follow up study, all procedures involved and were made aware they could withdraw at

any point without having to give a reason. It was made explicit that withdrawing from the study had no consequences for their clinical care. The informed consent of each participant was obtained in writing prior to commencement of the study.

There was the risk of hypoglycaemia occurring on the test day due to fasting for two hours. If hypoglycaemia was detected (<3.9mmol/L) or symptoms were reported by a participant, food and drink were immediately provided to restore a person's blood glucose level to within the normal range and they were withdrawn from the follow up study. This did not occur during the study.

8.2.8   Method of statistical analysis

Cognitive test data were extracted from CANTAB, entered into Excel and checked for accuracy. The delayed VRM data were recorded on a score sheet for each test session prior to entry into Excel, where it was checked. All subjective data were scored, entered and checked for accuracy in Excel.

The analytical approach was reviewed by the independent statistician (Quadt Consultancy BV, NL). A p-value of .05 was considered statistically significant. P values below 0.1 were considered trends. All data were analysed using SPSS version 22.0 (IBM Corp Inc., Armonk, NY, USA). All plotted data represent individual data points and means unless otherwise stated. Where data were transformed in order to normalise the distribution of residuals, the raw data scores are plotted for clarity.

Participant characteristics data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Analysis of participant characteristics was performed to test for changes since baseline using one way repeated measures ANOVAs with time as the within subjects factor for Townsend score, height, weight, BMI, health rating, blood glucose levels (capillary, and plasma), carbon monoxide (COppm and %COHb), anxiety, depression, cognitive failures data, FEV_1, FEV_1% predicted, FVC, FVC% predicted, oxygen saturation, HbA1c, SBP, DBP, pulse, CRP, vitamins A, D and E, serum creatinine, serum urea, and albumin. Changes in education, occupation, microbiology and the number of people receiving IV treatment at the time of testing were analysed using a Chi squared or Fisher's Exact test (when the expected cell frequencies were small). A correlation was performed on the follow up CFQ data with CDS to see the relationship between these two measures.

Cognitive data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Mixed ANCOVA's were performed on the cognitive test data using time as the within subjects factor. As there was an equal split of males and females, gender was not added as a between subjects factor. There was a wide variation in the ages of participants, and the duration of time people with CFRDTx were followed up. However, including both of these as covariates would reduce the df in model. Therefore scatterplots were produced to check for a relationship with each covariate and cognitive test outcome, and the covariate only included and retained in the model if significance was below .09. On tests where

progression through the different stages/levels of the test was dependent on participant ability, other covariates were added where appropriate. For example, on the PAL test, stages completed was added as a covariate for outcome measures of stages completed on the first trial, total trials and total errors; on the SSP, span length was added as a covariate for the outcome measures of total number of attempts, reaction time and errors. Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS to correct for familywise type 1 error (Roberts & Russo, 1990).

Two way[86] repeated measures ANCOVA's with age and time since baseline as covariates were performed on the subjective data in SPSS. Subjective data were checked for homogeneity of variance and skewness and appropriate transformations applied to normalise the distribution of residuals, if required (Tabachnick & Fidell, 2013). Gender was not included in the model as a between subjects factor because of the small sample size and there was an equal number of males and females. Age was included as a covariate and only retained in the model if the p value was below .09. Where significant main effects and interactions were observed, post hoc tests were calculated with Bonferroni corrections in SPSS.

8.3   **Results**

8.3.1   **Participants**

From the 18 people with CFRDTx at baseline, 8 (4M;4F) were retested.

8.3.1.1   **Loss to follow up**

Figure 8.2 shows the reasons for loss to follow-up in Study 4.

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[86] For sleep quality, a 2 (time with 2 levels; baseline and follow up) x 2 (period with 2 levels; week and previous night) ANOVA was conducted
For perceived stress, a 2 (time with 2 levels; baseline and follow up) x 2 (period with 2 levels; week and month) ANOVA was conducted

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┌─────────────────────────────────────────────────┐
│ Study 3: 18 people with CFRDTx (8M,10F)         │
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┌─────────────────────────────────────────────┐
│ Reasons for loss to follow up:              │
│                                             │
│ Deceased n=1 (1F)                           │
│                                             │
│ Did not want to take part n=3               │
│                                             │
│  •  no reason given n=1,                    │
│  •  deteriorating health warranting         │
│     transplantation of organ n=2            │
│                                             │
│ Not suitable time health wise n=6           │
│                                             │
└─────────────────────────────────────────────┘
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┌─────────────────────────────────────────────┐
│ Study 4: 8 people with CFRDTx (4M, 4F)      │
└─────────────────────────────────────────────┘
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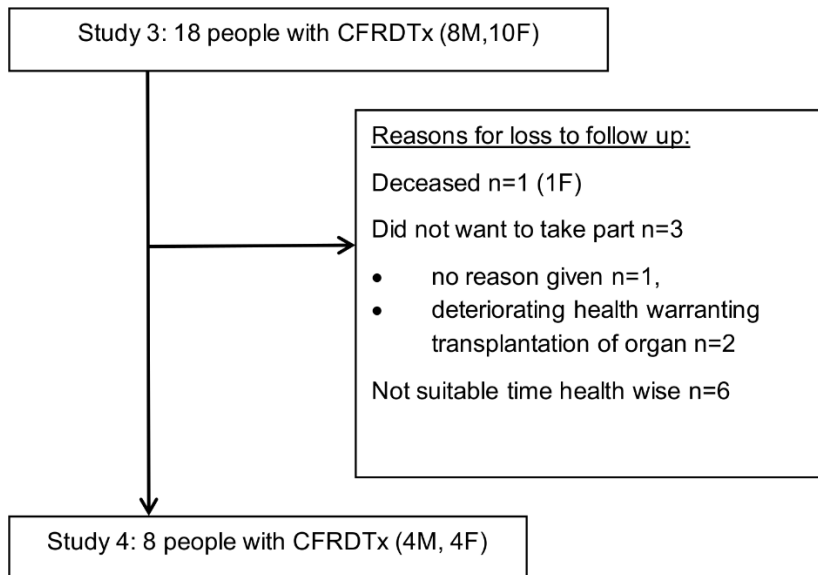
Figure 8.2 Study 4. Reasons for loss to follow up

8.3.1.2 **Participant characteristics**

Participants were retested after a period of 15.87 (SD ±4.45) months. All 8 participants were heterozygous F508del; 4 were homozygous. Table 8.1 below shows the participant and clinical characteristics for CFRDTx at baseline and follow up.

Table 8.1 Study 4. Participant characteristics at baseline and follow up for people with CFRDTx

	Baseline N=8 Mean (SE)	Follow up N=8 Mean (SE)	F (1,7)	*p* value	η_p^2
Age (years)	38.63 (3.63)	39.75 (3.69)	81.00	<.001	.92
Height (cm)	167.59 (4.01)	167.09 (4.29)	0.48	.51	.063
Weight (kg)	63.36 (4.58)	62.88 (4.92)	0.27	.62[87]	.037
BMI (kg/m^2)	22.50 (0.66)	22.05 (0.77)	0.91	.37[88]	.115
CFRD duration (years)	12.50 (3.02)	13.63 (2.98)	6.12	.043	.466
Tx duration (years)	6.98 (2.05)	8.13 (2.05)	48.16	<.001	.873
Fasting capillary blood glucose (mmol/L)	9.6 (0.93)	8.66 (0.96)	0.40	.55	.054
Plasma blood glucose (mmol/L)	7.45 (1.54)	6.56 (0.79)	0.09	.77[89]	.013
HbA1c (mmol/mol; IFCC)	58.63 (3.35)	57.25 (3.99)	0.29	.61	.040
N= with microvascular complications	0	0			
FEV$_1$	3.05 (0.23)	2.92 (0.15)	2.33	.17[90]	.250
FEV$_1$%predicted	92.25 (2.98)	91.38 (4.23)	0.05	.83	.007
FVC	3.65 (0.39)	3.53 (0.29)	1.09	.33	.135
FVC % predicted	91.63 (4.30)	91.13 (2.95)	0.28	.61[91]	.039
Oxygen saturation (%)	98.00 (0.38)	98.63 (0.38)	1.84	.22	.208
COppm	3.88 (0.48)	3.50 (0.50)	0.66	.44	.087
%COHb	1.25 (0.07)	1.23 (0.08)	0.14	.72[92]	.019
Health rating (1-10)	9.00 (0.33)	9.00 (0.38)	5.72	.048[93]	.449
Anxiety score	4.00 (1.25)	4.75 (1.18)	0.31	.59	.043
Depression score	1.50 (0.57)	1.00 (0.46)	0.66	.44	.086
SBP (mmHg)	130.50 (4.71)	132.50 (8.17)	0.08	.79	.011
DBP (mmHg)	79.13 (3.40)	79.50 (4.60)	0.01	.92	.002
Pulse (bpm)	93.13 (3.71)	85.75 (4.03)	1.70	.23	.195
Receiving IV's (n)	0	0			
CRP (mg/L)	8.64 (2.23)	5.00 (0.00)	38.67	<.001[94]	.85
Vitamin A (ng/mL)	2.58 (0.33)	2.98 (0.40)	3.72	.095[95]	.347
Vitamin D (ng/mL)	63.71 (5.47)	61.40 (6.58)	0.44	.53[96]	.059
Vitamin E (ng/mL)	32.81 (3.32)	35.44 (5.34)	0.45	.52[97]	.061
Serum creatinine (µmol/L)	120.50 (16.48)	122.00 (15.83)	0.04	.85[98]	.006
Serum urea (mmol/L)	10.93 (1.48)	11.10 (1.50)	0.002	.97[83]	<.001
Albumin (g/L)	41.88 (0.74)	43.75 (0.94)	2.51	.16	.264

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[87] Data were square root transformed due to moderate positive skewness
[88] Data at both time points were square root transformed due to substantial positive skew at baseline
[89] Data were inverse transformed due to severe positive skewness
[90] Data were reflected and logarithm transformed due to substantial negative skewness
[91] Data were reflected and square root transformed due to moderate negative skewness
[92] Data were inverse transformed due to positive skew at baseline
[93] Data were inverse transformed due to severe positive skew
[94] Data were logarithm transformed due to substantial skewness
[95] Data were square root transformed due to moderate positive skewness
[96] Data were logarithm transformed due to substantial positive skewness
[97] Data were square root transformed due to moderate positive skewness
[98] Data were inverse transformed due to moderate positive skewness

Table 8.1 shows that age, CFRD duration and time since transplantation had changed with the passage of time as expected. There were no changes in height, weight, BMI, blood glucose level (plasma, fasting), HbA1c, lung function (FEV$_1$, FEV$_1$% predicted, FVC, and FVC% predicted), oxygen saturation level, CO (ppm and %COHb), anxiety and depression score, SBP, DBP, pulse, number of people receiving IV treatment, vitamin D and E, and serum creatinine ad urea, albumin and the number of people with microvascular complications. There was a trend for vitamin A levels to have increased. Figure 8.3 shows that although there had been an improvement in fasting blood glucose and HbA1c levels, this was not significant.
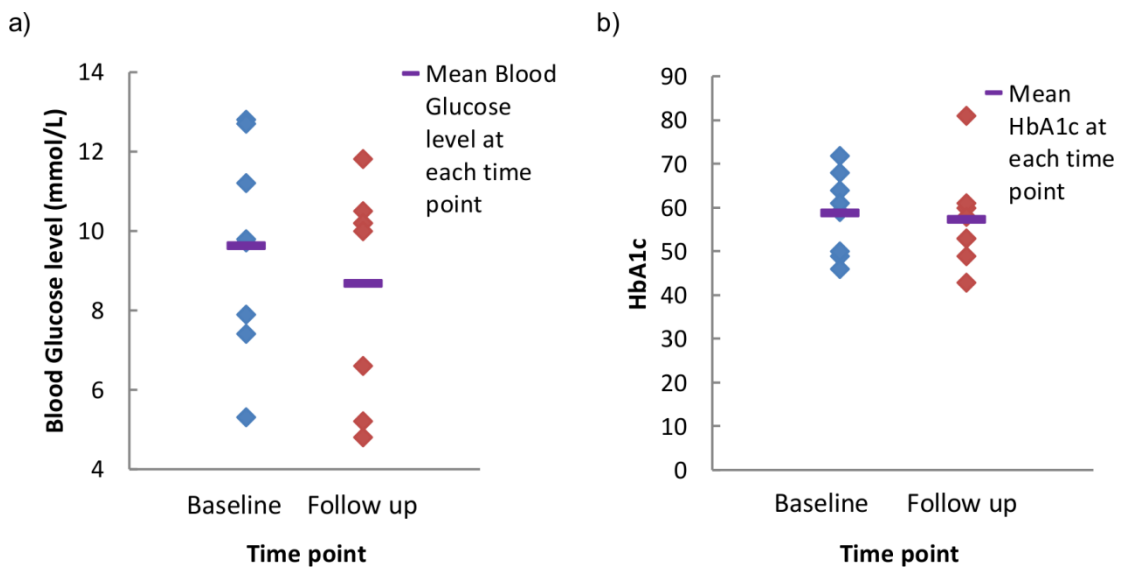
Figure 8.3 Study 4. Distribution of (a) fasting blood glucose levels and (b) HbA1c at baseline and follow up in people with CFRDTx

There was a significant improvement in CRP and a significant, albeit marginal, decline in subjective health rating. Figure 8.4 shows that at baseline, two participants had elevated CRP levels while at follow up, all participants had normal CRP levels.
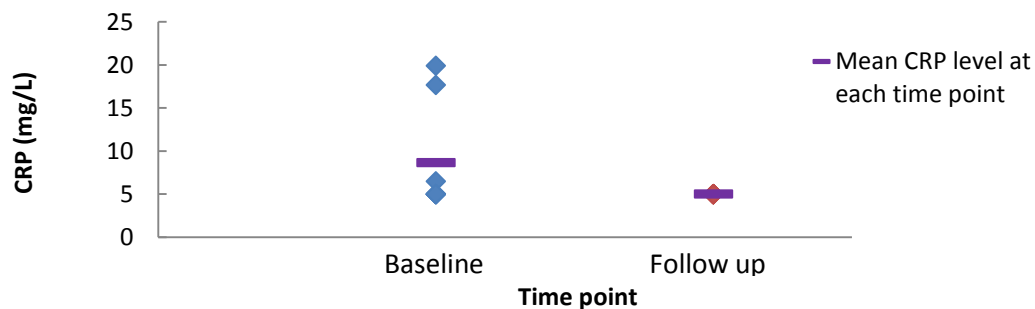
Figure 8.4 Study 4. Distribution of CRP levels at baseline and follow up in people with CFRDTx

Figures 8.5 shows there was no changed in education except one person had since completed their degree.
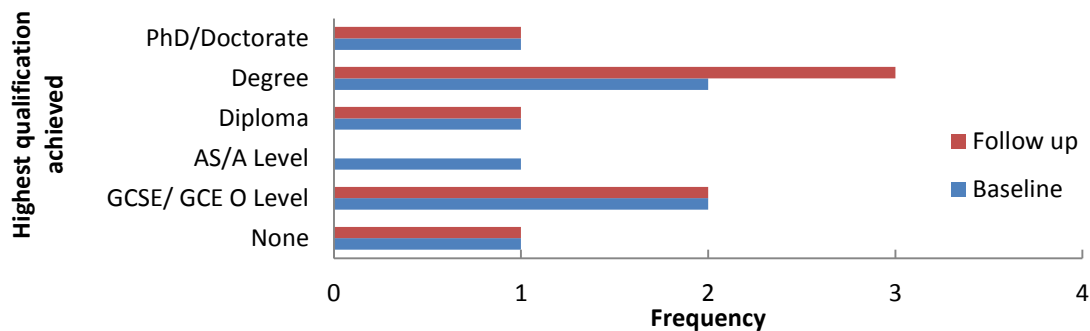
Figure 8.5 Study 4. Frequency of highest education qualification achieved at baseline and follow up in people with CFRDTx

Figure 8.6 shows that there was no change in the type of occupation except the person who was retired (due to ill health pre transplant) had now taken up full time employment again.
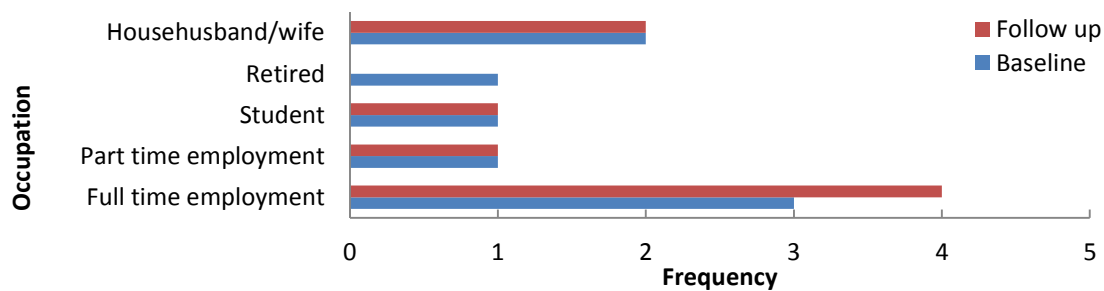
Figure 8.6 Study 4. Frequency of type of occupation at baseline and follow up in people with CFRDTx

Figure 8.7 shows there was no change in pulmonary infection except one individual now had chronic *P. aeruginosa* (previously *P. aeruginosa* negative).
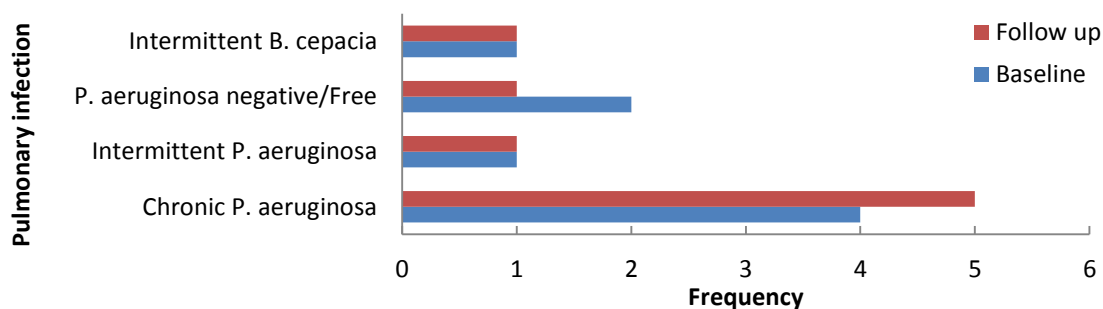
Figure 8.7 Study 4. Frequency of pulmonary infection at baseline and follow up in people with CFRDTx

8.3.2 Questionnaires

8.3.2.1 Sleep quality (LSEQ)

8.3.2.1.1 Ease of getting to sleep

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.28$, $p = .62$, $\eta_p^2 = .038$, or period, $F(1, 7) = 0.59$, $p = .47$, $\eta_p^2 = .078$ (see Figure 8.8). There was no significant time*period, $F(1, 7) = 0.005$, $p = .94$, $\eta_p^2 = .001$.
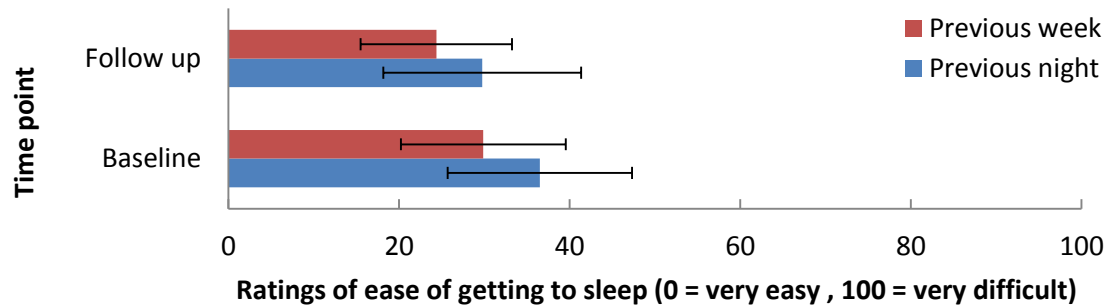
Figure 8.8 Study 4. Mean (±SE) ratings of ease of getting to sleep for the night before the testing session and previous week at baseline and follow up in people with CFRDTx

8.3.2.1.2 Time to get to sleep

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.14$, $p = .72$, $\eta_p^2 = .020$, or period, $F(1, 7) = 0.47$, $p = .52$, $\eta_p^2 = .063$ (see Figure 8.9). There was no significant time*period, $F(1, 7) = 1.66$, $p = .24$, $\eta_p^2 = .191$.
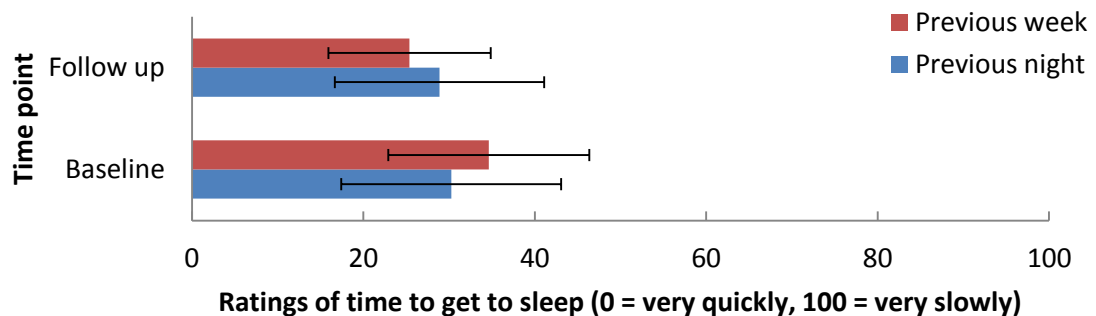
Figure 8.9 Study 4. Mean (±SE) ratings of time to get to sleep for the night before the testing session and previous week at baseline and follow up in people with CFRDTx

8.3.2.1.3 Restfulness of sleep

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.41$, $p = .54$, $\eta_p^2 = .056$, or period, $F(1, 7) = 0.05$, $p = .83$, $\eta_p^2 = .007$ (see Figure 8.10). There was no significant time*period, $F(1, 7) = 0.40$, $p = .55$, $\eta_p^2 = .055$.
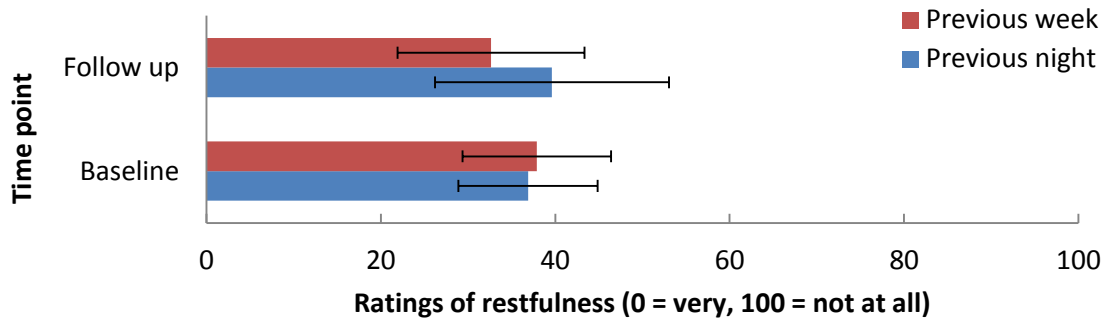
Figure 8.10 Study 4. Mean (±SE) ratings of restfulness for the night before the testing session and previous week at baseline and follow up in people with CFRDTx

8.3.2.1.4 Wakefulness

There were missing data for two participants at follow up. Data were square root transformed due to moderate positive skewness. The covariate for age was marginally significant, $F(1, 4) = 7.38$, $p = .053$, $\eta_p^2 = .648$. There was a trend for younger participants to report less periods of wakefulness for the night before the testing session and previous week at baseline but more periods for the night before the test session at follow up. There was no significant main effect of time, $F(1, 4) = 0.12$, $p = .75$, $\eta_p^2 = .03$, and period, $F(1, 4) = 0.34$, $p = .59$, $\eta_p^2 = .079$ (see Figure 8.11). There was no significant time*age interaction $F(1, 4) = 0.34$, $p = .59$, $\eta_p^2 = .077$, no period*age interaction, $F(1, 4) = 0.36$, $p = .58$, $\eta_p^2 = .083$, no time* period, $F(1, 31) = 3.35$, $p = .14$, $\eta_p^2 = .456$, and no time*period*age interaction, $F(1, 31) = 2.37$, $p = .20$, $\eta_p^2 = .372$.
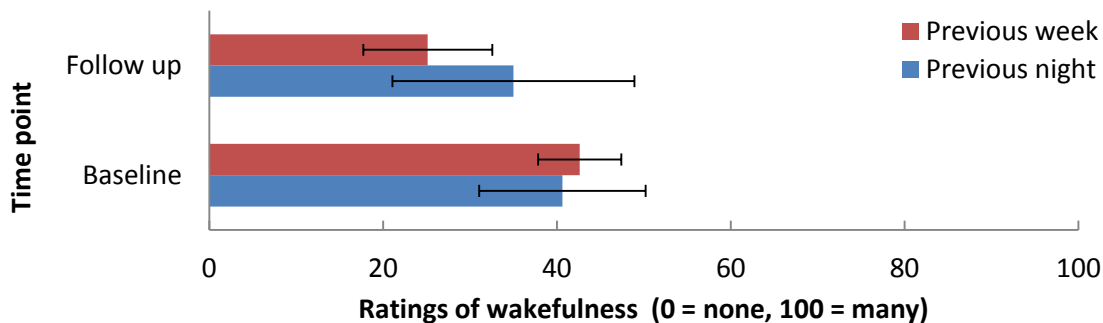
Figure 8.11 Study 4. Mean (±SE) ratings of periods of wakefulness during sleeping for the night before the testing session and previous week at baseline and follow up in people with CFRDTx

8.3.2.1.5 Ease of waking

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.27$, $p = .62$, $\eta_p^2 = .037$, or period, $F(1, 7) = 0.20$, $p = .67$, $\eta_p^2 = .028$ (see Figure 8.12). There was no significant time*period interaction, $F(1, 7) = 0.40$, $p = .85$, $\eta_p^2 = .006$.
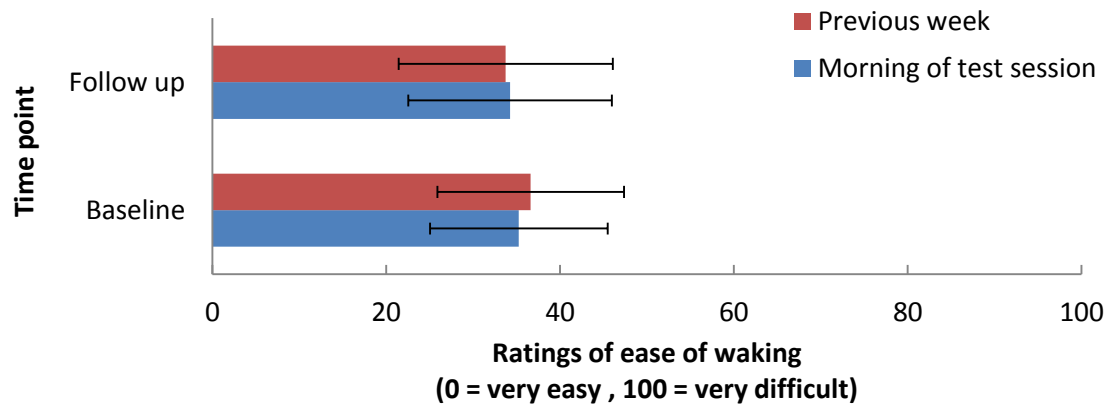
Figure 8.12 Study 4. Mean (±SE) ratings of ease of waking from sleep on the morning of the testing session and for the previous week at baseline and follow up in people with CFRDTx

8.3.2.1.6   Waking duration

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.008$, $p = .93$, $\eta_p^2 = .001$, or period, $F(1, 7) = 1.71$, $p = .23$, $\eta_p^2 = .197$ (see Figure 8.13). There was no significant time*period, $F(1, 7) = 0.04$, $p = .85$, $\eta_p^2 = .005$.
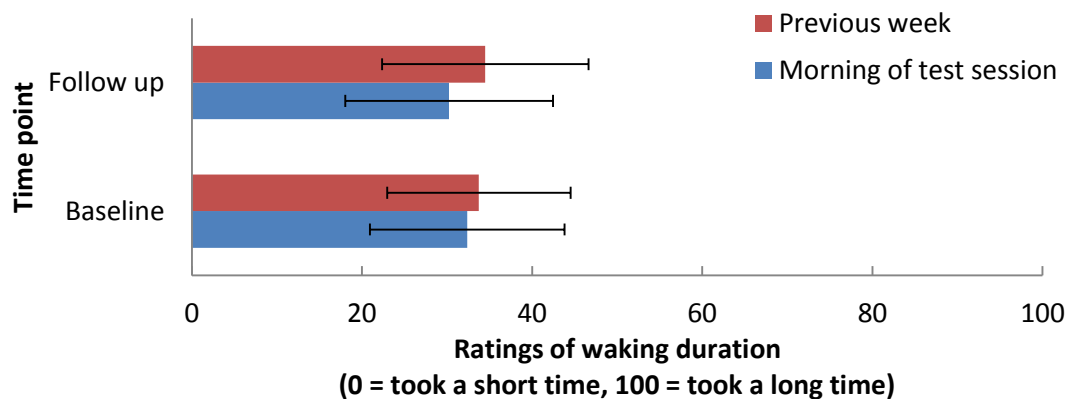
Figure 8.13 Study 4. Mean (±SE) ratings of waking duration on the morning of the testing session and for the previous week at baseline and follow up in people with CFRDTx

8.3.2.1.7   Alertness on waking

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.38$, $p = .56$, $\eta_p^2 = .051$, or period, $F(1, 7) = 0.69$, $p = .44$, $\eta_p^2 = .089$ (see Figure 8.14). There was no significant time*period, $F(1, 7) = 0.003$, $p = .96$, $\eta_p^2 < .001$.
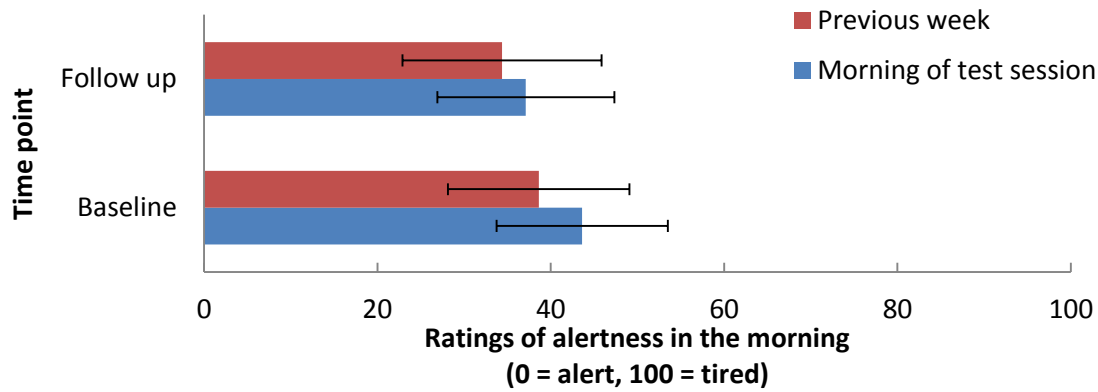
Figure 8.14 Study 4. Mean (±SE) ratings of alertness on the morning of the testing session and for the previous week at baseline and follow up in people with CFRDTx

8.3.2.1.8   Alertness 1 hour after waking

Data were square root transformed due to moderate positive skewness. There was no main effect of time, $F(1, 7) = 0.34$, $p = .58$, $\eta_p^2 = .046$, or period, $F(1, 7) = 1.43$, $p = .27$, $\eta_p^2 = .169$ (see Figure 8.15). There was no significant time*period, $F(1, 7) = 2.82$, $p = .14$, $\eta_p^2 = .287$.
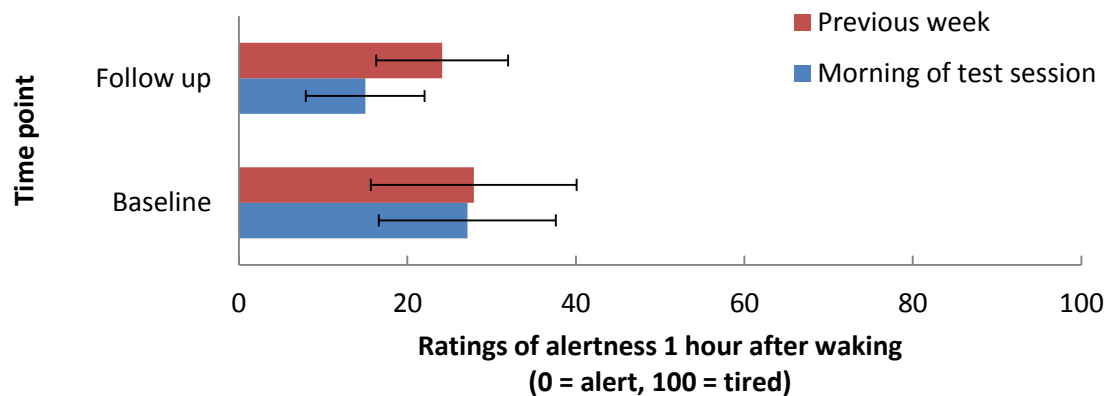
Figure 8.15 Study 4. Mean (±SE) ratings of alertness 1 hour after waking on the morning of the testing session and for the previous week at baseline and follow up in people with CFRDTx

8.3.2.2   **Perceived stress (PSS-10)**

There was no main effect of time, $F(1, 7) = 0.34$, $p = .58$, $\eta_p^2 = .046$, but there was a significant main effect of period, $F(1, 7) = 29.84$, $p = .001$, $\eta_p^2 = .810$ (see Figure 8.16), such that participants reported to have less stress in the previous week compared to previous month. There was no significant time*period, $F(1, 7) = 0.002$, $p = .97$, $\eta_p^2 < .001$.
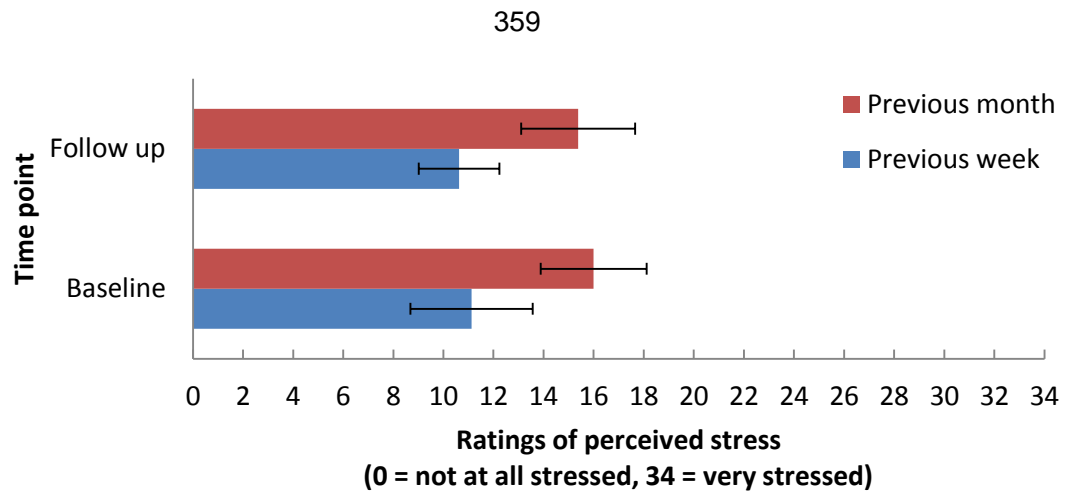
Figure 8.16 Study 4. Perceived stress ratings for the previous month and week before the test session for each group at baseline and follow up in people with CFRDTx

8.3.2.3 VAS Ratings of mood and mental alertness

8.3.2.3.1 Contentedness

There was no main effect of time, $F(1, 7) = 2.16$, $p = .19$, $\eta_p^2 = .236$ (see Figure 8.17).
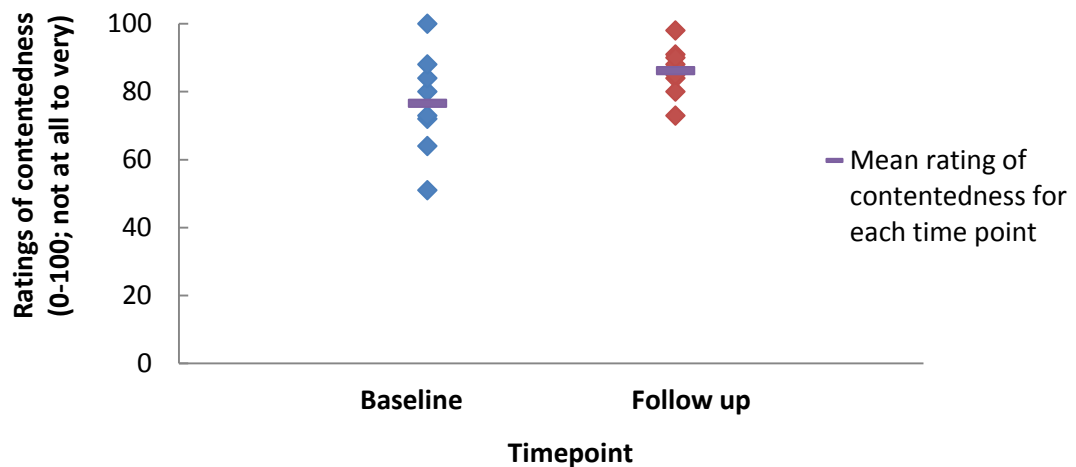
Figure 8.17 Study 4. VAS ratings of contentedness at baseline and follow up in people with CFRDTx

8.3.2.3.2 Irritability

Data were logarithm transformed due to substantial positive skewness. There was a trend for a main effect of time, $F(1, 7) = 4.60$, $p = .069$, $\eta_p^2 = .396$ (see Figure 8.18), such that participants tended to be less irritable at follow up.
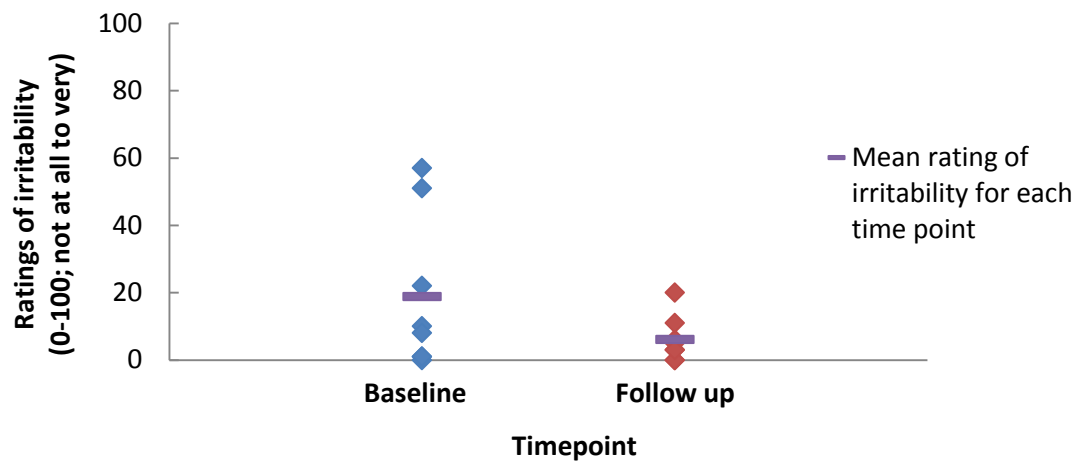
Figure 8.18 Study 4. VAS ratings of irritability at baseline and follow up in people with CFRDTx

8.3.2.3.3 Sleepiness

Data were square root transformed due to moderate positive skewness. There no main effect of time, $F(1, 7) = 1.23$, $p = .30$, $\eta_p^2 = .149$ (see Figure 8.19).
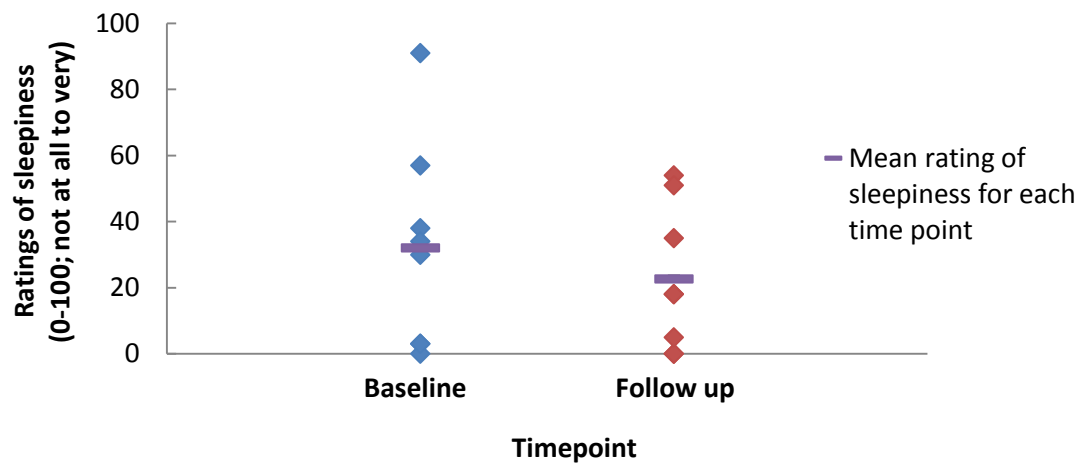
Figure 8.19 Study 4. VAS ratings of sleepiness at baseline and follow up in people with CFRDTx

8.3.2.3.4 Mental alertness

Data were reflected and square root transformed due to moderate negative skewness. There was no main effect of time, $F(1, 7) = 0.88$, $p = .38$, $\eta_p^2 = .112$ (see Figure 8.20).
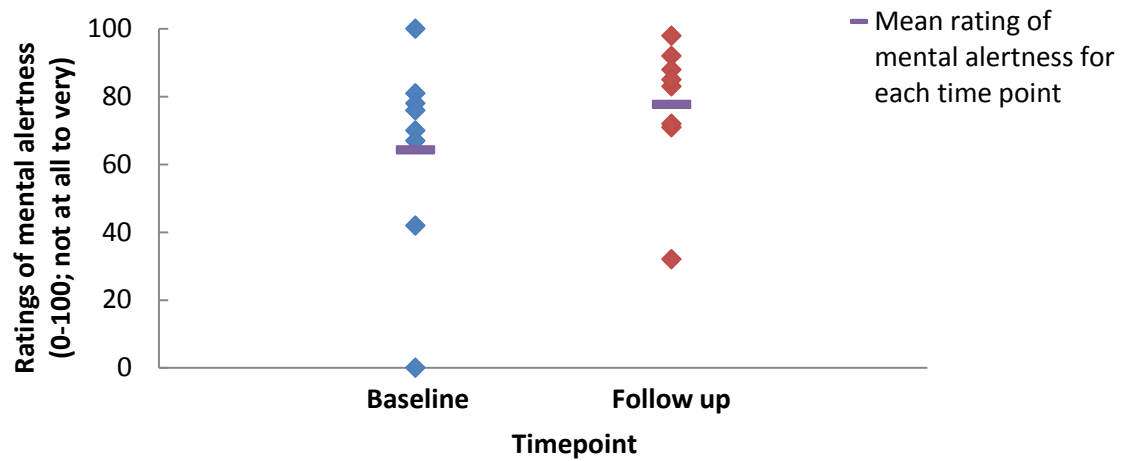
Figure 8.20 Study 4. VAS ratings of mental alertness at baseline and follow up in people with CFRDTx

8.3.2.3.5 Ability to concentrate

Data were reflected and square root transformed due to moderate negative skewness. There was no main effect of time, $F(1, 7) = 0.29$, $p = .61$, $\eta_p^2 = .040$ (see Figure 8.21).
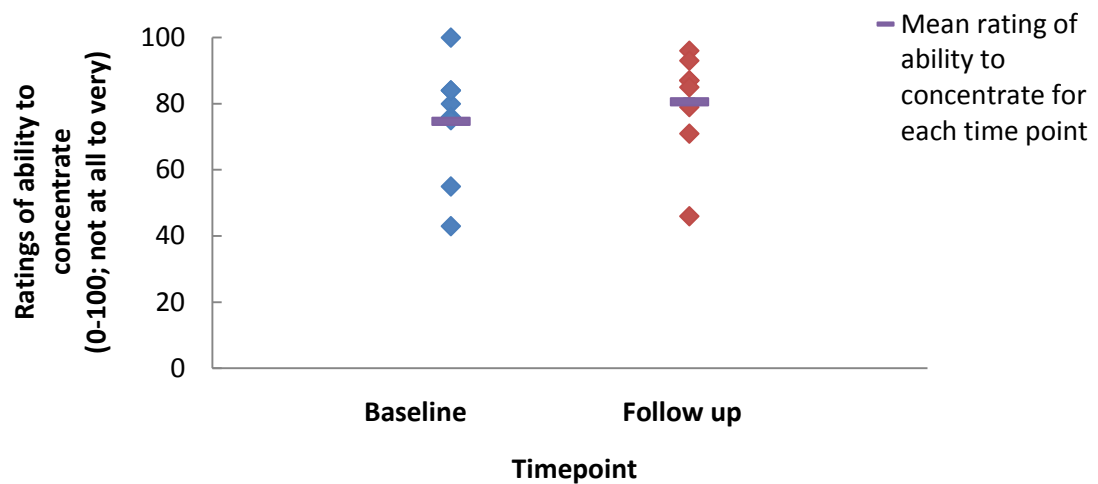
Figure 8.21 Study 4. VAS ratings of ability to concentrate at baseline and follow up

8.3.2.3.6 Feeling energetic

There was no main effect of time, $F(1, 7) = 0.29$, $p = .61$, $\eta_p^2 = .040$ (see Figure 8.22).
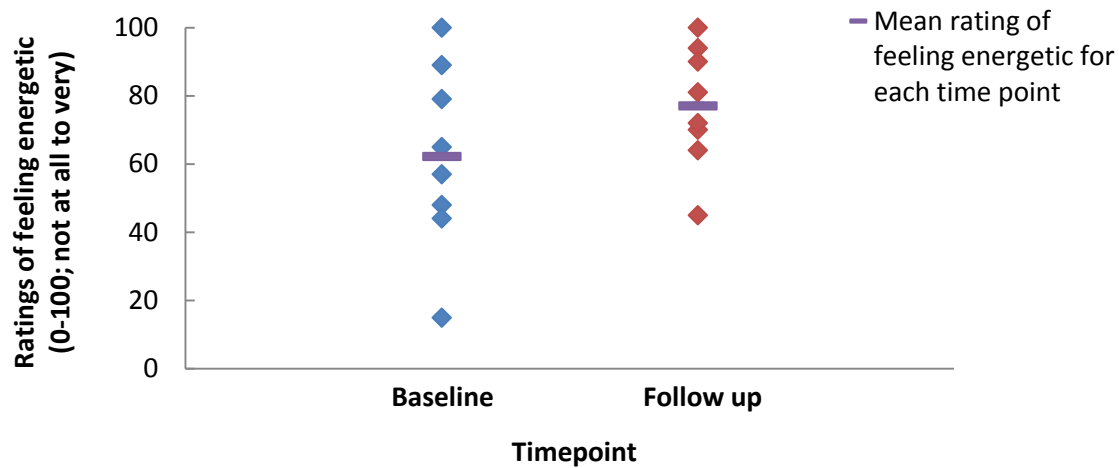
Figure 8.22 Study 4. VAS ratings of feeling energetic at baseline and follow up in people with CFRDTx

8.3.3 Subjective occurrences of minor daily cognitive errors

8.3.3.1 Cognitive Failures Questionnaire (CFQ)

Figure 8.23 shows the number of subjective occurrences of minor daily cognitive errors which occurred in the previous 6 months reported on the CFQ by each group (Figure a) and the number of subjective occurrences which occurred in the past week on the CDS (Figure b). For the CFQ, there was no significant main effect of time $F(1, 7) = 0.32$, p = .59, η_p^2 = .044.
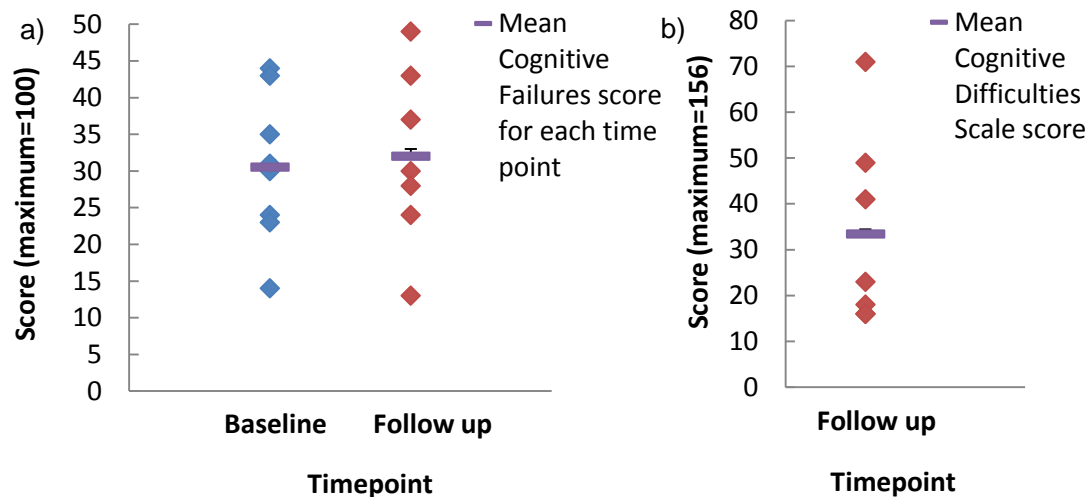
Figure 8.23 Study 4. (a) Cognitive Failures Questionnaire scores at baseline and follow up, and (b) the Cognitive Difficulties Scale score at follow up in people with with CFRDTx

8.3.3.2 **Cognitive Failures Questionnaire –for others (CFQ-for others)**

Seven partners/relatives/close friends completed the CFQ-for others at follow up. The mean scores are reported in Table 8.2. The maximum score is 32.

Table 8.2 Study 4. Subjective ratings of cognitive failures by partners/relatives/close friends of people with CFRDTx (N=2)

	Mean (SE)
Score	12.00 (4.00)

8.3.3.3 **Cognitive Difficulties Scale (CDS)**

The CDS was only administered at follow up, however scores on this questionnaire were strongly positively correlated with the follow up CFQ score, $r(8)= .883$, $p = .004$ (see Figure 8.23).

8.3.4 Cognitive Tests

Time of day can affect cognitive functioning (Schmidt et al., 2007). The Chi-Square test showed that the time of day at which testing was completed did not differ between baseline and follow up, $\chi^2(2, N = 8) = 0.53$, $p = .51$; see Figure 8.24.
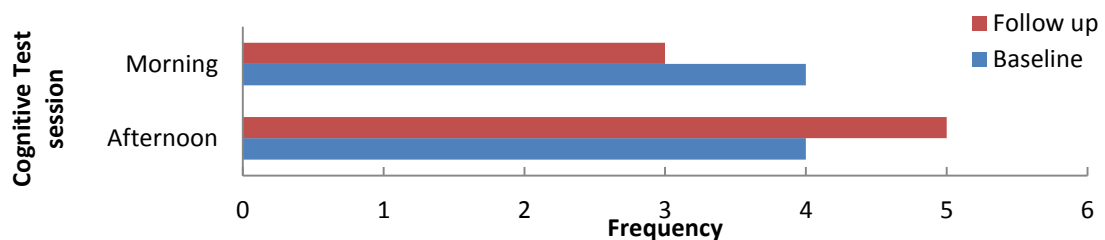
Figure 8.24 Study 4. Frequency of time of day testing was completed at baseline and follow up in people with CFRDTx

8.3.4.1 **Motor Screening Test (MOT)**

This test is an index of motor skill assessing both speed and accuracy (see section 5.2.3.3.1). For the outcome measure of total correct, people with CFRDTx correctly responded to all 10 crosses at baseline and follow up.

8.3.4.1.1 Mean error

Mean error is a measurement of accuracy (see Table 5.4; the mean distance between the centre of the cross and the location the subject touched on the screen). Data were square root transformed due to moderate positive skewness. Age was a significant covariate, $F(1,$

6) = 8.04, p = .03, η_p^2 = .573. Older participants had worse accuracy performance than younger participants. There was no significant main effect of time F(1, 6) = 0.55, p = .49, η_p^2 = .084, or a significant time*age interaction, F(1, 32) = 0.62, p = .46, η_p^2 = .094 (see Figure 8.25).

a)

b)
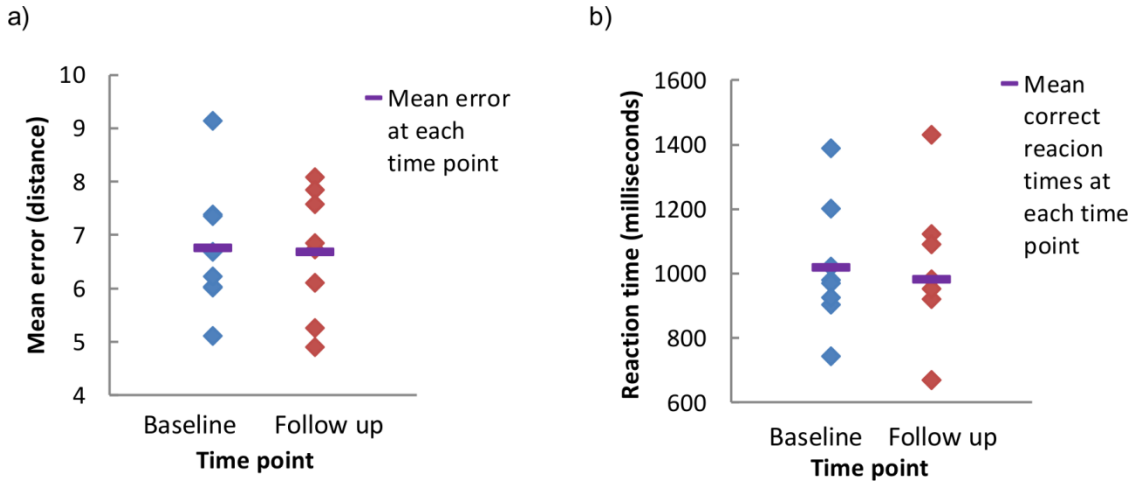
Figure 8.25 Study 4. (a) Mean error (measurement of accuracy) and (b) reaction time (milliseconds) for correct responses on the MOT at baseline and follow up in people with CFRDTx

8.3.4.1.2 Reaction time for correct responses

Data were square root transformed due to moderate positive skewness. The covariate for age was a trend, F(1, 6) = 4.25, p = .085, η_p^2 = .415. Older participants tended to have slower reaction times than younger participants. There was no significant main effect of time F(1, 6) = 0.31, p = .60, η_p^2 = .049, and no significant time*age interaction, F(1, 6) = 0.18, p = .69, η_p^2 = .029 (see Figure 8.25).

8.3.4.2 **Paired Associates Learning (PAL) test**

The outcome measures for the PAL tests are stages completed, stages completed on the first trial, first trial memory score, total trials, and total errors (see section 5.2.3.3.2, and Table 5.4 for a definition of each outcome variable).

8.3.4.2.1 Stages completed

All participants were at ceiling performance at both baseline and follow up.

8.3.4.2.2 Stages completed on first trial

Data were reflected and inverse transformed due to severe negative skewness. There was no significant main effect of time F(1, 6) = 3.32, p = .11, η_p^2 = .321 (see Figure 8.26). At baseline, 2 participants completed 5 stages, 3 participants completed 6 stages and 3 participants completed 7 stages on the first trial while at follow up, 2 participants completed 5 stages, and 6 participants completed 6 stages on the first trial.
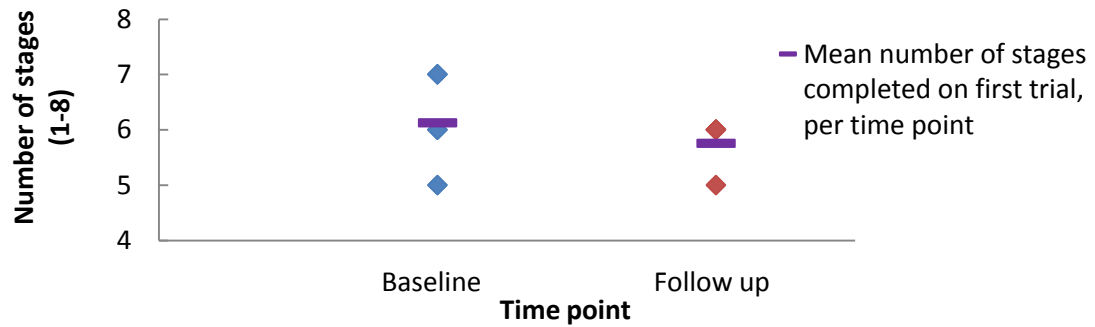
Figure 8.26 Study 4. Number of stages completed on the first trial on the PAL test at baseline and follow up in people with CFRDTx

8.3.4.2.3 First trial memory score

Data were reflected and logarithm transformed due to substantial negative skewness. The covariate for age was a trend, $F(1, 6) = 5.26$, $p = .062$, $\eta_p^2 = .467$. Older participants tended to locate fewer patterns correctly on the first trial of every stage than younger participants. There was no significant main effect of time $F(1, 6) = 0.26$, $p = .63$, $\eta_p^2 = .041$, and no significant time*age interaction, $F(1, 6) = 0.06$, $p = .81$, $\eta_p^2 = .010$ (see Figure 8.27).
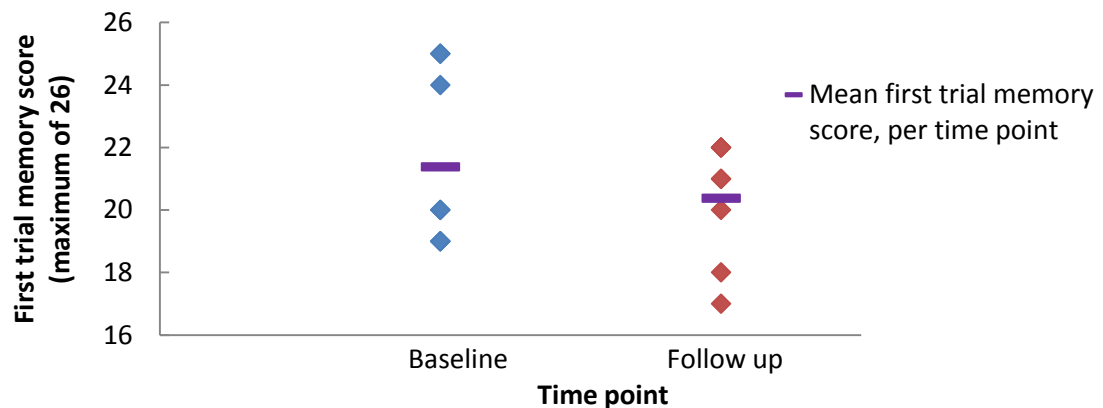
Figure 8.27 Study 4. First trial memory score on the PAL test at baseline and follow up in people with CFRDTx

8.3.4.2.4 Total trials

Data were inversely transformed due to severe positive skewness. There was no significant main effect of time $F(1, 7) = 0.58$, $p = .47$, $\eta_p^2 = .076$ (see Figure 8.28).
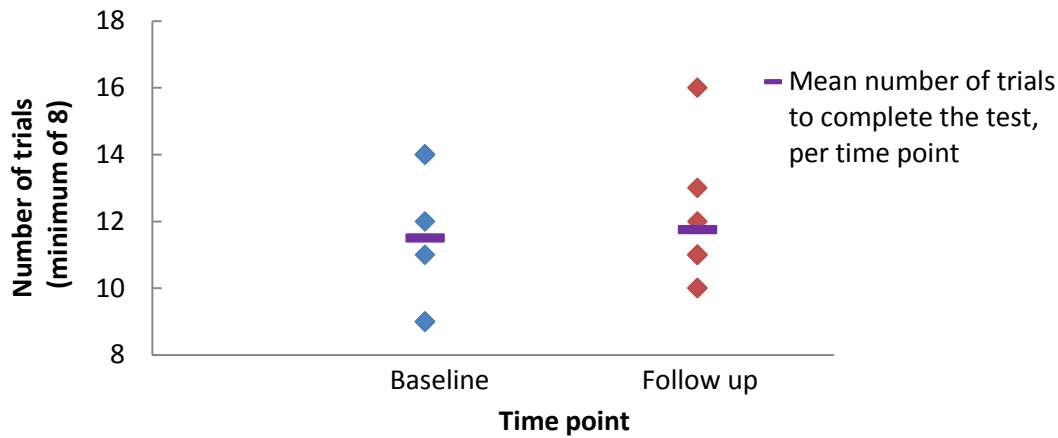
Figure 8.28 Study 4. Total trials on the PAL test at baseline and follow up in people with CFRDTx

8.3.4.2.5 Total errors

There was no significant main effect of time $F(1, 7) = 0.004$, $p = .95$, $\eta_p^2 = .001$ (see Figure 8.29).
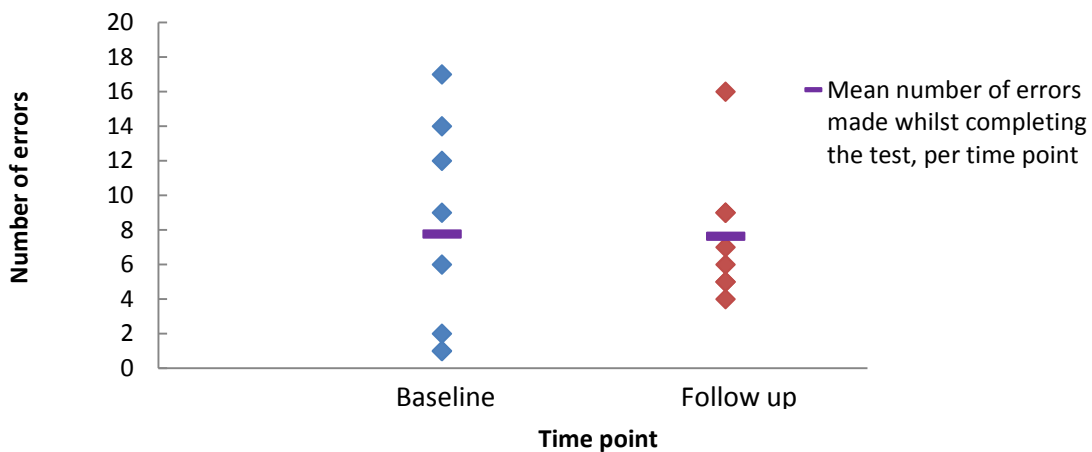
Figure 8.29 Study 4. Total number of errors produced on the PAL test at baseline and follow up in people with CFRDTx

8.3.4.3 **Verbal Recognition Memory (VRM)**

The outcome measures for the free recall test are the number of correctly recalled words, the number of novel words and the number of perseverations (number of times a participant repeated a word they had already successfully recalled from the word list). The outcomes measures for the recognition test are correct number of target words and number of false positives (see section 5.2.3.3.3; Table 5.4 for a definition of each outcome variable).

8.3.4.3.1 Immediate free recall

8.3.4.3.1.1 Number of correctly recalled words at immediate recall

Age was not a significant covariate, $F(1, 5) = 2.05$, $p = .21$, $\eta_p^2 = .290$, and time since baseline was not a significant covariate, $F(1, 5) = 1.32$, $p = .30$, $\eta_p^2 = .209$. There was no significant main effect of time $F(1, 5) = 0.28$, $p = .62$, $\eta_p^2 = .053$. There was a significant time*time since baseline interaction, $F(1, 5) = 25.18$, $p = .004$, $\eta_p^2 = .834$, such that those who completed the follow up testing within a shorter period of time recalled more words at follow up, while those with a longer duration of time recalled more words at baseline. There was a significant time*age interaction, $F(1, 5) = 19.51$, $p = .007$, $\eta_p^2 = .796$, such that older participants recalled more words at follow up, while younger participants recalled more words at baseline. Figure 8.30 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recalled at immediate free recall.
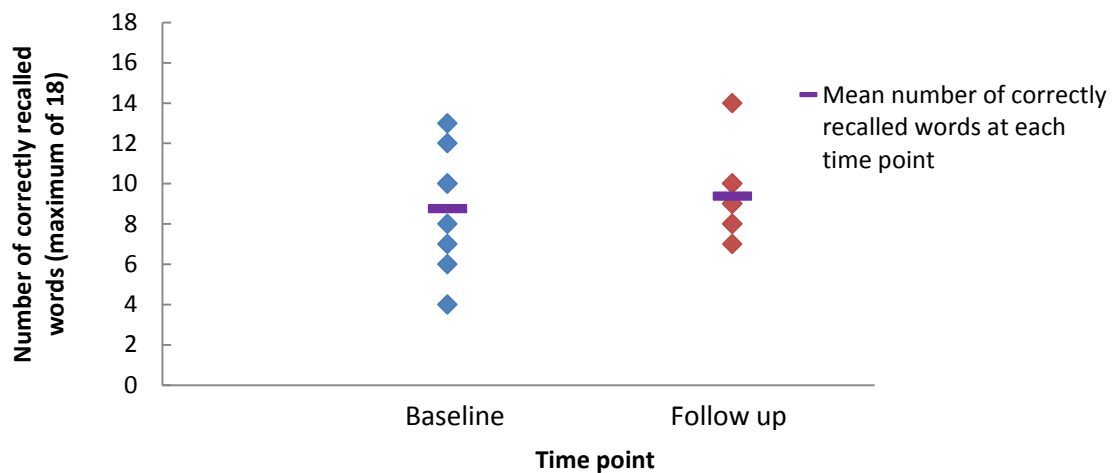
Figure 8.30 Study 4. Number of correctly recalled words at immediate free recall on the VRM test at baseline and follow up in people with CFRDTx

8.3.4.3.1.2 Number of novel words produced at immediate recall

There were too few data points for immediate novel words, with only one person generating one novel word at each time point.

8.3.4.3.1.3 Number of perseverations produced at immediate recall

Data were inverse transformed due to severe positive skewness. Age was a significant covariate, $F(1, 5) = 12.34$, $p = .017$, $\eta_p^2 = .712$ such that older participants repeated more words which they had successfully recalled than younger participants. Time since baseline was not a significant covariate, $F(1, 5) = 0.02$, $p = .89$, $\eta_p^2 = .004$. There was no significant main effect of time $F(1, 5) = 2.01$, $p = .22$, $\eta_p^2 = .287$ and no significant time*age interaction, $F(1, 5) = 0.32$, $p = .60$, $\eta_p^2 = .060$, but there was a trend for a significant time* time since baseline interaction, $F(1, 5) = 4.49$, $p = .088$, $\eta_p^2 = .473$. There was a trend for participants who completed the follow up after a shorter duration to make less repetitions at baseline, while those who completed follow up testing after a longer period to make less repetitions at follow up. Figure 8.31 shows that there was no overall difference between baseline and

follow up performance in the number of repetitions of correctly recalled words at immediate free recall. At baseline, 3 participants made 1 repetition, while at follow up one participant made one repetition, and 2 people made 2 repetitions.
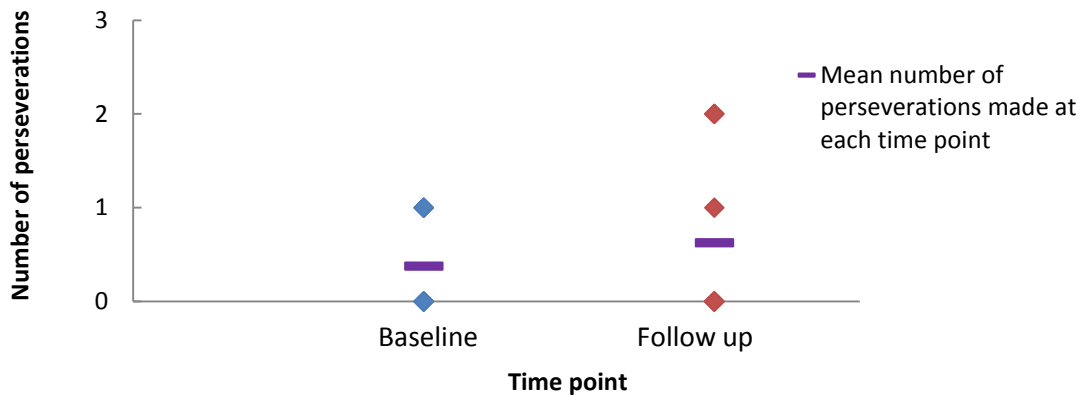
Figure 8.31 Study 4. Number of perseverations at immediate free recall on the VRM test in people with CFRDTx

8.3.4.3.2 Immediate recognition

8.3.4.3.2.1 Total number of correctly recognised target words (recognition task)

Data were reflected and logarithm transformed due to substantial negative skewness. Time since baseline was not a significant covariate, $F_{(1, 6)} = 0.07$, $p = .80$, $\eta_p^2 = .012$. There was significant main effect of time $F_{(1, 5)} = 8.09$, $p = .029$, $\eta_p^2 = .574$, but the post hoc tests showed no significant differences. There was a significant time*time since baseline interaction, $F_{(1, 5)} = 6.90$, $p = .039$, $\eta_p^2 = .535$, such that more words were correctly recognised at baseline, and participants who completed the follow up testing after a shorter duration correctly recognised more words at follow up while those with a longer duration recognised more words at baseline. Figure 8.32 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recognised target words at immediate recognition.
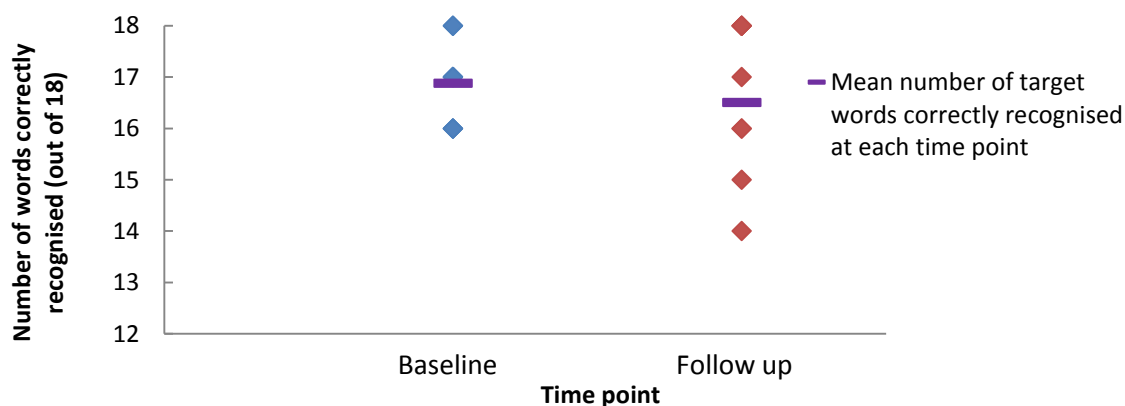
Figure 8.32 Study 4. Total number of correctly recognised target words at immediate recognition on the VRM test at baseline and follow up in people with CFRDTx

8.3.4.3.2.2   Total number of false positives (recognition task)

Data were logarithm transformed due to substantial positive skewness. There was no significant main effect of time F(1, 7) = 2.33, p = .17, η_p^2 = .250. Figure 8.33 shows that there was no overall difference between baseline and follow up performance in the number of words correctly recognised target words at immediate recognition. At baseline, 3 participants made 2 false positives, while at follow up, two participants made 1, and one person made 2 false positives.
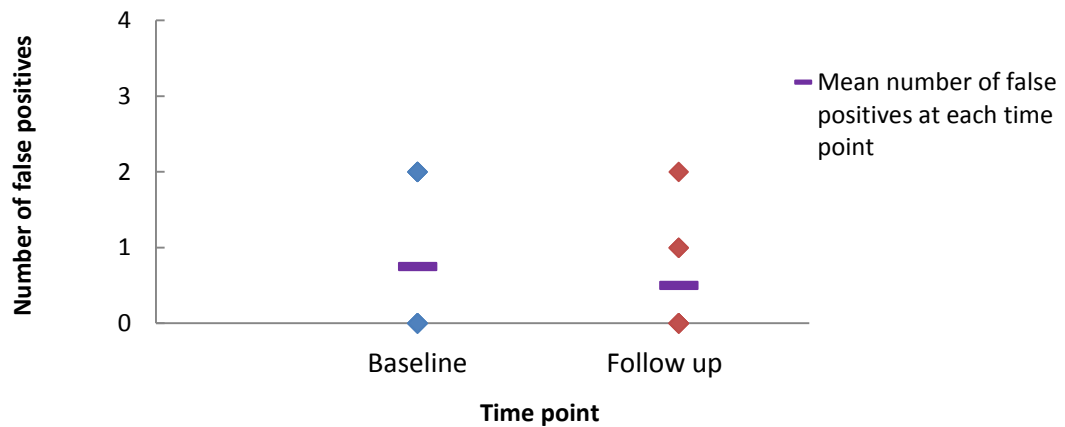
Figure 8.33 Study 4. Total number of false positives produced at immediate recognition on the VRM test, at baseline and follow up, in people with CFRDTx

8.3.4.3.3   Delayed free recall

8.3.4.3.3.1   Total number of correctly recalled words at delayed recall

Data were logarithm transformed due to substantial positive skewness at follow up. There was a trend for a significant main effect of time F(1, 7) = 4.85, p = .063, η_p^2 = .409, such that there was a trend for more words were recalled at follow up (see Figure 8.34).
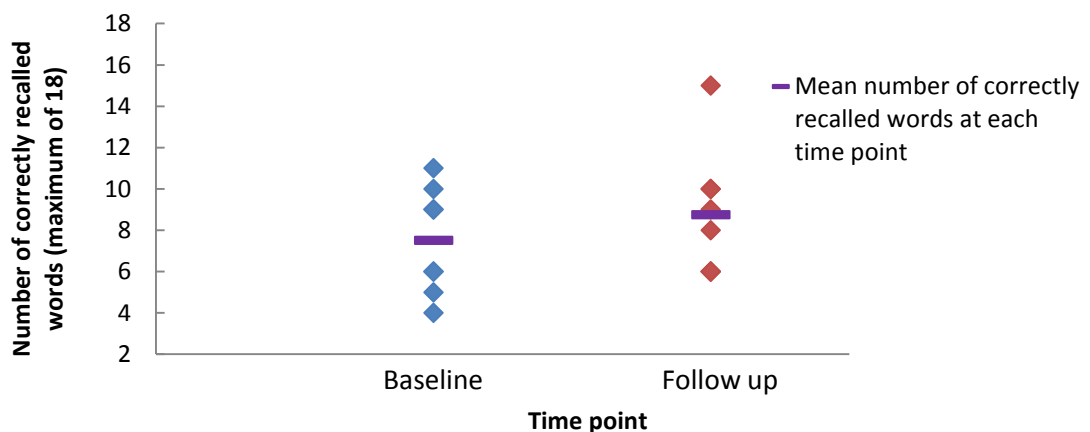
Figure 8.34 Study 4. Total number of correctly recalled words at delayed recall on the VRM test at baseline and follow up in people with CFRDTx

8.3.4.3.3.2   Number of novel words produced at delayed recall

There were too few data points for delayed novel words, with only one person generating one new word at baseline and 2 people generating one word at follow up.

8.3.4.3.3.3   Number of perseverations words produced at delayed recall

There were too few data points for delayed perseverations words. At baseline three participants made one repetition of a word successfully recalled, but no participants made any repetitions at follow up.

8.3.4.3.4   Delayed recognition

8.3.4.3.4.1   Total number of correctly recognised target words (recognition task)

Data were moderately negatively skewed and therefore reflected and a square root transformation was applied. Age was not a significant covariate, $F(1, 6) = 0.63$, $p = .46$, $\eta_p^2 = .095$. There was a trend for a significant main effect of time $F(1, 6) = 4.41$, p = .080, $\eta_p^2 = .424$, but the post hocs tests showed no differences between time points. There was a trend for a significant time*age interaction, $F(1, 6) = 5.28$, p = .061, $\eta_p^2 = .468$, such that younger participants tended to correctly recognised more words at follow up, while older participants correctly recognised more words at baseline. Figure 8.35 shows that there was a trend for fewer words to be successfully recognised at follow up.
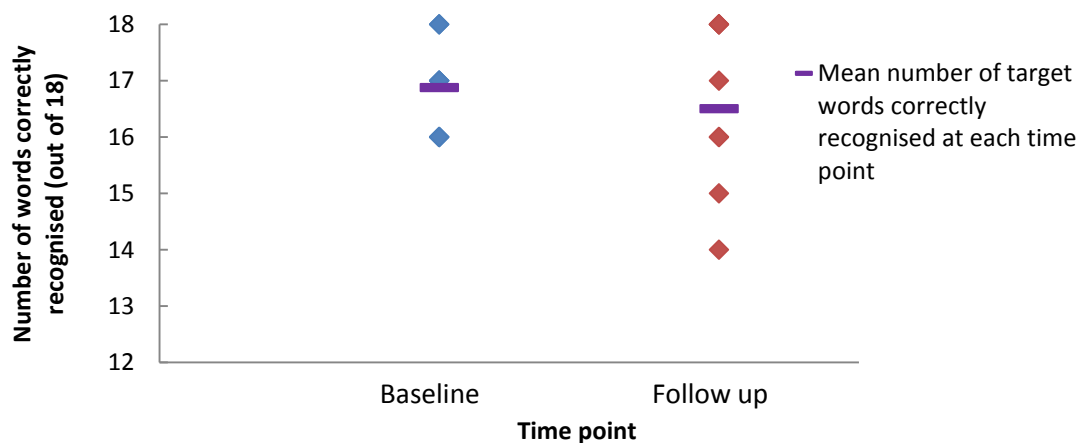
Figure 8.35 Study 4. Total number of correctly recognised target words at delayed recognition on the VRM test at baseline and follow up in people with CFRDTx

8.3.4.3.4.2   Total number of false positives (recognition task)

Data were substantially positively skewed and therefore a logarithm transformation was applied. There was a significant main effect of time $F(1, 7) = 5.79$, p = .047, $\eta_p^2 = .453$, such that more false positives were produced at follow up (see Figure 8.36).
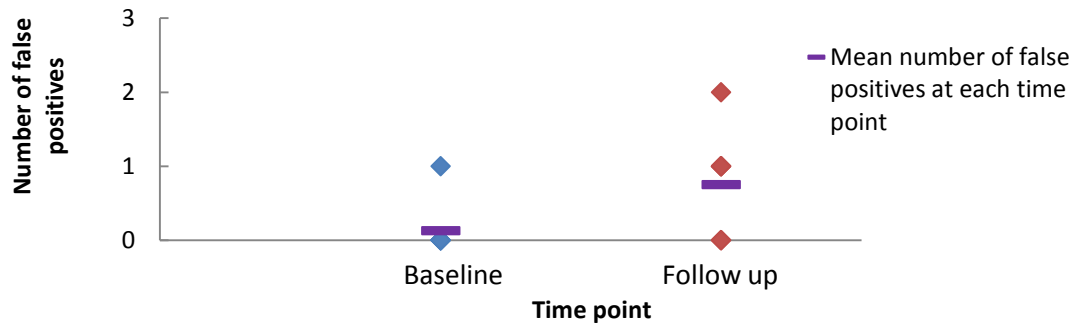
Figure 8.36 Study 4. Total number of false positives produced at delayed recognition on the VRM test at baseline and follow up in people with CFRDTx

8.3.4.4 Pattern Recognition Memory (PRM)

The outcome measures for immediate and delayed are the number of correctly recognised patterns and the reaction time to recognise the patterns (see section 5.2.3.3.4; Table 5.4 for a definition of each outcome variable).

8.3.4.4.1 Immediate pattern recognition

8.3.4.4.1.1 Number of correctly recognised patterns

Data were reflected and inverse transformed due to severe negative skewness. Age was not a significant covariate, $F(1, 6) = 2.40$, $p = .172$, $\eta_p^2 = .286$. There was a significant main effect of time $F(1, 6) = 9.10$, $p = .023$, $\eta_p^2 = .603$, but there were no significant differences on the post hoc tests. There was a significant time*age interaction, $F(1, 6) = 7.95$, $p = .030$, $\eta_p^2 = .570$, such that more patterns were recognised at follow up in younger participants, whereas more patterns were recognised at baseline in older participants. Figure 8.37 shows that at baseline 3 participants did not recognised all patterns (11 patterns n=2, 10 patterns n=1 patterns), while at baseline only one participant did not recognised all patterns.
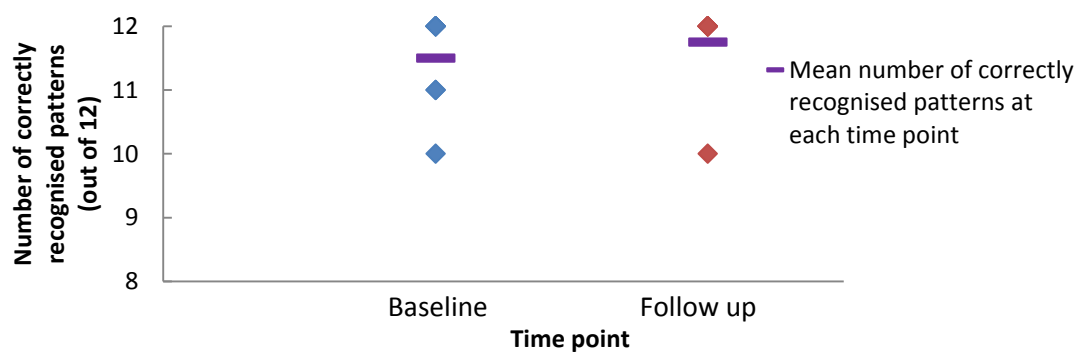
Figure 8.37 Study 4. Number of correctly recognised patterns at immediate recognition on the PRM test at baseline and follow up in people with CFRDTx

8.3.4.4.1.2   Reaction time for correctly recognised patterns

Data were logarithm transformed due to moderate positive skewness. There was no significant main effect of time $F(1, 7) = 0.11$, $p = .75$, $\eta_p^2 = .015$. Figure 8.38 shows that there was no difference in the reaction to correctly recognised patterns at immediate recognition at baseline and follow up.
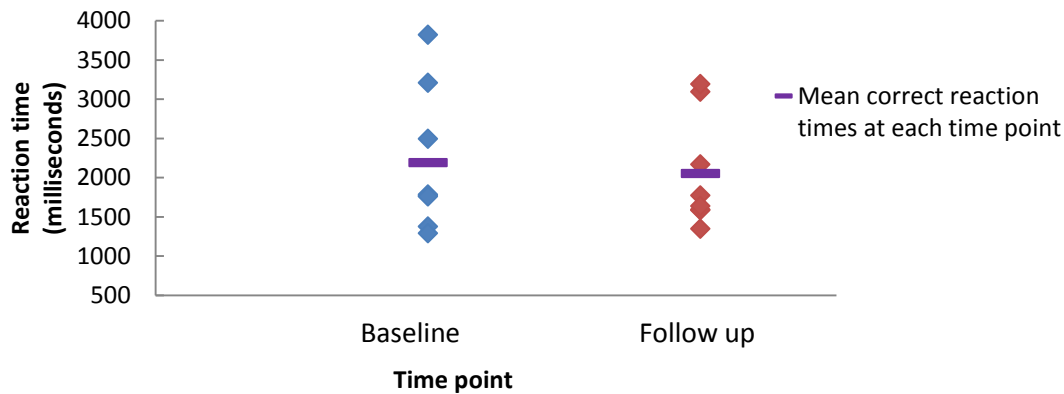
Figure 8.38 Study 4. Reaction time for correctly recognised patterns at immediate recognition on the PRM test at baseline and follow up in people with CFRDTx

8.3.4.4.2   Delayed pattern recognition

8.3.4.4.2.1   Number of correctly recognised patterns

Data were severely negatively skewed and therefore were reflected and an inverse transformation was applied. There was a significant main effect of time $F(1, 7) = 5.74$, $p = .048$, $\eta_p^2 = .451$, such more patterns were correctly recognised at follow up than baseline (see Figure 8.39).
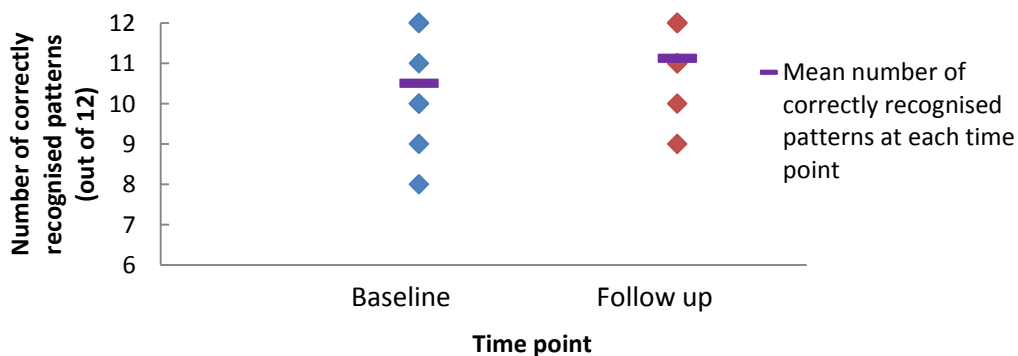
Figure 8.39 Study 4. Number of correctly recognised patterns at delayed recognition on the PRM test at baseline and follow up in people with CFRDTx

8.3.4.4.2.2   Reaction time for correctly recognised patterns

Data were logarithm transformed due to substantial positive skewness. Age was not a significant covariate, $F(1, 5) = 0.51$, $p = .51$, $\eta_p^2 = .092$ and time since baseline was not a significant covariate, $F(1, 5) = 1.30$, $p = .31$, $\eta_p^2 = .206$. There was no significant main effect of time $F(1, 5) = 0.05$, $p = .84$, $\eta_p^2 = .010$, but there was a significant time*time since baseline interaction, $F(1, 5) = 17.72$, $p = .008$, $\eta_p^2 = .780$ and a significant time*age interaction, $F(1, 5) = 19.52$, $p = .007$, $\eta_p^2 = .796$, such that younger participants were faster at baseline and older participants were faster at follow up. Furthermore, reaction times were faster at follow up in those who completed the follow up testing after a shorter duration, while those who completed testing after a longer duration had faster reaction times at baseline. Figure 8.40 shows that there was no difference in reaction time for correctly recognised patterns at delayed recognition at baseline and follow up.
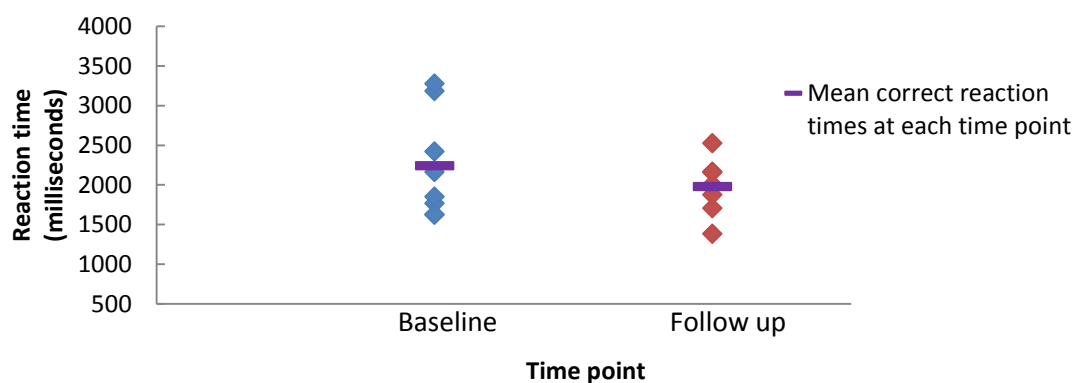
Figure 8.40 Study 4. Reaction time for correctly recognised patterns at delayed recognition on the PRM test, at baseline and follow up, in people with CFRDTx

8.3.4.5   **Rapid Visual Processing (RVP)**

There are a total of 36 target sequences to detect (see section 5.2.5.3.5) on the four minute task (9 per minute). The outcome measures for the RVP tests are: total hits, total false alarms, reaction time for hits, A' prime, and B' prime (see section 5.2.3.3.5, and Table 5.4 for a definition of each outcome variable).

8.3.4.5.1   Total hits (correct detections of target sequences)

There was no significant main effect of time $F(1, 7) = 0.90$, $p = .37$, $\eta_p^2 = .114$ (see Figure 8.41).
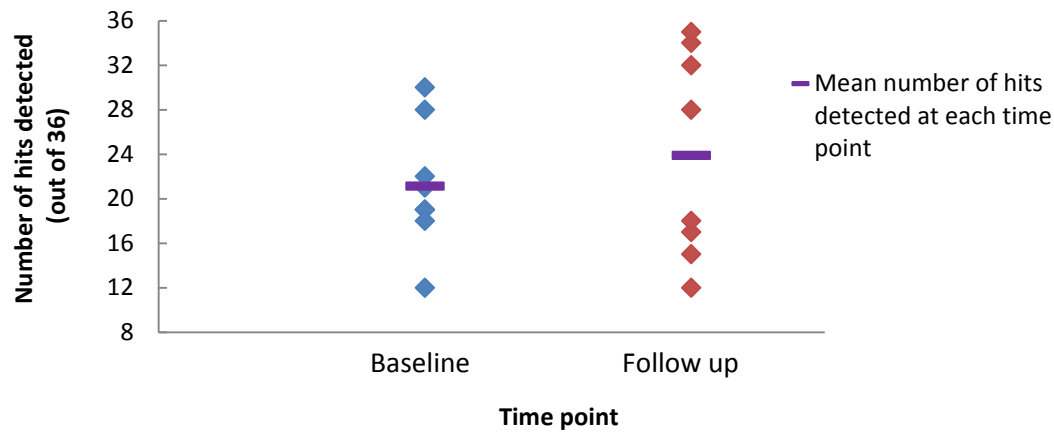
Figure 8.41 Study 4. Total hits (correct detections) on the RVP test, at baseline and follow up, in people with CFRDTx

8.3.4.5.2 Total false alarms

Data were square root transformed due to positive skew. There was no significant main effect of time $F(1, 7) = 1.56$, $p = .25$, $\eta_p^2 = .182$ (see Figure 8.42).
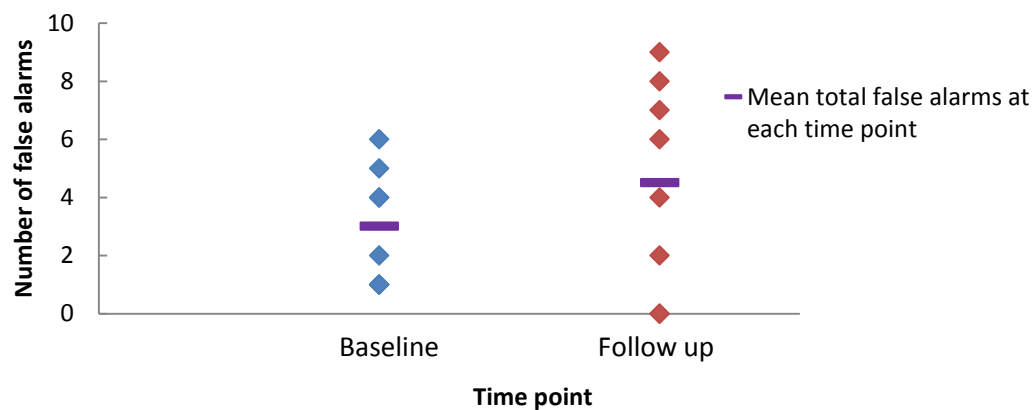
Figure 8.42 Study 4. Total number of false alarms produced on the RVP test, at baseline and follow up, in people with CFRDTx

8.3.4.5.3 Mean reaction time for hits

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 6) = 0.31$, $p = .60$, $\eta_p^2 = .049$. There was a trend for a main effect of time $F(1, 6) = 4.30$, $p = .084$, $\eta_p^2 = .417$, but there was no difference on the post hoc tests. There was a trend for a significant time*age interaction, $F(1, 6) = 3.97$, $p = .093$, $\eta_p^2 = .398$, such that younger participants tended to be faster at follow up, while older participants tended to be faster at baseline. Figure 8.43 shows that there was a trend for faster reaction times at follow up.
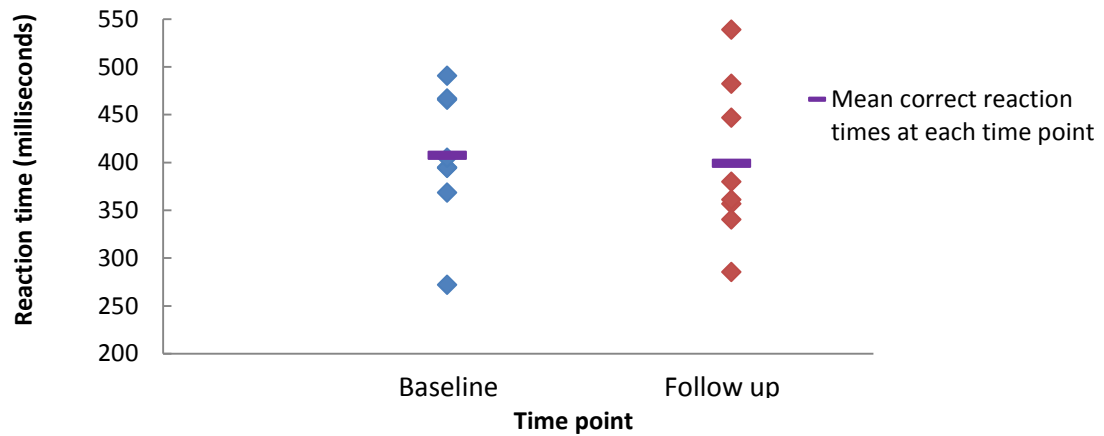
Figure 8.43 Study 4. Mean reaction time for hits on the RVP test, at baseline and follow up, in people with CFRDTx

8.3.4.5.4 A' Prime

Data were log transformed due to positive skew. Age was not a significant covariate, $F(1, 6) = 2.05$, $p = .20$, $\eta_p^2 = .254$. There was a trend for a significant main effect of time, $F(1, 6) = 4.74$, $p = .072$, $\eta_p^2 = .441$, but the post hoc tests revealed no significant differences. There was a trend for a significant time*age interaction, $F(1, 6) = 4.13$, $p = .088$, $\eta_p^2 = .408$. Figure 8.44 shows that there was no difference in the sensitivity to responding to targets at baseline and follow up.
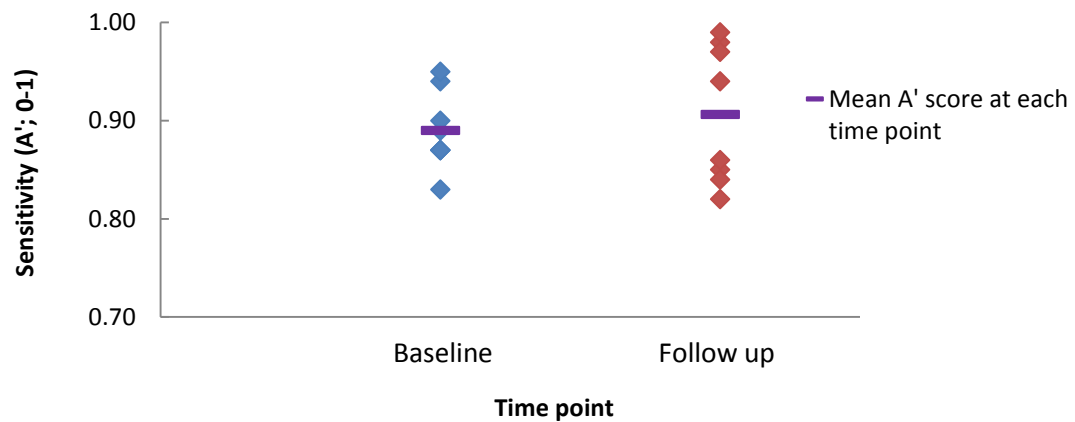
Figure 8.44 Study 4. A' prime (Sensitivity to the target, regardless of response tendency) on the RVP test, at baseline and follow up, in people with CFRDTx

8.3.4.5.5 B' Prime

Data were reflected and an inverse transformation applied due to severe negative skewness. Age was a marginally significant covariate, $F(1, 6) = 5.86$, $p = .052$, $\eta_p^2 = .494$. Older participants were more biased in their responding than younger participants. There was no significant main effect of time $F(1, 6) = 3.57$, $p = .11$, $\eta_p^2 = .373$. There was a significant time*age interaction, $F(1, 6) = 6.10$, $p = .048$, $\eta_p^2 = .504$, such that younger participants were less biased in their responding at baseline, while, older participants were considerably

more biased (i.e. more guess responding) at follow up. Figure 8.45 shows that there was no difference in bias in responding at baseline and follow up.
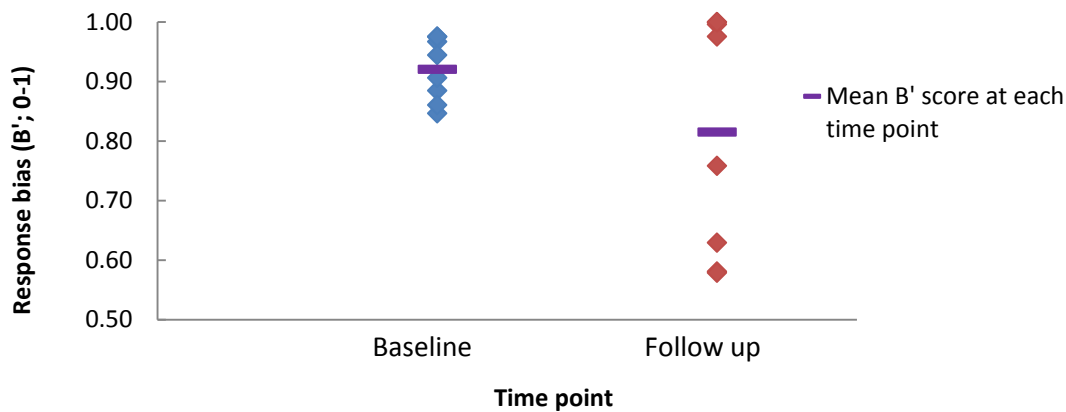
Figure 8.45 Study 4. B' prime (tendency to respond regardless of whether the target sequence is present) on the RVP test, at baseline and follow up, in people with CFRDTx

8.3.4.6 Spatial span (SSP)

The outcome measures for SSP are span length, number of attempts (overall), reaction time (mean time to first and last response), and errors (total and usage; see section 5.2.3.3.6, and Table 5.4 for a definition of each outcome variable). As the degree of test completion varies as a function of individual performance (i.e. test difficulty increases with each span length (2-9) and the test terminates if a sequence is not successfully recalled at 'n' span length after 3 attempts), span length was included as a covariate in the analyses for all subsequent SSP outcome measures.

8.3.4.6.1 Span length (longest number sequence successfully recalled)

There was no significant main effect of time $F(1, 7) = 0.64$, $p = .45$, $\eta_p^2 = .083$. Figure 8.46 shows that there was no difference in the highest span length achieved at baseline (span 5 n=3, span 6 n=4, span 9 n=1) and follow up (span 5 n=1, span 6, n=5, span 7 n=1, span 8 n=1).
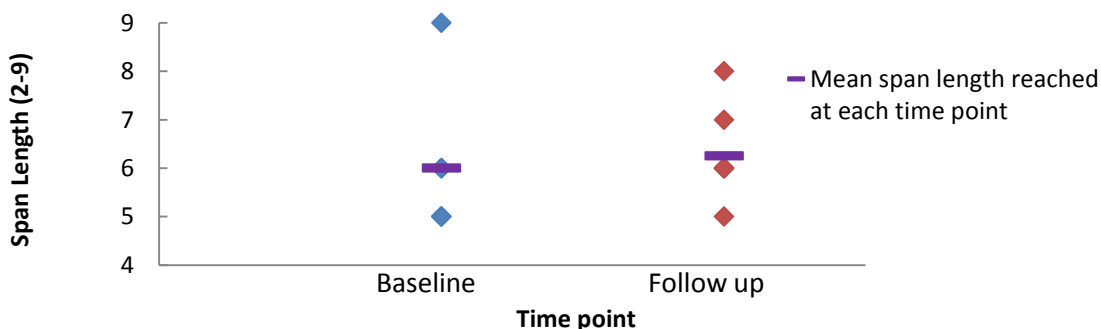
Figure 8.46 Study 4. Span length (longest number sequence successfully recalled; 2-9) on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.6.2 Total number of attempts

The covariate span length was a trend, $F(1, 6) = 4.65$, $p = .075$, $\eta_p^2 = .436$. There was no significant main effect of time $F(1, 6) = 1.33$, $p = .29$, $\eta_p^2 = .182$, and there was no significant time*span length interaction, $F(1, 6) = 1.51$, $p = .27$, $\eta_p^2 = .201$. Figure 8.47 shows that there was no difference in the number of attempts made to achieve the participant's highest span length at baseline and follow up.
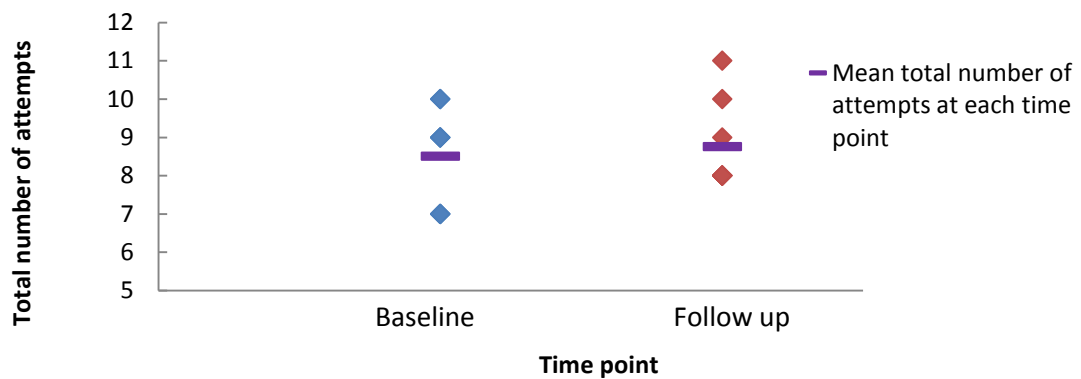
Figure 8.47 Study 4. Total number of attempts made at all levels reached on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.6.3 Reaction time outcome measures on the SSP test

8.3.4.6.3.1 Mean time to first response

Data were logarithm transformed due to substantial positive skewness. Span length was not a significant covariate, $F(1, 6) = 0.52$, $p = .50$, $\eta_p^2 = .079$. There was no significant main effect of time $F(1, 6) = 1.26$, $p = .30$, $\eta_p^2 = .174$, and no significant time*span length interaction, $F(1, 6) = 1.38$, $p = .28$, $\eta_p^2 = .187$. Figure 8.48 shows that there was no difference in mean time to first response at baseline and follow up.
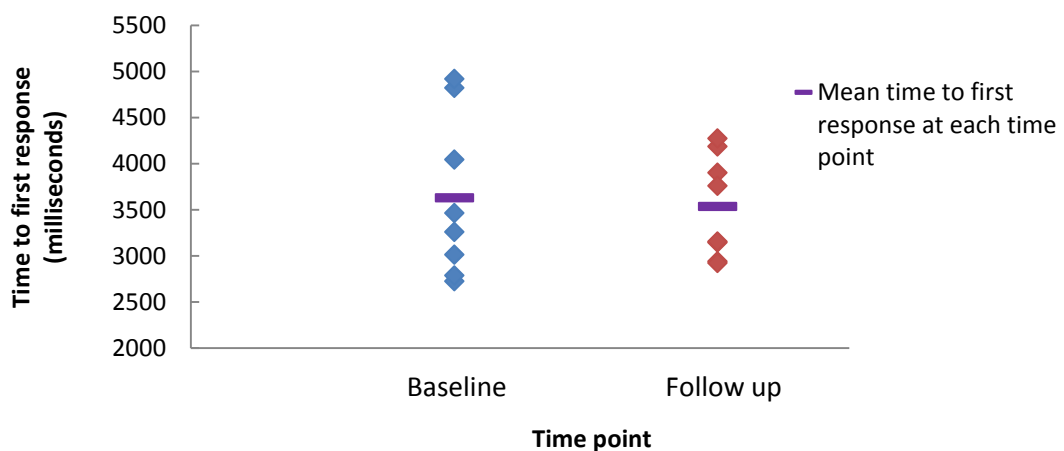
Figure 8.48 Study 4. Mean time to first response (milliseconds) on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.6.3.2 Mean time to last response

Data were inverse transformed due to severe positive skewness. Span length was not a significant covariate, $F(1, 6) = 0.92$, $p = .38$, $\eta_p^2 = .133$. There was no significant main effect of time $F(1, 6) = 1.09$, $p = .34$, $\eta_p^2 = .154$, and no significant time*span length interaction, $F(1, 6) = 1.34$, $p = .29$, $\eta_p^2 = .183$. Figure 8.49 shows that there was no difference in mean time to last response at baseline and follow up.
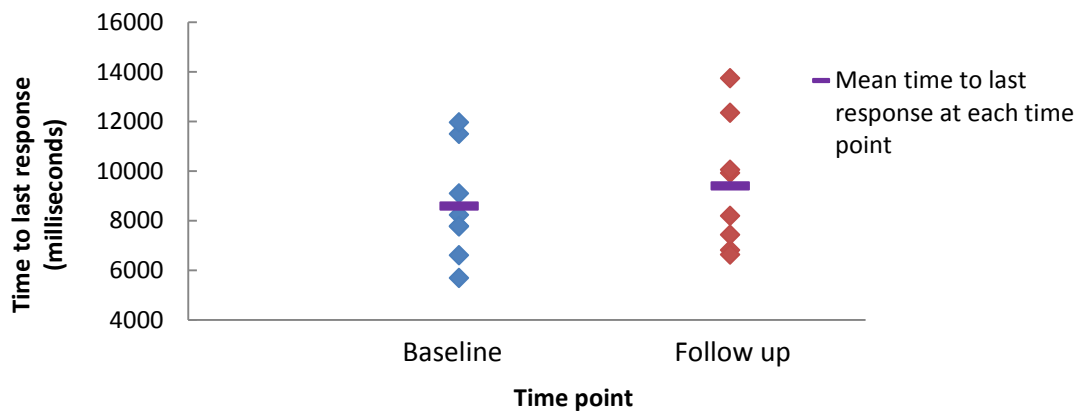
Figure 8.49 Study 4. Mean time to last response (milliseconds) on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.6.4 Errors

8.3.4.6.4.1 Total errors

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 5) = 0.08$, $p = .79$, $\eta_p^2 = .016$, and span length was not a significant covariate, $F(1, 5) = 0.98$, $p = .37$, $\eta_p^2 = .164$. There was a significant main effect of time $F(1, 5) = 8.76$, $p = .032$, $\eta_p^2 = .637$, such that there was a trend for more errors to be made at follow up ($p = .052$). There was no significant time*span length interaction, $F(1, 5) = 3.34$, $p = .13$, $\eta_p^2 = .401$, but there was a significant time*age interaction, $F(1, 5) = 13.28$, $p = .015$, $\eta_p^2 = .727$, such that younger participants made more errors at baseline, while older participants made more errors are follow up. Figure 8.50 shows that there was no difference in total errors at baseline and follow up.
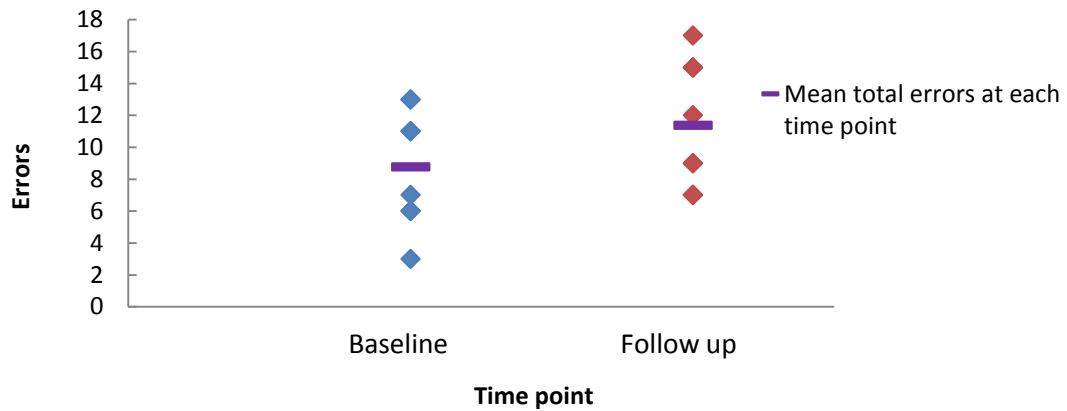
Figure 8.50 Study 4. Total number of errors produced whilst recalling sequences on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.6.4.2   Total usage errors

Data were square root transformed due to moderate positive skewness. Age was not a significant covariate, $F(1, 5) = 1.82$, $p = .24$, $\eta_p^2 = .267$, and span length was not a significant covariate, $F(1, 5) = 2.36$, $p = .19$, $\eta_p^2 = .320$. There was a significant main effect of time $F(1, 5) = 10.99$, $p = .021$, $\eta_p^2 = .687$, but the post hocs showed no significant differences. There was a trend for a significant time*span length interaction, $F(1, 5) = 5.16$, $p = .072$, $\eta_p^2 = .508$, and a significant time*age interaction, $F(1, 5) = 11.18$, $p = .020$, $\eta_p^2 = .691$ such that there was a tendency for fewer usage errors to be made for lower span lengths at follow up, and fewer errors for the higher span lengths at baseline. Furthermore, younger participants made less usage errors at follow up, whereas older participants made more usage errors at follow up. Figure 8.51 shows that there was no difference in total usage errors at baseline and follow up.
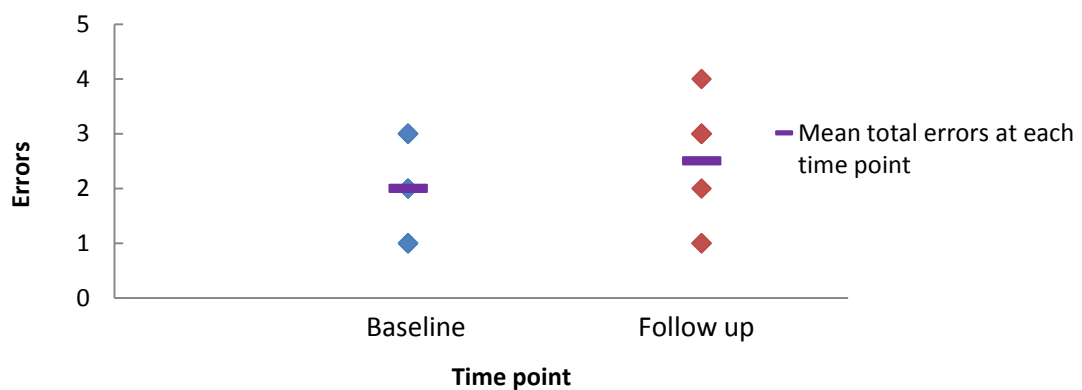
Figure 8.51 Study 4. Total number of usage errors produced on the SSP test at baseline and follow up, in people with CFRDTx

8.3.4.7 **Attention switching task (AST)**

A total of 160 responses were required per test administration. The outcome measures for AST are accuracy (correct trials), reaction time for correct trials, errors (omission and commission), congruency cost, and switch cost (see section 5.2.3.3.7, and Table 5.4 for a definition of each outcome variable). As there were an unequal number of switched and non-switched trials, reaction time for switched and non-switched trials and switch cost should be treated with some degree of caution.

8.3.4.7.1 Total correct trials

8.3.4.7.1.1 Total correct trials (overall accuracy)

Data were reflected and logarithm transformed due to substantial negative skewness. There was no significant main effect of time, $F(1, 7) = 1.69$, $p = .23$, $\eta_p^2 = .195$. Figure 8.52 shows that there was no difference in the number of total correct trials at baseline and follow up.
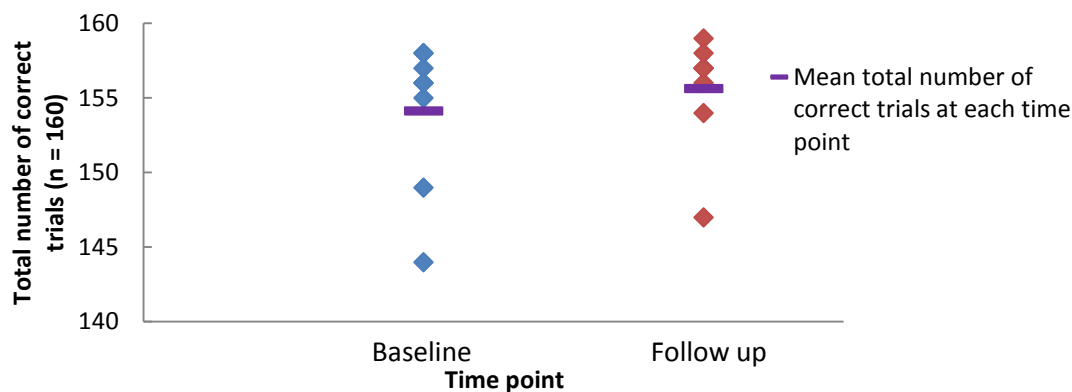
Figure 8.52 Study 4. Total number of correct trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.1.2 Mean reaction time for total correct trials

Data were inverse transformed due to severe positive skewness. The covariate of age was a trend, $F(1, 6) = 4.50$, $p = .078$, $\eta_p^2 = .428$ such that older participants responded slower than younger participants. There was no significant main effect of time, $F(1, 6) = 2.30$, $p = .18$, $\eta_p^2 = .277$. There was no significant time*age interaction, $F(1, 6) = 1.34$, $p = .29$, $\eta_p^2 = .182$. Figure 8.53 shows that there was no difference in reaction time for correct trials at baseline and follow up.
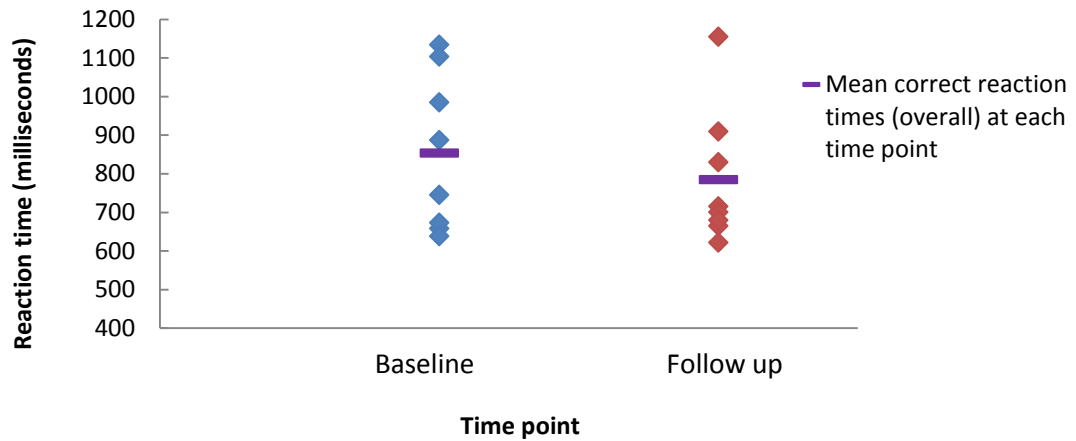
Figure 8.53 Study 4. Reaction time for correct trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.2   Direction trials

8.3.4.7.2.1   Total correct trials with direction as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. There was no significant main effect of time, $F(1, 7) = 3.44$, $p = .106$, $\eta_p^2 = .329$. Figure 8.54 shows that there was no difference in total correct direction trials at baseline and follow up.
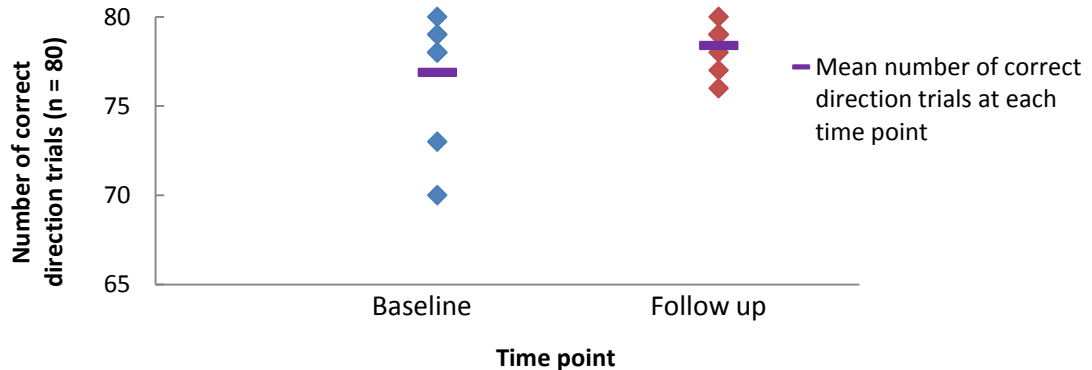
Figure 8.54 Study 4. Number of correct direction trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.2.2   Reaction time for correct trials with direction as the rule

Data were logarithm transformed due to substantial positive skewness. There was no significant main effect of time, $F(1, 7) = 1.67$, $p = .24$, $\eta_p^2 = .193$. Figure 8.55 shows that there was no difference in reaction time for correct direction trials at baseline and follow up.
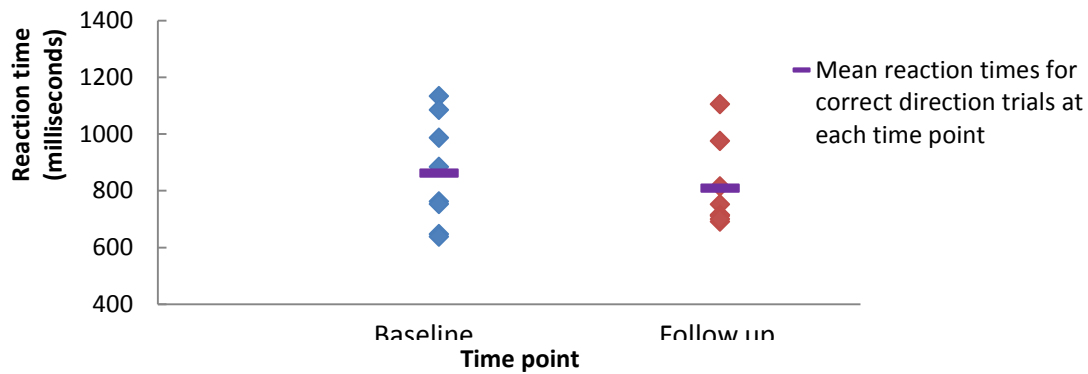
Figure 8.55 Study 4. Reaction time for correct direction trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.3   Side trials

8.3.4.7.3.1   Total correct trials with side as the rule

Data were reflected and logarithm transformed due to substantial negative skewness. Time since baseline was not a significant covariate, $F(1, 6) = 3.16$, $p = .13$, $\eta_p^2 = .345$. There was no significant main effect of time, $F(1, 6) = 3.53$, $p = .11$, $\eta_p^2 = .370$. There was a trend for a significant time*time since baseline interaction, $F(1, 6) = 3.93$, $p = .095$, $\eta_p^2 = .396$, such that there was a trend for younger participants to respond to more side trials correctly at baseline, while older participants responded to more side trials correctly at follow up. Figure 8.56 shows that there was no difference in the number of correct side trials at baseline and follow up.
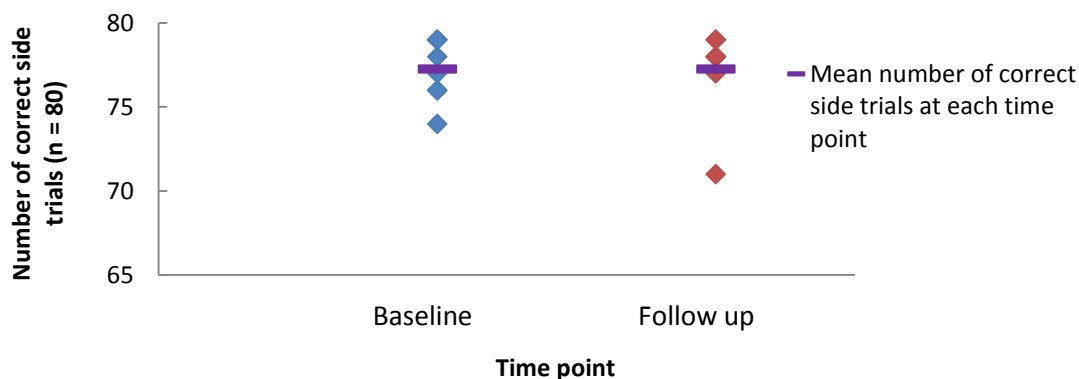
Figure 8.56 Study 4. Number of correct side trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.3.2   Reaction time for correct trials with side as the rule

Data were logarithm transformed due to substantial positive skewness. Age was a significant covariate, $F(1, 6) = 7.10$, $p = .037$, $\eta_p^2 = .542$ such that younger participants were faster to respond than older participants. There was no significant main effect of time, $F(1, 6) = 1.95$, $p = .21$, $\eta_p^2 = .246$. There was no significant time*age interaction, $F(1, 6) = 0.91$,

p = .38, η_p^2 = .131. , Figure 8.57 shows that there was no difference in reaction time for correct side trials at baseline and follow up.
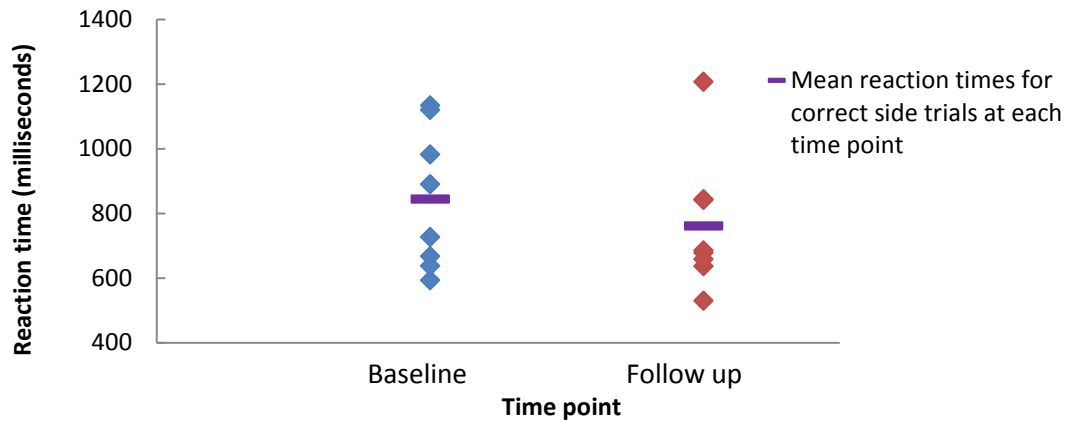
Figure 8.57 Study 4. Reaction time for correct side trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.4 Congruent trials

8.3.4.7.4.1 Total correct congruent trials

Data were reflected and inversely transformed due to severe negative skewness. Age was a significant covariate, $F(1,6)$ = 13.77, p = .010, η_p^2 = .697 such that younger participants correctly responded to more congruent trials than older participants. There was no significant main effect of time $F(1, 6)$ = 0.09, p = .77, η_p^2 = .015. There was no significant time*age interaction, $F(1, 6)$ = 0.12, p = .74, η_p^2 = .020. Figure 8.58 shows that there was no difference in correct congruent trials at baseline and follow up.
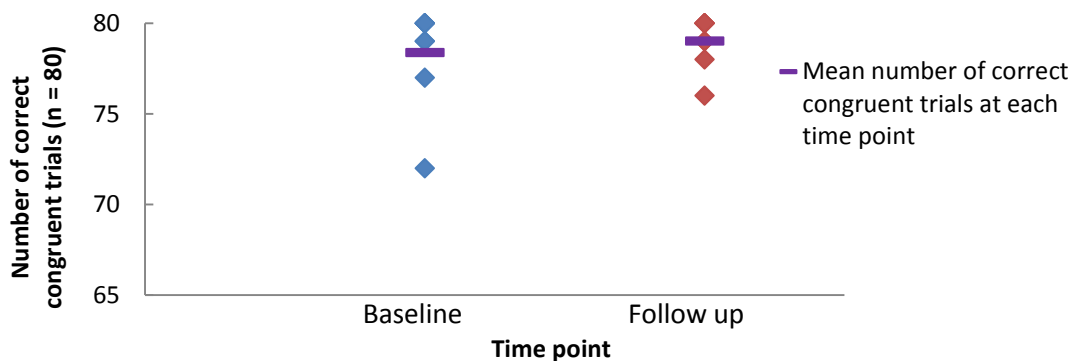
Figure 8.58 Study 4. Number of correct congruent trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.4.2 Reaction time for correct congruent trials

Data were square root transformed due to moderate positive skewness. There was no significant main effect of time, $F(1, 7)$ = 2.77, p = .14, η_p^2 = .283. Figure 8.59 shows that

there was no difference in reaction time for correct congruent trials at baseline and follow up.
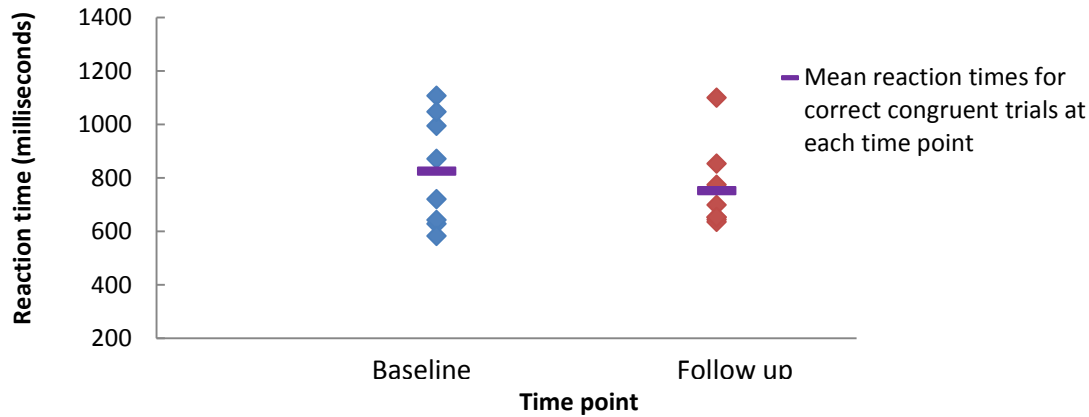
Figure 8.59 Study 4. Reaction time for correct congruent trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.5 Incongruent trials

8.3.4.7.5.1 Total correct incongruent trials

Data were reflected and a square root transformation was applied due to moderate negative skewness. There was no significant main effect of time, $F(1, 7) = 1.98$, p = .20, $\eta_p^2 = .220$. Figure 8.60 shows that there was no difference in correct incongruent trials at baseline and follow up.
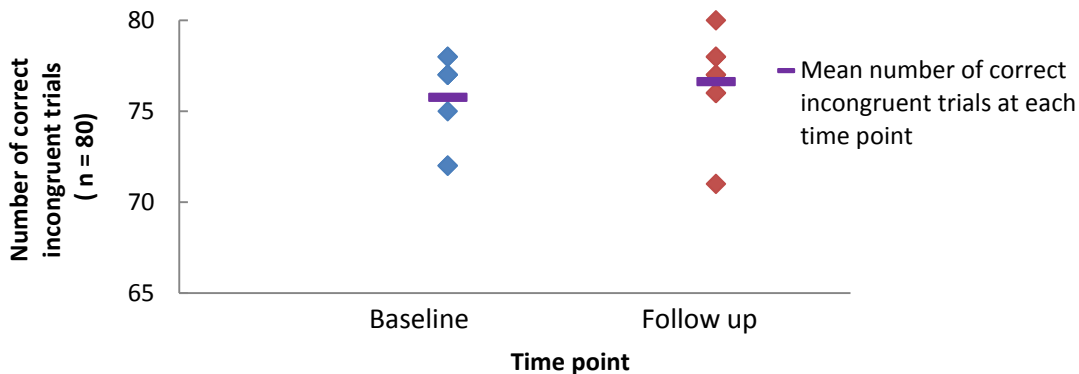
Figure 8.60 Study 4. Number of correct incongruent trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.5.2 Reaction time for correct incongruent trials

Data were logarithm transformed due to substantial positive skewness. Age was a significant covariate, $F(1, 6) = 6.17$, $p = .048$, $\eta_p^2 = .507$. Younger participants responded faster than older participants. There was a trend for a significant main effect of time, $F(1, 6) = 4.11$, $p = .089$, $\eta_p^2 = .407$, but the post hocs revealed no significant differences. There

was no significant time*age interaction, $F(1, 6) = 2.64$, $p = .16$, $\eta_p^2 = .306$. Figure 8.61 shows that there was no difference in reaction time for correct incongruent trials at baseline and follow up.
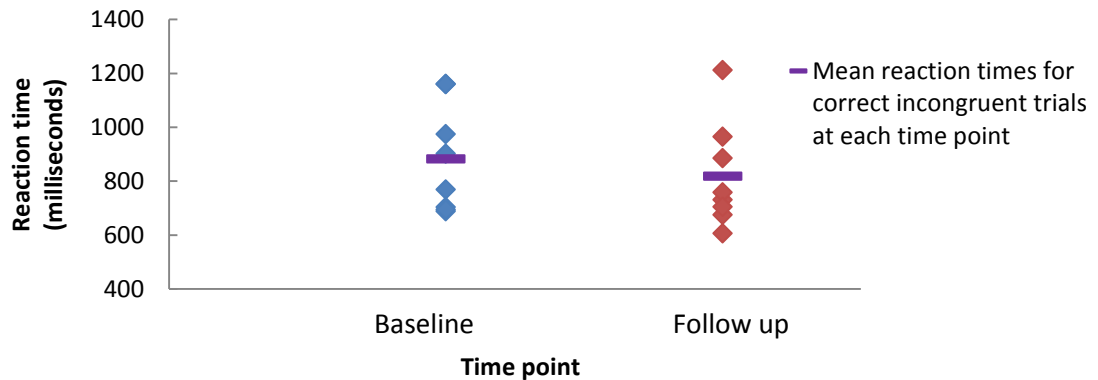
Figure 8.61 Study 4. Mean reaction time for correct incongruent trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.6 Switched trials

8.3.4.7.6.1 Proportion of correct switched trials

Data were reflected and inversely transformed due to severe negative skewness. There was a significant main effect of time $F(1, 7) = 8.53$, $p = .022$, $\eta_p^2 = .549$, such that participants correctly responded to a higher proportion switched trials at follow up (see Figure 8.62).
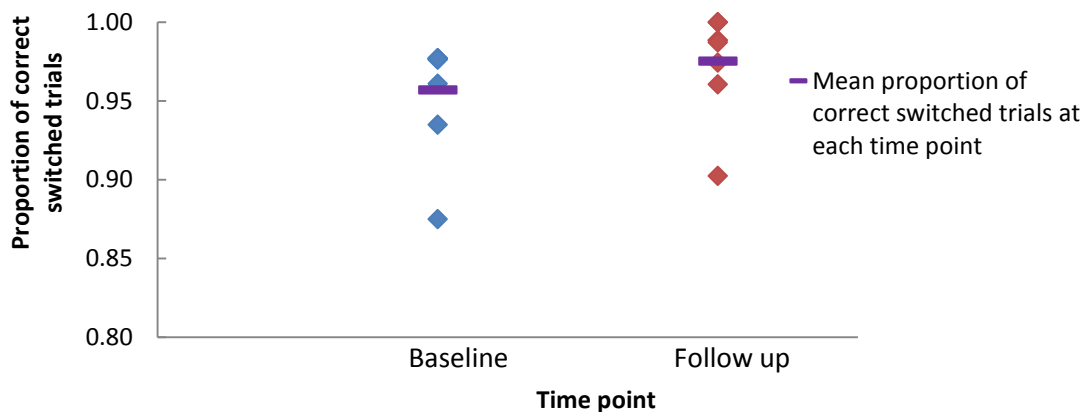
Figure 8.62 Study 4. Number of correct switched trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.6.2 Reaction time for correct switched trials

Data were square root transformed due to moderate positive skewness. Age was a significant covariate, $F(1, 6) = 6.62$ $p = .042$, $\eta_p^2 = .525$, such that younger participants responded faster than older participants. There was no significant main effect of time, $F(1, 6) = 0.94$, $p = .37$, $\eta_p^2 = .136$. There was no significant time*age interaction, $F(1, 6) = 0.34$,

$p = .58$, $\eta_p^2 = .053$. Figure 8.63 shows that there was no difference in reaction time for correct switched trials at baseline and follow up.
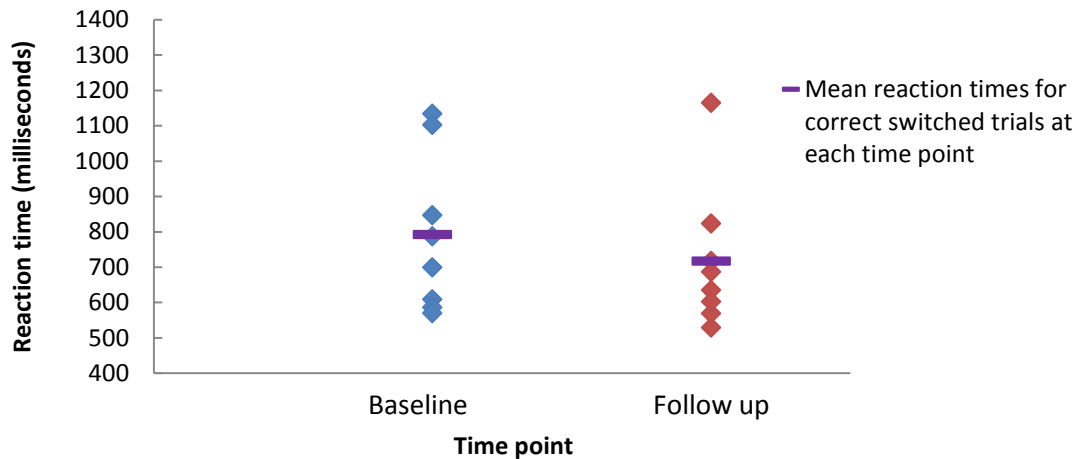
Figure 8.63 Study 4. Reaction time for correct switched trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.7 Non switched trials

8.3.4.7.7.1 Proportion of correct non switched trials

Data were reflected and inversely transformed due to severe negative skewness. There was no significant main effect of time, $F(1, 7) = 0.18$, $p = .69$, $\eta_p^2 = .025$. Figure 8.64 shows that there was no difference in the proportion of correct non switched trials at baseline and follow up.
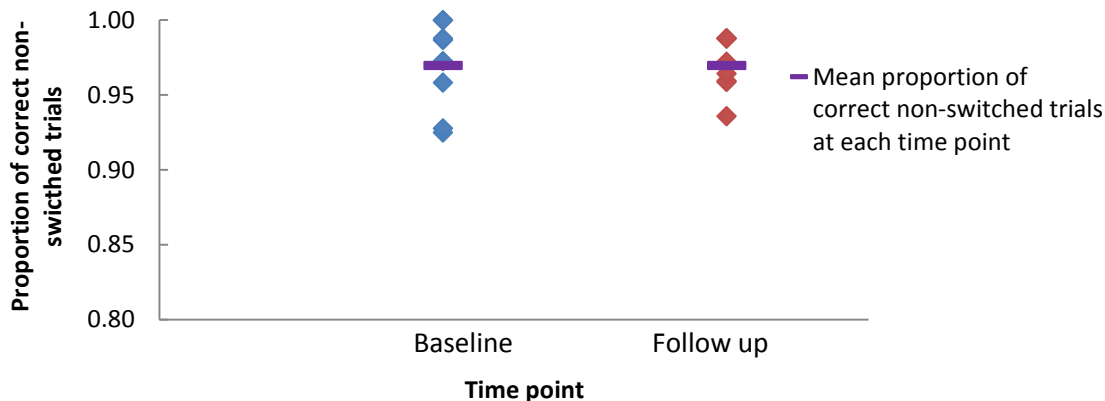
Figure 8.64 Study 4. Number of correct non-switched trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.7.2 Reaction time for correct non switched trials

Data were reflected and inversely transformed due to severe negative skewness. There was no significant main effect of time, $F(1, 7) = 1.75$, $p = .23$, $\eta_p^2 = .200$. Figure 8.65 shows that there was no difference in reaction time for correct non switched trials at baseline and follow up.
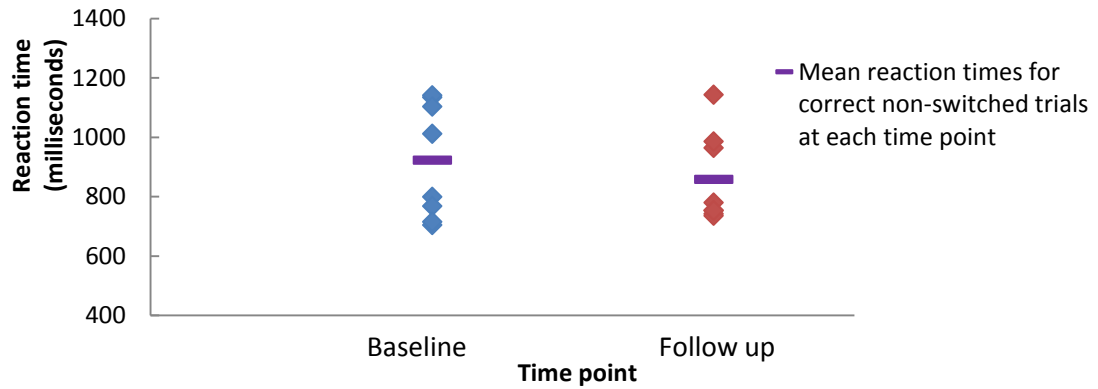
Figure 8.65 Study 4. Reaction time for correct non switched trials on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.8 Omission errors

Data were inverse transformed due to severe positive skewness. There was no significant main effect of time, $F(1, 7) = 0.33$, $p = .58$, $\eta_p^2 = .045$. Figure 8.66 shows that there was no difference in the number of omission errors produced at baseline and follow up.
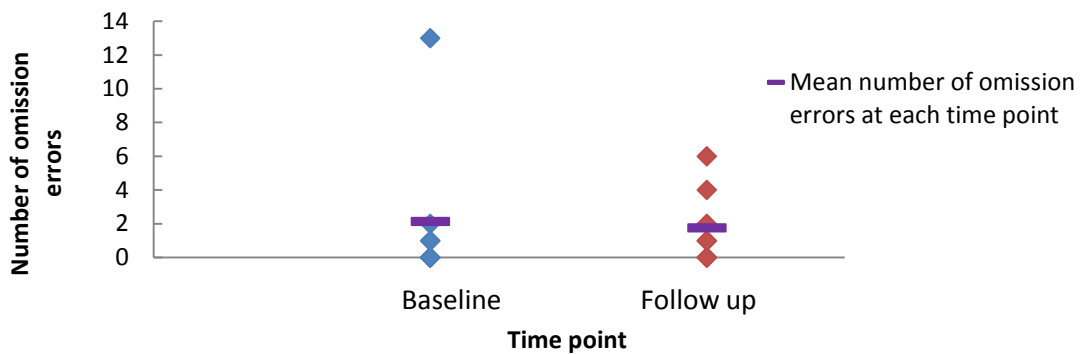
Figure 8.66 Study 4. Total number of omission errors produced on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.9 Commission errors

There were too few data points to perform analysis for commission errors. Only participant produced a commission error, and this was at baseline. This showed that participants did not, on the whole, respond too soon, either prior to the end of the pre-empt window or prior to the stimulus being shown, at both baseline and follow up.

8.3.4.7.10 Congruency cost

Data were square root transformed due to moderate positive skewness. Age was a significant covariate, $F(1, 5) = 44.86$, $p = .001$, $\eta_p^2 = .900$, and time since baseline was a significant covariate, $F(1, 5) = 10.59$, $p = .023$, $\eta_p^2 = .679$. Older participants were faster on congruent trials than younger participants. Longer duration since baseline was a predictor of faster reaction times on congruent trials than shorter duration. There was no significant main effect of time, $F(1, 5) = 1.55$, $p = .27$, $\eta_p^2 = .237$. There was no significant time*time

since baseline interaction, $F(1, 5) = 0.001$, $p = .97$, $\eta_p^2 < .001$, and no significant time*age interaction, $F(1, 5) = 1.95$, $p = .22$, $\eta_p^2 = .281$. Figure 8.67 shows that there was no difference in congruency cost at baseline and follow up.
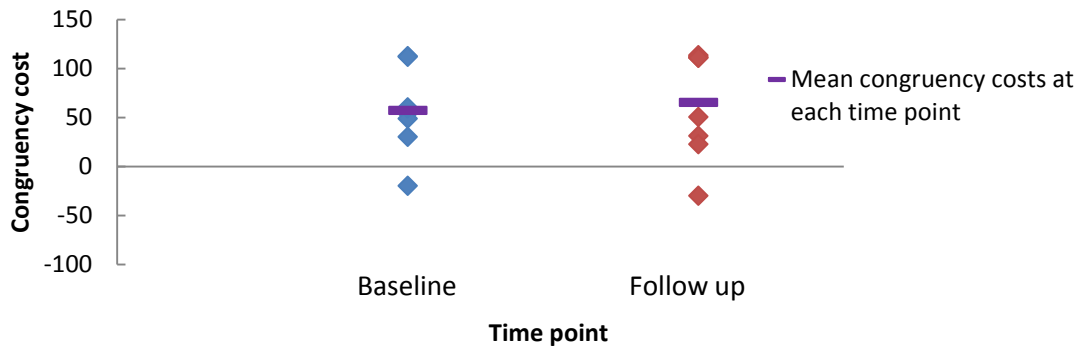
Figure 8.67 Study 4. Congruency cost for correct trials (subtraction of congruent from incongruent reaction times for correct trials) on the AST at baseline and follow up, in people with CFRDTx

8.3.4.7.11 Switch cost

Data were square root transformed due to moderate positive skewness. There was no significant main effect of time, $F(1, 7) = 0.001$, $p = .97$, $\eta_p^2 < .001$. Figure 8.68 shows that there was no difference in switch cost at baseline and follow up.
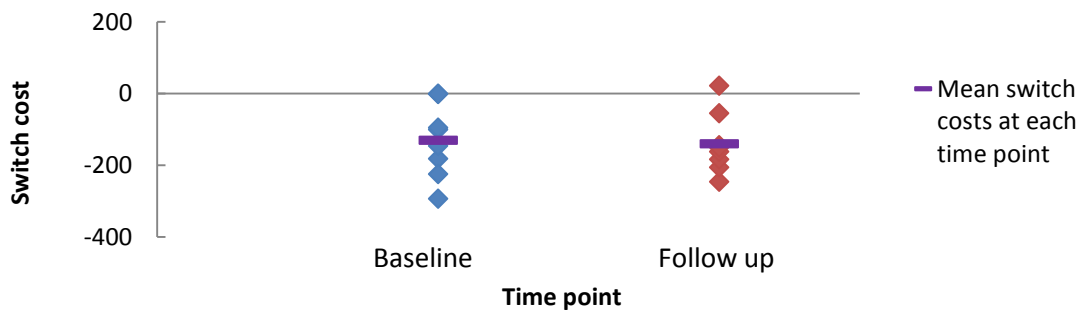
Figure 8.68 Study 4. Switch cost for correct trials (subtraction of switched from non switched reaction times) on the AST at baseline and follow up, in people with CFRDTx

8.3.5 Cognitive test evaluation questionnaire (CTEQ)

Table 8.3 shows the participants scores on the CTEQ at baseline and follow up.

Table 8.3 Study 4. Subjective experience of completing the cognitive test battery in people with CFRDTx at baseline and follow up

	Baseline N=8 Mean (SE)	Follow up N=8 Mean (SE)	F (1,7)	p value	η_p^2
Time pressure	23.13 (8.23)	25.50 (9.37)	0.08[99]	.78	.012
Test difficulty	45.50 (5.55)	41.38 (8.05)	0.57[100]	.47	.076
Ability to concentrate	86.38 (4.89)	86.38 (4.37)	0.001[101]	.98	<.001
Effort	94.13 (2.01)	88.63 (4.18)	1.22[102]	.31	.149
Performance	58.13 (4.99)	63.63 (5.53)	0.83	.39	.106
Frustration	38.88 (7.76)	36.38 (10.80)	0.16[103]	.70	.022

There was no difference in baseline and follow up scores for cognitive test difficulty, perceived time pressure, ability to concentrate, effort, performance and frustration experienced in completing the cognitive tests. Figure 8.69 shows that at baseline, VRM was rated the hardest test, whereas at follow up, SSP was rated the hardest. Figure 8.70 shows that at baseline, PRM and AST were rated equally the easiest tests, whereas at follow up, AST was rated by most as the easiest.
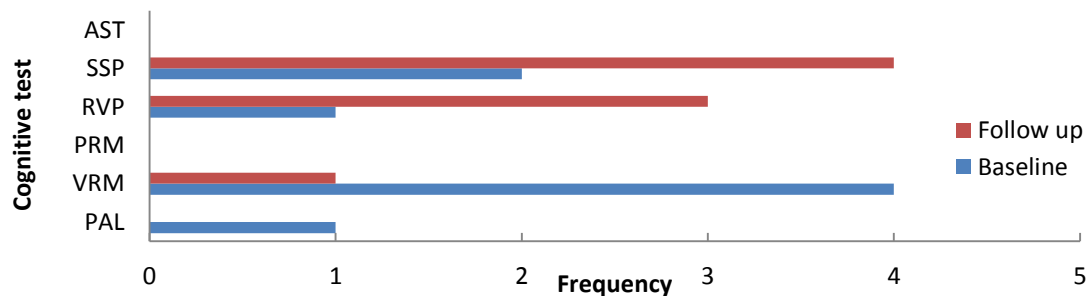
Figure 8.69 Study 4. Distribution of which was the hardest test from the cognitive battery at baseline and follow up in people with CFRD

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[99] Square root transformation applied due to moderate positive skewness
[100] Square root transformation applied due to moderate positive skewness
[101] Square root transformation applied due to moderate positive skewness
[102] Logarithm transformation applied due to substantial positive skewness
[103] Square root transformation applied due to moderate positive skewness
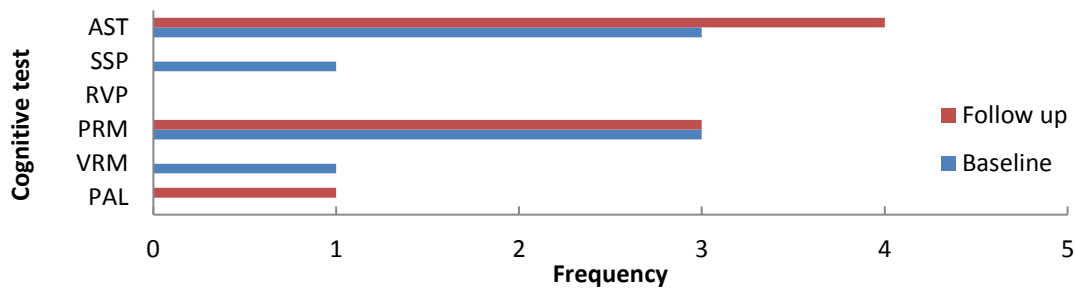
Figure 8.70 Study 4. Distribution of which was the easiest test from the cognitive battery at baseline and follow up in people with CFRD

8.4 Summary of findings

8.4.1 Participant characteristics

- From the 18 people with CFRDTx tested at baseline, 8 (4M; 4F) were retested in the present study.

- Participants were retested after a period of 15.87 (SD ± 4.45) months. All 8 participants were heterozygous F508del.

- There were no significant differences in clinical characteristics between baseline and follow up for weight, BMI, blood glucose (capillary, plasma), HbA1c, microvascular disease, lung function measures (FEV1, FEV1%predicted, FVC, FVC% predicted), oxygen saturation levels, number of people receiving IV treatment, CO (ppm and %COHb), health rating, anxiety and depression levels, SBP, DBP, pulse, vitamin D, E, serum creatinine and serum urea, and cognitive failures score.

- There was a trend for higher vitamin A levels, and a significant improvement in CRP levels (i.e. no indication of inflammation at follow up).

- There were no differences in education except one person had completed their degree since transplant. There were no differences in occupation except that the person who was retired (due to ill health pre transplant) had now taken up full time employment again.

- There was no difference from baseline to follow-up in terms of the time of day that testing took place.

8.4.2 Findings from the cognitive tests (Aim 1)

A detailed summary of the outcomes for each cognitive test is presented in Table 8.4. Taken together, the cognitive assessments made at baseline and follow-up indicate that:

- Overall, there was no change in performance for motor function (MOT), visual memory and new pattern learning (PAL), and attention and processing speed (RVP) over 18±6months.

- There was a trend for improved delayed verbal memory for free recall, but more errors were produced at recognition (VRM).
- Accuracy for delayed pattern recognition was worse but reaction time performance did not change (PRM).
- There was no change in working memory span length, but more errors (total and usage) were produced (SSP).
- Accuracy improved for cognitive flexibility (i.e. for switching trials), but this did not impact on reaction time.
- Being older was predictive of worse motor function, (accuracy and reaction time; MOT), immediate visual memory (PAL; first trial memory score), attention and processing speed, and cognitive flexibility (RVP; more guessing and AST accuracy and reaction time).
- Being younger was associated with improved immediate visual memory (PRM) and attention and processing speed (RVP) at follow up testing.
- Being older was associated with more errors on working memory (SSP) at follow up testing.
- Shorter duration since baseline testing was associated with improved verbal memory (VRM) and reaction time for delayed visual memory (PRM).

Table 8.4 Study 4. Summary of cognitive test outcomes for Aim 1: Changes in cognitive function over time; baseline and follow up ('+' better performance, '-' worse performance, '0' no difference)

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Age (covariate)	Time since baseline (covariate)	Interaction Time*age/Time*time since baseline
MOT	Mean error	0	Older -	0	n/a
	Reaction time	0	Older -	0	n/a
PAL	Stages completed	0	0	0	n/a
	Stages completed on first trial	0	0	0	n/a
	First trial memory score	0	Older – (trend)	0	n/a
	Total trials	0	0	0	n/a
	Total errors	0	0	0	n/a
VRM	Immediate free recall	0	0	0	Shorter duration +
	Immediate novel words	0	0	0	n/a
	Immediate perseverations	0	Older -	0	Shorter duration +
	Immediate target recognition	0	0	0	Shorter duration +
	Immediate false alarm recognition	0	0	0	n/a
	Delayed free recall	(trend)+	0	0	n/a
	Delayed novel words	0	0	0	n/a
	Delayed perseverations	0	0	0	n/a
	Delayed target recognition	0	0	0	Younger +
	Delayed false alarm recognition	-	0	0	n/a

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Age (covariate)	Time since baseline (covariate)	Interaction Time*age/Time*time since baseline
PRM	Immediate number correct	0	0	0	Younger +
	Immediate reaction time	0	0	0	n/a
	Delayed Number correct	-	0	0	n/a
	Delayed reaction time	0	0	0	Older + and shorter duration +
RVP	Total hits	0	0	0	n/a
	False Alarms	0	0	0	n/a
	Mean reaction time for hits	0	0	0	Younger +
	A' Prime	0	0	0	n/a
	B' Prime	0	Older –(trend)	0	Younger +
SSP	Span length	0	0	0	n/a
	Total number of attempts	0[104]	0	0	n/a
	Mean time to first response	0[105]	0	0	n/a
	Mean time to last response	0[106]	0	0	n/a
	Total errors	-(trend)[107]	0	0	Older -
	Total usage errors	-[108]	0	0	Younger +, and lower span +

[104] Span length was included as a covariate in the model, but was not significant
[105] Span length was included as a covariate in the model, but was not significant
[106] Span length was included as a covariate in the model, but was not significant
[107] Span length was included as a covariate in the model, but was not significant
[108] Span length was included as a covariate in the model, but was not significant

Test	Outcome measure	Change in cognition over time (baseline to follow-up)	Age (covariate)	Time since baseline (covariate)	Interaction Time*age/Time*time since baseline
AST	Total correct trials	0	0	0	n/a
	Mean reaction time for correct trials	0	Older -	0	n/a
	Correct direction trials	0	0	0	n/a
	Mean reaction time for direction trials	0	0	0	n/a
	Correct side trials	0	0	0	Older +
	Mean reaction time for side trials	0	Older -	0	n/a
	Correct congruent trials	0	Older -	0	n/a
	Mean reaction time for congruent trials	0	0	0	n/a
	Correct incongruent trials	0	0	0	n/a
	Mean reaction time for incongruent trials	0	Older -	0	n/a
	Correct switched trials	+	0	0	n/a
	Mean reaction time for switched trials	0	Older -	0	n/a
	Correct non-switched trials	0	0	0	n/a
	Mean reaction time for non-switched trials	0	0	0	n/a
	Omission errors	0	0	0	n/a
	Commission errors	0	0	0	n/a
	Congruency cost	0	Older +(congruent trials)	Longer + (congruent trials)	n/a
	Switch cost	0	0	0	n/a

8.4.3   Findings from the subjective ratings questionnaires (Aim 2 and 3)

- Overall there was no difference between sleep quality at baseline and follow up except periods of wakefulness during the night were fewer at follow up.

- Younger participants had more periods of wakefulness during the night before the test session compared to the previous week.

- There was no change in levels of perceived stress since baseline. Participants reported feeling more stressed during the past month compared to the past week.

- There was no change in mood since baseline, except a trend for people to report feeling less irritable.

- There were no differences in the number of subjective minor daily cognitive errors made within the past 6 months. The number of reported errors made within the past week (CDS) correlated highly with those reported within the previous 6 months (CFQ).

- There were no differences in the participant's experience of completing the cognitive test battery as assessed by the cognitive workload measure.

- At follow up, SSP was rated the hardest test (previously VRM), and AST as the easiest (previously joint PRM and AST).

8.5   Discussion

The first aim of the study chapter was to investigate whether cognitive function had changed over a period of 18 (±6) months in people with CFRDTx. The second aim was to investigate whether the number of subjective cognitive daily errors had changed over this period of time. The third aim was to investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period.

8.5.1   Aim 1: To investigate whether cognitive function had changed over a period of 18 (±6) months in people with CFRDTx

The present study found overall that there were no changes in cognitive function for motor function, visual memory and new pattern learning, and attention and processing speed over an 18±6month period (see section 8.4.2). Cognitive decline was evident for pattern recognition, and the domains of working memory and verbal memory also showed some decline insofar as more errors were produced to maintain baseline testing performance. Furthermore, although there was an improvement in response to switching trials on the task of cognitive flexibility, older age was a predictor of slower reaction times for these trials. Therefore accuracy may have improved at the expense of speed in older people post transplant. On the whole, the findings suggest that cognitive function remained stable over a period of 18±6months.

Participants had, on average, been diagnosed with CFRD for 13.5 years, and were 8 years post transplant. Over the follow up period of 18±6 months, glycaemic control had remained stable. As glucose regulation and cognitive function are tightly linked, it is therefore unlikely that

cognitive function would have changed. This suggests that duration of diabetes in people with CFRDTx does not have a negative impact on cognitive function over time, and that stable HbA1c may be a protective factor against decline (West et al., 2014). However, as some patients were tested one year since baseline, the duration of follow up period may not have been long enough to produce significant changes in glycaemic control to cause vascular changes within the brain of sufficient impact to lead to changes in cognitive function.

Although not significantly different, there was a suggestion that glycaemic control may have improved over time in people with CFRDTx. Fasting blood glucose levels had, on average, decreased to nearer the normal levels found in healthy individuals but remained in the IGT range (9.6 to 8.7mmol/L). It may be that glucose regulation had improved due to follow up testing occurring after a longer period since transplant (Valour et al., 2013, Hadjiliadis et al., 2005) and this offered some protection against cognitive decline in people with CFRDTx.

The INSPIRE study (Smith et al., 2014) assessed cognitive function in people who were post lung transplant after a mean period of 9 (4-12) years and found that lower executive function and memory scores were independently associated with greater mortality. As people in the present study were on average 8 years post transplant and showing no signs of decline after a short follow up period, it would be of interest to follow these people up again to assess whether changes in cognitive function are evident over a longer period, and whether any such cognitive decline is associated with mortality.

Although overall cognitive function did not show evidence of a decline, except for visual memory, there were effects of being younger and a shorter duration from baseline being associated with better cognitive function. Being older was predictive of worse motor function, immediate visual memory, attention and processing speed, working memory and cognitive flexibility. It may be that the shorter duration (i.e. a minimum of one year) in follow up testing may not be a sufficient period of time for significant changes to cognitive function to manifest. These findings also suggest that having a transplant at an earlier age may be beneficial with respect to cognitive function.

8.5.1.1 Subjective evaluation of cognitive performance

There were no differences between baseline testing and follow up on the cognitive workload measures. However, what participants considered the hardest and easiest tests had changed. The test perceived as the hardest cognitive test changed from VRM at baseline to SSP at follow-up. At follow up, performance on both these tests was maintained at the expense of an increase in the number of errors made. However, as the SSP test gets progressively harder, the number of errors made by a participant influences how many attempts at each level they had to perform to progress, a participant may have become more aware of their performance, compared to the VRM test where there is a set number of stimuli on the recognition task to respond to. PRM and AST were rated equally easy at baseline whereas AST was rated at easiest at follow-up. This may reflect that participants were aware that they exhibited cognitive decline on the PRM test and increased their subjective rating of its difficulty.

8.5.2 Aim 2: To investigate whether the number of subjective cognitive daily errors had changed over this period of time.

There was no difference in the subjective reporting of daily minor cognitive errors which had occurred in the past 6 months (CFQ) at follow up. This suggests that participants did not perceive their cognitive function to have declined over the time since baseline testing. Furthermore, the scores on the CDS were found to be highly correlated with the number of daily minor errors reported on the CFQ, as was the case in Study 2 (Chapter 6). However, as levels of depression were low in people with CFRDTx, this cannot be an explanation for the frequency reported in the present study. Instead, the number of daily cognitive errors may be explained by people returning to a free living less restrictive lifestyle after transplantation, and the reasons for daily cognitive errors may be more reflective of those common to their healthy peers.

8.5.3 Aim 3: To investigate whether there are any differences in clinical characteristics or subjective evaluations of sleep, stress, mood and mental alertness at follow up, compared to baseline testing which might be associated with any change in cognitive functioning over the same period

Due to the small sample size, gender differences in cognitive function could not be examined in this study. However there was an equal number of males and females in the follow up.

As levels of depression remained stable in people with CFRDTx, this may explain offer a further explanation for the failure to observe change in cognitive function. Although not significant, people with CFRDTx reported lower levels of depression at follow up, which may reflect a longer period since transplantation and the reduction of poor health which stopped their disease from being the main focus of their life.

There was no change in clinical parameters between baseline testing and follow up except for CRP levels. At baseline testing, some participants showed slightly elevated CRP levels indicating signs of inflammation. At follow up, there were no clinical signs of inflammation in people with CFRDTx. Lack of inflammation may have either acted as a protective factor against cognitive decline, or may explain the improvements in some aspects of cognitive function. Even low levels of inflammation (> 5mg/L) have been associated with impairments in cognitive flexibility (Lasselin et al., 2016) which would support the latter point.

Sleep quality has been shown to affect cognitive functioning in non – transplanted people with CF (Dancey et al., 2002, Dobbin et al., 2005). There were no differences in sleep quality between baseline testing and follow up except for fewer periods of wakefulness, which would reflect better sleep quality. Therefore, the lack of change in sleep quality contribute to the lack of change in cognitive function over time. Although younger participants reported they had more periods of wakefulness during the night before the test session, this was not reflected in their cognitive performance, and being younger was actually a predictor for better performance for some of the cognitive tests. Younger age may therefore be associated with greater cognitive resilience despite poorer sleep.

8.6 **Conclusion**

The present study found no changes in cognitive function after a period of 18±6months in a small sample of people with CFRDTx. Larger numbers of participants and a longer follow up period since baseline, with intermediate testing to profile the trajectory of cognitive function over time would provide more definitive answers as to the impact of transplant on cognitive function in people with CFRDTx.

Chapter 9

General Discussion

This thesis has considered the effect of CF on cognitive function in a series of studies as described in Figure 4.1. These studies were conducted in order to answer the research questions formulated in Chapter 4 and each of these is considered in turn below.

9.1 Does CF impact on cognitive function?

The impact of CF on cognitive function was examined in Study 1 (Chapter 5) which showed that both patient groups (CFRD and CFND) were significantly worse than healthy controls on domains of (visual, verbal and working) memory, attention and processing speed, and cognitive flexibility. Several mechanisms may explain the observed association between CF and cognitive impairment. However, as CF is a multi-system disease, it is unlikely that one mechanism alone can explain the impairment observed across a range of cognitive domains. Candidate mechanisms underlying the observed cognitive impairment in CF are considered below.

9.1.1 P. aeruginosa and lung function

Although there is only a weak correlation between genotype and lung function (Bell et al., 2015), the majority of patients included in Study 1 were heterozygous F508del. Therefore, impairment in the cognitive domains observed is likely to be characteristic of people with moderate to severe disease, irrespective of genotype. People with CF in the study were aged on average, approximately 30 years and had, on average, moderate lung function disease. In the present study, over two thirds of participants were chronically infected with *P. aeruginosa* which has been associated with a more rapid decline in lung function. This may have had an indirect effect on cognitive function.

9.1.2 Hypoxia

The brain requires an exogenous supply of blood glucose and oxygen to meet its requirements to function adequately, and therefore any evidence of cerebral hypoxia could lead to a negative impact on cognition due to reduction in oxidative glucose metabolism. Despite oxygen saturation levels being normal at the time of testing, transient hypoxia is frequently seen in people with CF during periods of PEs. Studies have shown hypoxia can cause vascular changes (Areza-Fegyveres, Kairalla, Carvalho, & Nitrini, 2010), which may explain in part, the degree of cognitive impairment seen in CF. Administration of oxygen in healthy individuals has been shown to have beneficial effects on immediate and delayed verbal memory, attention and processing speed (Scholey, Moss, Neave, & Wesnes, 1999; Scholey, Moss, & Wesnes, 1998). This suggests that the impairment observed in CF particularly that seen in domains of verbal memory, attention and processing speed may be a consequence of lower levels of oxygen and lung function

disease. It is also possible that PI, IGT and CFRD may explain the impaired cognitive performance seen in people with CF in Study 1 and this is considered in section 9.2.1 below.

9.1.3 CFTR

Recent research has shown that CFTR is not only present in the pancreas (Guo et al., 2014), but in the brain as well (Guo, Su, McNutt, & Gu, 2009). In the pancreas, CFTR plays a role in the regulation of insulin secretion and therefore even individuals who have a NGT OGTT result experience some degree of glucose tolerance abnormalities. In the brain, there is widespread and abundant expression of CFTR in neurons. Therefore, the underlying gene defect may be a mechanism for cognitive impairment in people with CF. The finding that CFTR is in the brain also has implications for cognitive functioning in general. In support of people with CF being susceptible to cognitive impairment because of the underlying disease, there is some evidence that people with CF have structural central nervous system (CNS) abnormalities as there is a higher prevalence of Chiari malformations compared to the general population (Needleman et al., 2000). Therefore, it has been suggested that CFTR plays a role in the development of the CNS (Patel, Raol, & Jea, 2011) and could be a causal factor in the subtle cognitive impairments observed between the people with CF and controls in Study 1.

9.1.4 Delayed diagnosis and treatment

A delay in CF diagnosis may contribute to the degree of cognitive impairment that an individual shows. It has already been demonstrated that a delay in CF diagnosis impacts upon growth and nutrition (Bridges, 2016), therefore it is plausible that such a delay may also impact upon brain development. In the present study, CF diagnosis was relatively early due to the early uptake of a screening programme in Leeds. Therefore, although there was a significant difference in diagnosis between CFRD and CFND, delayed diagnosis is unlikely to be a mechanism for cognitive impairment in this study.

9.1.5 Malnutrition

There is an evolutionary drive to sustain and maintain brain function and therefore it is unsurprising that the supply of energy to the brain is prioritised. This is supported by the Selfish Brain Theory (Peters et al., 2004). Between birth and the age of 3 years, there is substantial brain development and malnutrition will have lasting detrimental effects on cognitive function. Children who do not receive adequate nutrition are at risk for failing to reach their developmental potential in cognitive, motor, and socio-emotional abilities which may continue into adolescence and adulthood. In CF, it is not an impoverished environment which leads to malnourishment but nutrient malabsorption is a feature of the disease. Therefore, despite the prioritisation of energy to the brain, people with CF are also likely to be deficient in other nutrients which are necessary for brain function. The assumption that malnutrition is a mechanism for cognitive impairment is supported by Koscik et al. (2005) who found that a prolonged period of vitamin E deficiency in people with CF has deleterious effects for cognitive function later in life.

9.1.6 Depression

Higher levels of depression were evident in people with CF compared to healthy controls. Higher levels of depression have been observed previously in people with CF, and the development of CFRD has been shown to increase the risk. Research has shown that depression is associated with cognitive impairment (Papazacharias & Nardini, 2012). Therefore, the comorbidity of depression and having CF may exacerbate degree of cognitive impairment. However, this was not formally investigated in the study, and therefore future research is needed to assess if those who showed the highest depression scores also showed the worse cognitive performance, and in which domains.

9.2 Is cognitive function worse in people with CFRD than people with CF who are not diabetic?

Study 1 found that cognitive function was worse in people with CFRD than in CFND on all cognitive domains, but a significant difference was only found for processing speed. This poorer performance in people with CFRD reflects disease trajectory.

9.2.1 Disease severity

Participants with CFRD were older than participants with CFND as diabetes develops as function of disease duration. Lung function in CF is negatively associated with age (E. Kerem et al., 2014). Therefore, the poorer cognitive performance observed in people with CFRD may be related to the finding that these people also have slightly worse lung function compared to the CFND.

9.2.2 PI and glucose tolerance

Unlike lung function, there is a strong correlation between genotype and phenotypic expression of pancreatic dysfunction (Simmonds, 2013). In Study 1, people with CF all showed PI and had either developed CFRD or could be considered highly susceptible to developing CFRD in the future. Impaired glucose regulation has been associated with impaired cognition (Lamport et al., 2009). Therefore, cognitive impairment may have occurred as a consequence of glucose tolerance abnormalities in people with CF. Deficits were commonly seen on tasks of memory and processing speed which concur with previous literature on the effects of diabetes on cognition (Awad et al., 2004; Brands et al., 2005; Lamport, Dye, Mansfield, & Lawton, 2013). Moreover, the effects observed confirm the findings that memory is the cognitive domain most susceptible to disruption by poor glucose tolerance (Lamport et al., 2009).

People with IGT have been shown to have visual memory impairments (Lamport, Lawton, et al., 2014). Therefore, the relatively impaired cognitive performance seen on the domain of visual memory and new pattern learning in people with CFND may reflect variability of glucose regulation in CF. It is possible that despite having a NGT result, at the time of testing people with CFND were experiencing IGT, or had previous periods of undetected IGT.

9.2.3 Hypoglycaemia

The hippocampus is highly sensitive to episodes of hypoglycaemia (McEwen, 1997). In CF, multiple therapies are prescribed for both prevention and treatment. People with CF receive insulin therapy before a confirmed diabetes diagnosis to prevent deterioration in health during times of clinical instability. Furthermore, it has been documented that severe hypoglycaemia causes brain damage and cognitive impairment (Bree, Puente, Daphna-Iken, & Fisher, 2009; R. J. Wright, Frier, & Deary, 2009), but recurrent subtle episodes of mild hypoglycaemia may also lead to cognitive impairment (Lamport et al., 2009). Exogenous insulin secretion does not mimic peak insulin secretion in the same way as endogenous insulin secretion, with insulin often being released in between meals. This can result in mild hypoglycaemic episodes which are undetected due to their occurrence outside meal times. Therefore, it is possible that in some people with CF, intervention with insulin may be premature. Furthermore, the more hypoglycaemic episodes a person experiences, the lower their threshold for the brain to respond to internal signals which indicate a hypoglycaemic episode i.e. super-sensitivity occurs. Therefore, although people with CF may not have been hypoglycaemic at the time of testing, early initiation of insulin may have led to subtle undetected episodes of hypoglycaemia, which over time could have had a significant impact on sensitive aspects of cognitive function.

9.2.4 Age of and insidious onset of CFRD

As mentioned in section 9.2.2, processing speed has commonly been found in people with diabetes but not in people who have NGT (Awad et al., 2004; Brands et al., 2006; Lamport, Lawton, et al., 2014). In addition to the brain undergoing rapid development during the early years of life, there is significant remodelling during adolescence. Although there is no consensus as to what constitutes the ending of adolescence, some argue it begins around 10 years and ends around age 25. People with CF develop diabetes around the ages of 18 -21 years, with the mean age being 21 years in the UK. Despite being considerably younger than people who develop diabetes in the general population, people with CF may be experiencing episodes of prolonged hyperglycaemia, or hypoglycaemia during late adolescence and early adulthood. Both hyper and hypo-glycaemia can potentially cause vascular changes which might result in impaired cognitive function even at a younger age than is seen in type 2 diabetes in the general population.

9.2.5 Pulmonary Exacerbations (PEs)

PEs have been shown to affect cognitive functioning in CF (Dobbin et al., 2005a). There was no significant difference between people with CFRD and CFND in terms of the frequency of people receiving IV treatment. Therefore the incidence of PE at the time of testing cannot explain the difference in performance of people with CFRD. However, there were slightly higher frequency of people with CFND receiving IV treatment at the time of testing, which could have possibly contributed to the visual memory and new pattern learning impairment seen in these patients. However, as Dobbin et al., (2005a) did not report the proportion of people with CFRD in their sample, or assess visual memory in their study, it can only be speculated that PEs are associated with impairment in this domain.

9.2.6 Sleep quality

People with CFRD reported that their sleep quality was generally worse than people with CFND and healthy controls which may reflect disease trajectory. Sleep quality has previously been shown to influence cognitive functioning in people with CF (Dancey et al., 2002), but the effect of diabetes on sleep quality was not investigated. Mood and mental alertness was also shown to be significantly worse in people with CFRD. This study highlights that in people with CF who have moderate lung disease, sleep quality is more significantly compromised in people with CFRD than CFND compared to healthy controls, and that sleep quality may be a mediator of the relationship between CFRD and impaired cognitive function.

9.3 Does cognitive function decline over time in people with CFRD?

Study 2 (Chapter 6) showed no overall decline in cognitive performance across the entire test battery in people with CFRD over a 1-3 year period. Over the period of follow-up, there was a significant decline in lung function which may suggest that there is a lag between change in lung function and changes within the brain that might lead to a change in level of performance. In this sample there was also no change in glucose regulation at follow up. Thus glucose tolerance did not improve in this sample. Given the well documented link between blood glucose levels and performance in healthy adults and in IGT, T1DM and T2DM (Benton, 1995; Cox et al., 2005; Cukierman-Yaffe et al., 2009; Jacobson et al., 2007; Lamport et al., 2009; Scholey, Harper, & Kennedy, 2001; Sommerfield et al., 2004; Sunram-Lea, Owen, & Robertson, 2015), it could be suggested that this is a more important mechanistic process related to cognitive function in people with CFRD. If this relationship is also true in CF, then one would not expect a change in cognitive performance when an improvement of glucose regulation has not occurred.

9.3.1 Gender and age differences

There were however, a number of factors which predicted cognitive performance in people with CFRD. For instance, being female was a significant predictor of better performance on verbal memory and reaction time for visual memory whilst being male was a significant predictor of slower reaction times on working memory tasks. Being younger was a predictor of better performance at follow up for visual memory and new pattern learning while age significantly predicted worse accuracy on tasks of working memory. A longer disease duration was consistently found to be a predictor of worse performance for attention and processing speed, and cognitive flexibility tasks.

9.4 Does transplantation improve cognitive function in people with CFRD?

Study 3 (Chapter 7) showed that cognitive function is not improved post transplant in people with CFRD despite the evident improvements in lung function. This finding directly contradicts previous research which found cognitive function to be improved in adults after lung transplantation (Hoffman et al., 2012; Smith, Rivelli, et al., 2014). These mechanisms for the lack of improvement in cognition are discussed below.

9.4.1 Duration since transplantation

Despite improvements in subjective evaluations of sleep, stress and mood in people with CFRDTx, this did not translate to improved cognitive function. This could be explained by the fact on average participants were 9 years post transplant. Previous research which has shown a benefit of lung transplantation on cognitive function in CF assessed cognition at a time point close to transplantation, and at a relatively short time after transplantation. Therefore, the improvement in cognitive function may be a reflection of the significant improvement in lung function from pre to post transplant, in conjunction with reduced fatigue. As Study 3 was cross sectional, it is unknown how cognitive function may have changed, if at all, as a function of time, both in relation to pre transplant, and since transplantation. It might be that there is a window of opportunity to see improvements in cognitive function which was missed in the current study due to the considerable period between transplant and testing. Despite people undergoing lung and liver transplantation, other organs can still be affected by CF disease as abnormal CFTR is still present throughout the rest of the body. People with CF can develop post transplant complications such as renal failure. Two people in the study had received subsequent kidney transplants and as lung transplantation is not a cure for non pulmonary CF related disease, it might not be realistic to expect the dramatic and sustained improvement in cognition to be stable in people with CF.

9.4.2 Effect of diabetes

The findings presented in this thesis support the hypothesis that diabetes is an important mechanism for cognitive impairment in CF and that no change in performance would be seen in the absence of an improvement in blood glucose and HbA1c from pre to post transplantation in the patient groups.

The sample considered in Study 3 namely, people with CFRDTx, CFRD and controls (see Figure 4.1), were matched on age, gender and education. People with CFRD and controls were a subsample of those who participated in Study 1 and carefully selected to match the people with CFRD who had undergone transplant (i.e. CFRDTx). The key differentiating cognitive domain on which they differed from controls was processing speed. This supports the notion that CFRD is associated with a slowing in processing speed demonstrated in Study 1 (Chapter 5). The slowing of processing speed in people with CFRD, but not controls was expected and highlights the robustness of this finding since it was reproducible in a reduced sample of participants.

There were two cognitive domains where there was a difference in the profile of cognitive impairment seen in people with CFRDTx and CFRD. People with CFRDTx were shown to have slowing in processing speed on an attention task (RVP), while people with CFRD were shown to have slowing in processing speed on a task of cognitive flexibility (AST), for the harder type of trials i.e. incongruent and switched. Slowing in processing speed was not seen on the attention task in Study 1, therefore, this finding is unique to CFRDTx. It may however, reflect a speed-accuracy trade-off for this test as people with CFRDTx had a better accuracy at detecting target sequences.

9.4.3 Adherence and glycaemic control

Glycaemic control was not different between people with CFRD and CFRDTx. People who are CFRDTx experience an improved QoL post transplant as the burden of ill health is alleviated to some extent. People who have received a kidney transplant experience improved appetite which has a positive impact on insulin sensitivity and diabetes control (Cashion et al., 2014). Therefore in people with kidney failure, transplantation has an immediate effect on diabetes control. This is not mirrored in people who receive a lung transplant although the increase in level of physical activity may be expected to have a positive impact on diabetes and cognitive function. The lack of improvement in cognition may therefore be explained as people with CFRDTx return to being a free living individual capable of achieving the same life goals as their peers. Their approach to self management of medications may become lax in the light of their improved health such that they are not so dependent on medication and exert less control over their diet than they did prior to the transplant. These factors and the psychological impact of having received a transplant to restore their lung function and improve their quality of life and ability to function as a normal adult leads to a reactive lack of adherence to treatment or CF management regimes. All these factors coupled together could lead to a worsening of glycaemic control post transplant.

9.4.4 Effect of immune suppressants and sepsis

Other possible factors affecting cognitive function in people with CFRDTx may be the multiple potent immune suppressants including steroids which are associated with medical complications (see Chapter 1, section 1.5.5.2.1.3). Furthermore, it is not infrequent for people who are post lung transplant to have improved diabetes as the diseased lungs are removed. The resulting reduction in sepsis on pulmonary infection may have an impact on cognitive function.

9.5 Does cognitive function decline over time in people with CFRD who are post transplant?

There was no evidence of a decline in cognitive function in people with CFRDTx after a period of 18±6months. There was no change in glucose regulation at follow up and therefore as glucose and cognitive function are tightly linked (see section 9.2.3 above), it is unlikely there would be any change in cognitive function. There is evidence that people who were younger, and people who were tested after a shorter period of time since the baseline testing performed better at follow up. This suggests there may be a window of opportunity for improvements in cognitive function in people who are CFRDTx. However the follow up period was relatively short, the longer term effects are not known, and the sample size was very small so that it is difficult to draw any firm conclusions about whether there is any cognitive decline in people who are CFRDTx. How these people would have performed cognitively in the absence of a transplant is also unknown. It may be postulated that transplantation may have maintained cognitive function and prevented cognitive decline but this supposition requires verification in future longitudinal studies (see section 9.8 below).

9.6 **Strengths of the research**

The thesis has answered an important clinical question as to whether CFRD is associated with cognitive impairment, in people whose lives are already significantly impacted by their genetic disorder. Although CF is one of the most common autosomal recessive diseases affecting Caucasians (O'Riordan et al., 2008) with a carrier frequency is 1 in 25 in the UK (Schram, 2012), it is still considered a rare disease. The inclusion of all four studies on the NIHR CRN portfolio database contributes to the understanding of the cognitive correlates and consequences of CF and its treatment.

The studies included in this thesis addressed key questions regarding the effect of diabetes and transplant and represent some of the first large scale studies of cognitive function in CF (see Figure 4.1). The assessment of various cognitive domains using a computerised validated cognitive test battery and the multivariate approach to analysis which permitted control for multiple covariates are further strengths of the studies conducted.

The recruitment rate was excellent for Study 1 and Study 3 with baseline data collected from a total of 116 patients in a Unit of 399 patients. Only 24 patients declined to take part in either of the two studies. The recruitment rate was also excellent for Study 2 and 4, where the main reason for loss to follow up was death or ill health. These two factors are to be expected in research with people who have a chronic life limiting respiratory disorder. Of the 67 patients who had CFRD at baseline, five had died by the time the follow up studies had started (i.e. within a period of 12 months). This highlights that despite significant improvements in treatment and a corresponding increase in median life expectancy, morbidity and mortality is still an important factor in CF. Smith, Blumenthal, et al. (2014) showed that pre transplant cognitive function is a predictor of post transplant mortality. As baseline data has been collected for 98 patients pre transplant, future research could explore the relationship between pre transplant cognitive function and post transplant longevity.

9.7 **Limitations of the research**

Inevitably a study which aims to examine the effects of chronic and life shortening disease over time will be affected by participant loss as occurred to some degree in studies 2 and 4. One strategy in the current research was to examine differences in cognitive function between people with CFND and CFRD, including those with CFRD who had had a transplant, in comparison to normal healthy controls i.e. to adopt a cross-sectional design as in studies 1 and 3. A significant weakness of such designs is that despite attempts to match the groups they could vary on unmeasured characteristics which nevertheless, may influence cognitive function. Thus it is not possible to conclude that the differences observed between the patients with CF and healthy controls are solely due to the presence of disease.

In the studies presented in this thesis, a limitation which could be levied at the longer term studies is that there was loss to follow up. However, it has been demonstrated above that such losses which occurred were unrelated to the aim of the study and actually a feature of the disease i.e. participant loss was not selective in terms of cognitive function but may well have been in relation to disease severity. This suggests that any effects observed in relation to

disease severity or trajectory may well be underestimates of the true impact of CF on cognitive function.

A further limitation is that the follow up period was relatively short i.e. participants were retested after a minimum of 12 months in Study 2 and 4. A trend for lung function decline was evident in people with CFRD after a 1-3 year period (Study 2), but this may not have been long enough for cortical changes within the brain to be detectable. Therefore, decline in cognitive function may not have occurred or was too subtle to be detected. A longer follow up period would allow further investigation and provide support for the conclusions drawn.

The converse is true in the follow up of people with CF post transplant (Study 4). These patients were tested around 9 years post transplant and followed up after a further two years with little cognitive change detected. It is difficult to determine whether these patients would have shown greatest change in cognitive function immediately after transplant and subsequently experienced stable function or whether they have experienced slower decline over this decade than would be the case in non-transplanted patients or indeed whether transplant had no effect on cognition irrespective of the time window of testing. It is also hard to match such patients with either other people with CF or normal controls since there are many parameters on which they might differ. It would have been best to study people with CF pre and sequentially post transplant to explore the varying potential influences on cognition. However, this was not possible due to the time limitation of the PhD and the number of people with CF undergoing transplantation per year on the Leeds adult CF Unit.

The selection of appropriate tests to detect differences between groups and change over time in CF was difficult because there was very little previous research to draw upon. The CANTAB test battery was chosen on the basis of previous research in patient samples and sensitivity to pharmaceutical and nutritional interventions. CANTAB showed high sensitivity in Study 1, not only detecting differences in cognitive function between patient groups and healthy controls, but also between people with CFRD and CFND. However, CANTAB was not sufficiently sensitive to detect the more subtle cognitive differences between people with CFRD who had or had not had a transplant (Study 3). A further problematic aspect of the CANTAB battery was the lack of parallel forms for some tests. Thus the follow up studies had to use some of the same test versions on the CANTAB system. However, the fact that stimuli are presented in pseudo-random order and there was at least one year between baseline and follow up in all participants, will likely have reduced any practise effects. As there was no significant improvement in performance on any one cognitive domain, this was not believed to have occurred. This does not imply that CANTAB was sufficiently sensitive to detect change in cognitive function over time in these patients and indeed it may be the case that cognitive function had changed but the test battery was unable to detect these changes.

9.8 Future research

The research presented in this thesis has indicated that there are differences in cognitive function between people with CF and healthy controls. Moreover, glucose control has been implicated as a possible causal factor in the effects seen and indeed the lack of cognitive

changes in some studies. Further research might therefore utilise new technology to verify this hypothesis. The use of CGMS as part of a free living study would allow investigation of whether people with CF experience undetected episodes of hypoglycaemia or periods of elevated hyperglycaemia which may be of relevance and help explain the degree of cognitive impairment found in people with CF. It would also provide more detailed information which could potentially negate the results of OGTTs which are one-off tests, possibly influenced by activity and prior dietary intake and have relatively poor reproducibility but yet are the basis for clinical decisions at present (Sir, Brussaard, Bravenboer, Hospital, & Bravenboer, 1991).

As CFTR is present in the brain, it is hypothesised that the new CFTR potentiator (Ivacaftor) and corrector (Lumacaftor) therapy for people with CF may have positive effects on cognitive function. The effects of Ivacaftor on cognitive function have been investigated in only one study to date. This placebo controlled cross over trial with 28 days of treatment in 20 adults with CF and G551D mutation (mean age= 32.5 years, FEV_1%predicted= 54.5) administered the MoCA (Nasreddine et al., 2005); a cognitive screening assessment used to detect dementia and mild cognitive decline (Button, Edgeworth, Finlayson, et al., 2015; Button, Edgeworth, Wilson, et al., 2015). Following active treatment (150mg twice daily), total score and arithmetic (subtraction of 7's) scores on the MoCA were shown to improve significantly, and there was a trend for improvement in word fluency (letter F) and delayed verbal recall. However, it is not clear whether parallel versions of the test were used and the sensitivity of this assessment in CF is not established. Furthermore the data were analysed using change from baseline which can increase the likelihood of detecting a significant effect (Van Breukelen, 2006) and it would been have more appropriate to use baseline as a covariate as in the studies presented in this thesis. The authors also fail to mention whether there were any carry-over effects of Ivacaftor on cognition or whether there were any differences in cognition at baseline. Of importance, it is not yet known whether the new CFTR therapies can cross the BBB. This discovery and the demonstration of reliable effects of CFTR therapies on cognitive outcomes would strengthen the suggestion that CFTR is a mechanism for cognitive dysfunction in CF.

The first brain imaging study in CF was published in 2015 and showed that in two adult males (mean 32.5 years, homozygous F508del) without current hypoxaemia, scattered ischemic lesions in white matter areas were present in areas associated with memory, learning, mood and sleep (Woo et al., 2015). However, cognitive function was not assessed. The authors postulate that CFTR dysfunction, malnutrition or chronic hypoxaemia may have caused these alterations in brain structure. Incorporating brain imaging using structural and/or functional MRI in a future study would throw light on the relationship between cortical anatomy and activation (via blood flow and oxygen utilisation), and objectively measured aspects of cognitive performance.

9.9 Clinical implications

The finding that people with CFRD and CFND show some degree of cognitive impairment is of clinical significance and has implications for self care and disease management. CF is a complex disease and people have to adhere to onerous treatment, which places a high demand

on cognitive functioning, in order to remain well (Peckham & Whittaker, 2009). Any degree of cognitive impairment may be detrimental to people with CF not only in terms of adherence, but also emotionally, and may impact on their QoL. Impairment in cognition not only has a negative effect on adherence (Feil, Zhu, & Sultzer, 2012), but has also been shown to interfere with an individual's ability to cope with their illness, and can affect their chances of employment and performance at work.

The life expectancy of people with CF is continually increasing, with the median age of survival in the UK now 45.1 years old. This therefore means, that people with CF have the ability to achieve age-related goals like their peers e.g. participate in education, have a career, 'running a house', juggling work and family life etc. Although the cognitive deficits observed are subtle, they may be sufficient enough to interfere with the ability to perform everyday tasks (McCrimmon et al., 2012). Therefore, achieving these every day goals may require more effort in those with CF. Moreover, achieving these goals will be further hindered as cognitive deficits are likely to be exacerbated during periods of high cognitive demand. It is important to note that deficits rarely occur in isolation (Wong et al., 2014), but together, they may have practical implications for people with CF. Having the ability to detect sequences and respond as quickly as possible on the Rapid Visual Processing task, for example, relates to everyday tasks which require sustained concentration and focus for a particular period of time such as driving. Furthermore, as people with CF strive to continue working, problems with concentration and focus may also impact upon presenteeism (see section 1.6.6.). Manual jobs, or working in a fast-paced environment may require the individual with CF to expel more effort in order to keep an adequate level of productivity, particularly if they are unwell, which may further have a negative effect on the health of the individual.

Having the ability to remember locations, a list of words, and patterns on the Paired Associates Learning, Verbal Recognition, and Pattern Recognition Memory Tests, respectively, relates to everyday tasks such as remembering where you left your keys, shopping or medication lists, people's names, and which tablets/drugs are which. Memory deficits can lead to compromised adherence to medication. Given daily treatment is a rigorous regime in CF (which includes physiotherapy, taking enzyme tablets with food, oral, nebulised and occasionally IV antibiotics), minor errors in doses or specific timings, or forgetting to take treatment, may lead to compromised safety or efficacy of treatment. Creating lists for everyday activities, e.g. going shopping, may expel the frustration in failing to recall an item.

Executive function deficits may also have an impact in engaging with more complex behaviours. Having the cognitive flexibility to switch between the two different rules on the Attention Switching Task relates to everyday tasks such as the ability to return to a task after being interrupted, or performing two tasks simultaneously. As people with CF are required to take treatment throughout the day, despite distractions which are unavoidable in busy and often unpredictable lifestyles (Stilley et al., 2010), this may have implications for taking the correct dose of medication, or memory lapses if interrupted e.g. forgetting if that they haven't taken a certain medication. It may also relate to their ability to perform everyday tasks such as keeping a track of finances (e.g. paying bills), or holding a conversation whilst performing another task e.g. cooking or ability to follow a television programme at ease.

People with CFRD also have the added complication of insulin therapy (Wong et al., 2014). In addition to remembering to take treatment, people with CFRD also need to make clinical judgements regarding how much insulin to take. A too high dose may result in hypoglycaemia, which as discussed in Chapter 3 (section 3.3.3.2) and section 9.2.3 above, may have a potentially negative impact on an individual's health and may increase their vulnerability to illness as well as to exacerbate impairment of cognitive function. As people with CF are living longer, it will be important for the individual with CFRD to maintain responsibility with regards to looking after their diabetes without the assistance of a carer to maintain quality of life. Depression also has a negative effect on diabetes self-management and therefore, interventions to improve levels of depression may also have a positive effect on glycaemic control as well as quality of life (Mut-Vitcu et al., 2016; Camp et al., 2015).

Psychological support may be of importance to people with CFRDTx in order to preserve health and cognitive function. Despite improvements in factors which have been shown to be associated with cognitive impairment, such as sleep, mood and depression, lack of diabetes control may still be a plausible mechanism for cognitive impairment in people with CFRDTx.

9.10 Overall conclusion

This thesis examined whether people with CFRD show similar impairments to those commonly observed in people with T1DM and T2DM, whether cognitive function declines over time in people with CF, and whether transplantation in people with CFRD can improve or prevent a decline in cognitive function. Cognitive impairment in all cognitive domains assessed was evident in people with CFRD, and was apparent to a lesser degree in people with CFND, compared to healthy matched controls. There was no evidence of decline over a 1-3 year period, although this may not have been long enough to measure the effects of vascular changes within the brain (if any occurred) on cognitive endpoints. Transplantation in people with CFRD does not seem to confer beneficial effects on cognitive function but may suggest that cognitive function did not decline. This failure to detect a change may have been confounded by the length of time since transplantation such that the window of opportunity to detect improvements in cognition had elapsed. It is also possible that cognitive function was maintained when it would have declined had a transplant not taken place. The recent discovery that CFTR is present in the pancreas and the brain has important implications for the effects of the new CFTR potentiator and corrector therapies on cognitive function in CF and this aspect of CF treatment needs to be explored.

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Appendices

Appendix A: CANTAB outcome measures which are a function of measures reported in the thesis.

Test	Outcome measure reported in the thesis	Outcome measures which are functions of others
MOT	Total trials	Total errors
PAL	Stages completed	Pattern succeeded on
		Pattern reached
	Total trials	Mean trials to success
	Total errors	Mean errors to success
VRM	Total false positives (recognition)	Total distractors
PRM	Total correct	Total incorrect
	Total number correct	Percentage correct
RVP	Total hits	Total misses
	A' prime	Calculated from 'probability of hit'
	B' prime	and 'probability of false alarm'
AST	Total correct	Total incorrect
	Total correct	Percentage correct

Appendix B: VRM word list used in each study

Word List used in Study 1 and 3	Word list used in Study 2 and 4
Fun	Bag
Ski	Bin
Ring	Cage
Tack	Clay
Vest	Food
Feast	Hair
Peach	Milk
Motor	Hook
Towel	Seed
Bandit	Wood
Wallet	Square
Diamond	Island
Lobster	Record
Soldier	Salute
Speaker	Knuckle
Chestnut	Railroad
Breakfast	Squirrel
Alligator	Orchestra

Appendix C: Sleep Evaluation Questionnaire- Last night

Each of the following questions are about LAST night's sleep. Answer the questions by placing a vertical mark through the line in the place that best indicates your answer.

1. Last night, how EASY was it to get to sleep?

very   very

easy   difficult

2. How QUICKLY did you get to sleep last night?

very   very

quickly   slowly

3. What was the QUALITY of your sleep last night?

very   not at all

restful   restful

no periods of   many periods of
wakefulness   wakefulness

4. What was your pattern of AWAKENING like this morning?

very   very

easy   difficult

took   took

short time   long time

5. How did you FEEL ON AWAKENING this morning?

alert   tired

6. How did you feel 1 HOUR AFTER awakening this morning?

alert   tired

Appendix D: Sleep Evaluation Questionnaire- Typical Night

Each of the following questions are about a **TYPICAL night's sleep over the past WEEK**. Answer the questions by placing a vertical mark through the line in the place that best indicates your answer.

1. In a typical night, how EASY was it to get to sleep?

very _____ very

easy difficult

2. In a typical night, how QUICKLY did you get to sleep?

very _____ very

quickly slowly

3. What was the QUALITY of your sleep in a typical night?

very _____ not at all

restful restful

no periods of_____ many periods of

wakefulness wakefulness

4. What was your pattern of AWAKENING like in a typical morning?

very _____ very

easy difficult

takes a _____ takes a

short time long time

5. How did you usually FEEL ON AWAKENING?

alert _____ tired

6. How did you usually feel 1 HOUR AFTER awakening?

alert _____ tired

Appendix E: Perceived Stress Scale – Last Month

The questions in this scale ask you about your feelings and thoughts during the **LAST MONTH**. In each case you will be asked to indicate by circling *how often* you felt or thought a certain way.

0=never   1=Almost Never   2=Sometimes   3=Fairly Often   4=Very Often

1. In the last month, how often have you been upset about something that has happened unexpectedly?	0	1	2	3	4
2. In the last month, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last month, how often have you felt nervous and 'stressed'?	0	1	2	3	4
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last month, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last month, how often have you been able to control the irritations in your life?	0	1	2	3	4
8. In the last month, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last month, how often have you been angered because of things that were outside your control?	0	1	2	3	4
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Appendix F: Perceived Stress Scale – Last week

The questions in this scale ask you about your feelings and thoughts during the **LAST WEEK**. In each case you will be asked to indicate by circling *how often* you felt or thought a certain way.

0=never   1=Almost Never   2=Sometimes   3=Fairly Often   4=Very Often

1. In the last week, how often have you been upset about something that has happened unexpectedly?	0	1	2	3	4
2. In the last week, how often have you felt that you were unable to control the important things in your life?	0	1	2	3	4
3. In the last week, how often have you felt nervous and 'stressed'?	0	1	2	3	4
4. In the last week, how often have you felt confident about your ability to handle your personal problems?	0	1	2	3	4
5. In the last week, how often have you felt that things were going your way?	0	1	2	3	4
6. In the last week, how often have you found that you could not cope with all the things that you had to do?	0	1	2	3	4
7. In the last week, how often have you been able to control the irritations in your life?	0	1	2	3	4
8. In the last week, how often have you felt that you were on top of things?	0	1	2	3	4
9. In the last week, how often have you been angered because of things that were outside your control?	0	1	2	3	4
10. In the last week, how often have you felt difficulties were piling up so high that you could not overcome them?	0	1	2	3	4

Appendix G: Hospital Anxiety and Depression Scale (HADS)

HAD Scale

Name: Date:

We are aware that emotions play an important part in most illnesses. If we know about these feelings then we will be able to help you more.

This questionnaire is designed to help us know how you feel. Read each item and place a firm tick in the box opposite the reply which come closest to how you have been feeling in the past week.

Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box per question

I feel tense or 'wound up':
- Most of the time.............................
- A lot of the time...............................
- Time to time, Occasionally..................
- Not at all.......................................

I still enjoy the things I used to enjoy:
- Definitely as much............................
- Not quite so much.............................
- Only a little....................................
- Hardly at all...................................

I get a sort of a frightened feeling as if something awful is about to happen:
- Very definitely and quite badly..............
- Yes, but not too badly........................
- A little, but it doesn't worry me.............
- Not at all.......................................

I can laugh and see the funny side of things:
- As much as I always could..................
- Not quite so much now.......................
- Definitely not so much now..................
- Not at all.......................................

Worrying thoughts go through my mind:
- A great deal of the time......................
- A lot of the time...............................
- From time to time but not too often.........
- Only occasionally..............................

I feel cheerful:
- Not at all.......................................
- Not often.......................................
- Sometimes.....................................
- Most of the time...............................

I can sit at ease and feel relaxed:
- Definitely.......................................
- Usually...
- Not often.......................................
- Not at all.......................................

I feel as if I am slowed down:
- Nearly all the time...........................
- Very often......................................
- Sometimes.....................................
- Not at all.......................................

I get a sort of frightened feeling like butterflies in the stomach:
- Not at all.......................................
- Occasionally...................................
- Quite often.....................................
- Very often......................................

I have lost interest in my appearance:
- Definitely.......................................
- I don't take so much care as I should
- I may not take quite as much care....
- I take just as much care as ever.......

I feel restless as if I have to be on the move:
- Very much indeed...........................
- Quite a lot......................................
- Not very much.................................
- Not at all.......................................

I look forward with enjoyment to things:
- As much as I ever did........................
- Rather less than I used to...................
- Definitely less than I used to...............
- Hardly at all...................................

I get sudden feelings of panic
- Very often indeed.............................
- Quite often.....................................
- Not very often.................................
- Not at all.......................................

I can enjoy a good book or radio or TV programme:
- Often..
- Sometimes.....................................
- Not often.......................................
- Very seldom...................................

Do not write below this line

Appendix H: Visual Analogue Scales for ratings of mood and mental alertness

Please answer the following questions by placing a **vertical mark** through the line.

Regard the ends of each line as indicating the most extreme sensation you have ever felt.

1. How **contented** do you feel now?

Not at all _____ Very

Contented   Contented

2. How **irritable** do you feel now?

Not at all _____ Very

Irritable   Irritable

3. How **sleepy** do you feel now?

Not at all _____ Very

Sleepy   Sleepy

4. How **mentally alert** do you feel now?

Not at all _____ Very

Alert   Alert

5. How **easy** are you finding it **to concentrate** now?

Not at all _____ Very

Easy   Easy

6. How **energetic** do you feel now?

Not at all _____ Very

Energetic   Energetic

Appendix I: Cognitive Test Evaluation Questionnaire

Please answer the following questions by placing a **vertical mark** through the line.

Regard the ends of each line as indicating the most extreme sensation you have ever felt.

1. How much **TIME PRESSURE** did you feel due to the rate/pace of the tests?

None at all   _____   A large

Amount

2. How **DIFFICULT** did you find these tests today?

Not at all   _____   Extremely

Difficult   Difficult

3. How much did you **CONCENTRATE** during these tests?

A small   _____   A large

Amount   Amount

4. How **HARD DID YOU TRY** in these tests?

Not at all   _____   Extremely

Hard   Hard

5. How **WELL** do you think you **PERFORMED** in these tests?

Not at all   _____   Extremely

Well   Well

6. How **FRUSTRATING** did you find these tests today?

Not at all   _____   Extremely

Frustrating   Frustrating

7. Which test did you find the **HARDEST** today?

……

8. Which test did you find the **EASIEST** today?

……..

Appendix J: The Cognitive Failures Questionnaire

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others.

We want to know how often these things have happened to you in the <u>past 6 months</u>.

Please circle the appropriate number.

		Very often	Quite often	Occasion-ally	Very rarely	Never
1.	Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2.	Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3.	Do you fail to notice signposts on the road?	4	3	2	1	0
4.	Do you find you confuse right and left when giving directions?	4	3	2	1	0
5.	Do you bump into people?	4	3	2	1	0
6.	Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7.	Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8.	Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9.	Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10.	Do you lose your temper and regret it?	4	3	2	1	0
11.	Do you leave important letters unanswered for days?	4	3	2	1	0
12.	Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13.	Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0

14.	Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15.	Do you have trouble making up your mind?	4	3	2	1	0
16.	Do you find you forget appointments?	4	3	2	1	0
17.	Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18.	Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19.	Do you daydream when you ought to be listening to something?	4	3	2	1	0
20.	Do you find you forget people's names?	4	3	2	1	0
21.	Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22.	Do you find you can't quite remember something although it's "on the tip of your tongue"?	4	3	2	1	0
23.	Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24.	Do you drop things?	4	3	2	1	0
25.	Do you find you can't think of anything to say?	4	3	2	1	0

Appendix K: Debriefing questionnaire

Cognition in Cystic Fibrosis patients and matched controls

ID Number: _____   Date: _____

Recruitment

1. How did you find out about the study?

……

……

……………………………………………………………………………………

2. Why did you decide to take part in the study?

……

……………………………………………………………………………………………

………………………………………………………………………………………………………

………………………………………………………………………………………………………

3. Did you have any concerns about taking part?

……

……

………………………………………………………………………………………………

Study Procedures

4a.<u>CF Patients</u>: Did you find the study fitted into your health assessment (without too much disruption)?

……………………………………………………………………………………………………..……..………

……

4b.<u>Controls</u>: Did you find the study convenient to participate in?

……..…………

…….…..

5. Was there any part of the study you were unhappy with?

………

………

………

6. What do you think the importance of this study is?

……………………………………………………………………………………………………..………

………

……………………………………………………………………………………………………….…

Cognitive Tests

7. What did you think of the tests?

……

……

…………………………………………………………………………

8. Were there any tests in particular which you found hard? Why? (duration, pace etc)

……

……

…………………………………………………………………………………….......................................

9. Were there any tests in particular which you found easy?

……

……

……

10. Did you try your best in all the tests? (Please be honest)

……

……

……

11. During the study was there anything in your personal life (e.g. exams) which may have affected your performance (e.g. concentration) on any of the tests of mental performance?

………

………

………

12. Did the tests make you think about your memory &/or attention in day-to-day life?

………

………

………

………

In General

13. Is there anything else you would like to tell us?

………

………

………

………

………

………

………

………

………

………………………………………………………………………………………………………

Appendix L: The finger prick blood glucose standard operating procedure (SOP)

A Step by Step Guide to Taking a Finger Prick Blood Glucose Reading

1.Wash your hands using soap and warm water. Rinse and dry your hands thoroughly.

2. Remove a test strip from the pot

Contact Bars →

← **Test Strip Wells**

3. Insert the test strip into the test port with the contact bars end first and facing up (green side). Push the test strip in firmly until it will go no further. The meter will then turn on automatically. After 2-3 seconds the 'blood drop symbol' will flash.

N.B. The meter will automatically switch off after 2 minutes if no blood has been applied on the test strip. If this happens remove the test strip and insert again.

4. Hold the Unistik 3 body and twist off the grey lancet cap until you feel it separate from the yellow body. Don't pull, just twist. Dispose of the grey cap in the bin.

5. Choose a site as indicated by the shaded areas on pictures.
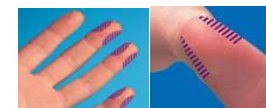
6. Hold the Unistik device firmly against the chosen site and press the release button. To obtain a drop of blood, massage the sample site, taking care not to squeeze too hard at the site

7. The blood drop on your finger is positioned next to the top edge of the test strip until the blood has been drawn into the test strip wells.

8. Your blood glucose result appears on the display in 4 seconds. The meter automatically turns off when you remove and discard the used test strip.

9. The single-use needle retracts immediately after sampling leaving the device safe for immediate disposal. Use the sharps container provided.

Appendix M: Investigator information sheet for patients with Cystic Fibrosis

A study investigating the memory, attention and executive function of people with Cystic Fibrosis (CF)

My name is Helen Chadwick. I'm a PhD student at the Institute of Psychological Sciences, University of Leeds.

My PhD is a collaboration between the University of Leeds and Leeds Teaching Hospitals NHS Trust. It is funded by the Medical Research Council and Leeds Teaching Hospitals NHS Trust (the Adult Cystic Fibrosis Unit and the Diabetes Centre)

My PhD is investigating Cystic Fibrosis, related-diabetes and the effect of both these conditions upon cognition (memory, attention and executive function e.g. problem solving skills) and wellbeing.

I completed my BSc (Hons) in Psychology at the University of Leeds in 2009. I subsequently completed my MSc in Psychological Approaches to Health at the University of Leeds graduating in 2010.

The first study of my PhD is looking at whether people who have Cystic Fibrosis and those who have developed the related form of diabetes have any clinical cognitive impairment. This is the first-known study investigating this. These impairments could be problems with memory (e.g. being able to remember a list of words, being able to recall these words after a period of time, being able to recognise words you have seen before, being able to recognise shapes you have seen) or attention (e.g. being able to follow a pattern/rule and remember it, being able to concentrate for a long time). The results of this study will be used towards my PhD qualification.

You have been approached as you fit the criteria to be a potential participant in the study. The Participant Information Sheet for patients with Cystic Fibrosis explains the study in more detail. If you are happy to take part, or would like more information, please do not hesitate to contact me.

My number and email address is at the bottom of the Participant Information Sheet.

Thank you for taking your time to read this,

Helen

Appendix N: Participant information sheet for patients with Cystic Fibrosis

A study investigating the mental performance of people with Cystic Fibrosis (CF)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the study is being done and what it would involve for you.

Please take time to read the following information carefully and talk to others about the study if you wish. One of our team is available to go through the information sheet with you and answer any questions you have. Please take your time to decide whether or not you wish to take part.

Please ask if anything is unclear or if you would like more information.

What is the research about?

This study has been designed to investigate mental performance (e.g. memory, attention, reaction time) in Cystic Fibrosis patients (those with and without the related form of diabetes) compared with that of healthy (Non-Cystic Fibrosis, Non-Diabetic) people. It will be the first study to examine this to date. Furthermore, it will also examine whether there is a difference in mental performance between those who have transplants and those who have not.

The study will be carried out under the supervision of Dr Daniel Peckham and Dr Michael Mansfield (St James's University Hospital, Leeds) and Professor Louise Dye and Dr Clare Lawton (University of Leeds).

Why have I been asked to take part?

You have been invited to take part because you have Cystic Fibrosis or Cystic-Fibrosis with diabetes, are aged over 16 years of age and are not pregnant (or been pregnant in the past 6 months). For patients who are NOT post-transplant, you will also have been tested for diabetes in the last 12 months.

Your unaffected (i.e. healthy) family and friends can also take part in the study if they wish. If you would like an information sheet for them, please contact Helen Chadwick whose details are at the end of this sheet.

Do I have to take part?

It is up to you to decide whether or not to take part. Your decision will not affect the standard of care you receive in any way.

If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. Even if you decide to take part you are still free to withdraw at any time without having to give a reason.

<u>What will I have to do?</u>

There is only one study session (lasting about 1.5 hours) and this will be either incorporated into your routine health assessment (at either the Cystic fibrosis Unit, at St James's University Hospital or at the Outpatient's Clinic at Seacroft Hospital, Leeds) or arranged to be completed in your own home to minimise inconvenience to you. Testing can be arranged for your next routine health assessment, <u>or</u> if convenient, completed in your home between now and your next health assessment. You will need to fast for two hours (i.e. no food, or drink, except water) before the start of testing. If you are a smoker, we also ask that you do not smoke within these two hours.

At the start of the session, you will be free to ask any questions you may have about any aspect of the study. If you are still willing to participate in the study, you will be asked to sign a consent form (giving your consent to take part in the study) and complete a questionnaire which asks you various details about yourself e.g. contact details, age, education, health. We will obtain other information from your medical records with your permission.

You will then be asked to complete several short questionnaires about your:

- sleep quality last night and over the past week
- perceived stress over the past week and month
- anxiety and depression levels
- mood and mental alertness

Next, we will measure your carbon monoxide levels. This will be done using a Smokerlyzer. You will take a deep breath, hold for 15 seconds, and then blow it all out into the machine. We will also measure your blood sugar level using a finger prick diabetic kit.

Following this we will ask you to complete 7 tests of mental performance which usually takes around 45 minutes. We will then ask you to complete 3 more short questionnaires:

One asking about the tests you have just completed e.g. 'how you feel you performed on the tests?', 'which test you found the easiest?', 'which test you found the hardest?'

One asking you about minor mistakes which may have happened in your daily life within the past 6 months e.g. 'Do you find you forget whether you've turned off a light or locked the door?'

One asking you about your experience of taking part in the study.

Once you have completed the last questionnaire, you will be free to ask any further questions about the study and have these questions answered.

Below is a summary of what will happen during the study:

```
┌─────────────────────────────────────────────────────────────────────┐
│     Test session incorporated into either your health assessment OR   │
│                          in your own home                             │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│   Opportunity to ask questions about the study and have them answered │
│                           satisfactorily.                             │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│           Still want to take part: Sign the Consent Form              │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│               Complete Recruitment Information sheet                  │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│                    Complete 6 Questionnaires:                         │
│  • sleep quality last night (1) and over the past week (2)            │
│  • perceived stress over the past week (3) and month (4)              │
│        • anxiety and depression levels (5)                            │
│            • mood and mental alertness (6)                            │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│        Blood sugar level and carbon monoxide level measured           │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│        7 Tests of Mental Performance on a touch screen computer       │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│                    Complete 3 questionnaires:                         │
│  • About the tests of mental performance you have just finished       │
│     • Minor mistakes which may have happened in daily life            │
│        • Experiences about taking part in the study                   │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│       Debriefed and compensated with a £10 Love to Shop Voucher       │
└─────────────────────────────────────────────────────────────────────┘
                                  │
                                  ▼
┌─────────────────────────────────────────────────────────────────────┐
│                       End of Testing Session                          │
└─────────────────────────────────────────────────────────────────────┘
```

What are the tests of mental performance?

There are 7 tests in total which will assess brain functions such as memory, reaction time, attention and problem solving skills. The tests are not designed to trick you. We just ask that you complete the tests to the best of your ability.

The tests are administered on a touch-screen computer, although some tests will require you to push a button instead of touching the screen. Helen will be in the room with you so if you are unsure about anything you have to do as part of these tests, you will be able to ask.

What are the benefits of taking part?

Taking part in this research will contribute to the growing research on Cystic Fibrosis. It will help contribute to the limited research into whether people with Cystic Fibrosis who develop Cystic Fibrosis-Related Diabetes have any problems with mental performance. Previous research has shown that people with Type 1 and Type 2 Diabetes develop problems with mental performance, but this is unknown in the Cystic Fibrosis-Related Diabetes population.

As we are including patients who are post-transplant, we will also investigate whether there is any difference in mental performance between patients who have and haven't had a transplant.

It also gives you an activity to complete during your routine health assessment whereas otherwise you may be waiting around. The cognitive tests are designed to be fun.

What are the disadvantages of taking part?

The time taken to complete the study has been kept to a minimum. There is only one testing session, which can be in the morning or afternoon. We will arrange your test session to be either at the same appointment as your routine health assessment, or completed in your own home, to minimise inconvenience to you.

The risks associated with blood sampling include fainting, bruising and discomfort. All researchers are fully trained in blood sampling and first aid. They will take every step to minimise any of the risks associated.

Who has reviewed this study?

All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Yorkshire & the Humber – Leeds West NHS Research Ethics Committee (reference: 13/YH/0219).

Will my taking part in the research be kept confidential?

The study is subject to ethical guidelines set out by the British Psychological Society and the NHS. All information that is collected from you during the course of the study will be treated in the strictest of confidence at all times and will only be used for the purposes of this research.

After initially completing the consent form and recruitment information questionnaire you will be given a unique study identity code. All data will then be recorded safely using this code and not your name. The link between your name (and other personal data) and your unique study identity code will be maintained and stored securely at the Institute of Psychological Sciences, University of Leeds or at St James's University Hospital and will only be accessible to the research team.

Individuals will not be identifiable from any details in reports, presentations or scientific publications based on the results of the study.

Who is organising and funding the research?

This research is funded by the Medical Research Council and NHS. It is collaboration between the University of Leeds and Leeds Teaching Hospitals NHS Trust.

What will happen to the results of the research study?

The anonymised results from the study will be used towards an educational qualification (PhD) by a member of the research team (Helen Chadwick).

Anonymised results may also be presented at conferences and/or in scientific journals. Individuals will not be identifiable from any details in reports, presentations or scientific publications based on the results of the study.

Will I receive anything for taking part?

Upon completion of the study, you will receive a £10 Love to Shop Voucher to compensate you for your time and effort.

If, for whatever reason, we cannot combine the testing session with your routine health assessment, and testing cannot be completed in your home, we will reimburse your travel expenses up to the value of £10.

If I want to take part or get more information what do I do next?

If you have any questions or would like to volunteer to take part in this study, please contact:

Helen Chadwick

PhD Student & Research Psychologist (St James's University Hospital, Leeds)

Institute of Psychological Sciences

University of Leeds

Tel: 0113 343 2275 (Office)

Email: h.k.chadwick@leeds.ac.uk

Other contacts:

Dr Daniel Peckham	Dr Michael Mansfield
Clinical Lead for Cystic Fibrosis	Consultant for Diabetic patients
Tel: 0113 XXX XXXX	Tel: 0113 XXX XXXX

Appendix O: Consent form for patients with Cystic Fibrosis

CONSENT FORM FOR PATIENTS WITH CYSTIC FIBROSIS

Study Title: A study investigating the mental performance of people with Cystic Fibrosis (CF)

	Please Initial
1. I confirm I have read and understood the Participant Information Sheet for Patients with Cystic Fibrosis dated 04.09.2014 (Version 3) for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
2. 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.	
3. I understand that the testing session will involve completing some questionnaires, tests of mental performance and having my blood sugar and carbon monoxide measured.	
4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking 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.	

Name of Participant (print name)	Signature	Date

Name of Researcher	Signature	Date

Appendix P: Participant information sheet for healthy controls

A study investigating the mental performance of people with Cystic Fibrosis (CF)

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the study is being done and what it would involve for you.

Please take time to read the following information carefully and talk to others about the study if you wish. One of our team is available to go through the information sheet with you and answer any questions you have. Please take your time to decide whether or not you wish to take part.

Please ask if anything is unclear or if you would like more information.

What is the research about?

This study has been designed to investigate mental performance (e.g. memory, attention, reaction time) in Cystic Fibrosis patients (those with and without the related form of diabetes) compared with that of healthy (Non-Cystic Fibrosis, Non-Diabetic) people. It will be the first study to examine this to date.

The study will be carried out under the supervision of Dr Daniel Peckham and Dr Michael Mansfield (St James's University Hospital, Leeds) and Professor Louise Dye and Dr Clare Lawton (University of Leeds).

What criteria must I meet to take part?

In order to take part in the study, you must:

- Be aged over 16 years of age
- Be in good health
- Not take any regular medication (excluding the Pill)
- Not have any known Impaired Glucose Tolerance or diabetes
- Not be pregnant or have had a pregnancy in the previous 6 months
- Have adequate comprehension of English (written and verbal)
- Be the same gender and roughly the same age and education level as a Cystic Fibrosis patient taking part in the study (the research team will make sure you are suitable)

If you do not meet ALL of the above criteria you will not be able to take part. If you do meet these criteria, please read on.

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 asked to sign a consent form. Even if you decide to take part you are still free to withdraw at any time without having to give a reason.

What will I have to do?

To minimise inconvenience to you, a member of the research team will make sure you meet all the inclusion criteria before the study session is arranged. There is only one study session (lasting about 1.5 hours) which will take place at the Human Appetite Research Unit (HARU) at the Institute of Psychological Sciences, University of Leeds.

You will need to fast for two hours (i.e. no food, or drink, except water) before arriving. If you are a smoker, we also ask that you do not smoke within these two hours before arriving.

On arrival you will be free to ask any questions you may have about any aspect of the study. If you are still willing to participate in the study, you will be asked to sign a consent form (giving your consent to take part in the study) and complete a questionnaire which asks you various details about yourself e.g. contact details, age, education, health.

You will then be asked to complete several short questionnaires about your:

- sleep quality last night and over the past week
- perceived stress over the past week and month
- anxiety and depression levels
- mood and mental alertness

Next, we will measure your carbon monoxide levels. This will be done using a Smokerlyzer. You will take a deep breath, hold for 15 seconds, and then blow it all out into the machine. We will also measure your blood sugar level using a finger prick diabetic kit. You can see step-by-step procedures before you consent to take part in the study.

Following this we will ask you to complete 7 tests of mental performance which usually takes around 45 minutes. We will then ask you to complete 3 more short questionnaires:

One asking about the tests you have just completed e.g. 'how you feel you performed on the tests?', 'which test you found the easiest?', 'which test you found the hardest?'

One asking you about minor mistakes which may have happened in your daily life within the past 6 months e.g. 'Do you find you forget whether you've turned off a light or locked the door?'

One asking you about your experience of taking part in the study.

Once you have completed the last questionnaire, you will be free to ask any further questions about the study and have these questions answered.

Below is a summary of what will happen during the study.

Arrival at the Human Appetite Research Unit (HARU)

↓

Opportunity to ask questions about the study and have them answered satisfactorily.

↓

Still want to take part: Sign the Consent Form

↓

Complete Recruitment Information sheet

↓

Complete 6 Questionnaires:

- sleep quality last night [1] and over the past week [2]
- perceived stress over the past week [3] and month [4]
- anxiety and depression levels [5]
- mood and mental alertness [6]

↓

Blood sugar level and carbon monoxide level measured

↓

7 Tests of Mental Performance on a touch screen computer

↓

Complete 3 questionnaires:

- About the tests of mental performance you have just finished
- Minor mistakes which may have happened in daily life

↓

Debriefed and compensated with a £10 Love2Shop Voucher and travel expenses reimbursed up to the value of £10.

↓

End of Testing Session

What are the tests of mental performance?

There are 7 tests in total which will assess brain functions such as memory, reaction time, attention and problem solving skills. The tests are not designed to trick you. We just ask that you complete the tests to the best of your ability.

The tests are administered on a touch-screen computer, although some tests will require you to push a button instead of touching the screen. A researcher will be in the room with you so if you are unsure about anything you have to do as part of these tests, you will be able to ask.

What are the benefits of taking part?

Taking part in this research will contribute to the growing research on Cystic Fibrosis. It will help contribute to the limited research into whether people with Cystic Fibrosis who develop Cystic

Fibrosis-Related Diabetes have any problems with mental performance. Previous research has shown that people with Type 1 and Type 2 Diabetes develop problems with mental performance, but this is unknown in the Cystic Fibrosis-Related Diabetes population.

What are the disadvantages of taking part?

The time taken to complete the study has been kept to a minimum. There is only one testing session, which can be in the morning or afternoon.

The risks associated with blood sampling include fainting, bruising and discomfort. All researchers are fully trained in blood sampling and first aid. They will take every step to minimise any of the risks associated.

Who has reviewed this study?

All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Yorkshire & the Humber – Leeds West NHS Research Ethics Committee (REF: 13/YH/0219, 22/08/2013).

Will my taking part in the research be kept confidential?

The study is subject to ethical guidelines set out by the British Psychological Society and the NHS. All information that is collected from you during the course of the study will be treated in the strictest of confidence at all times and will only be used for the purposes of this research.

After initially completing the consent form and recruitment information questionnaire you will be given a unique study identity code. All data will then be recorded safely using this code and not your name. The link between your name (and other personal data) and your unique study identity code will be maintained and stored securely at the Institute of Psychological Sciences, University of Leeds or at St James's University Hospital and will only be accessible to the research team.

Individuals will not be identifiable from any details in reports, presentations or scientific publications based on the results of the study.

Who is organising and funding the research?

This research is funded by the Medical Research Council and NHS. It is collaboration between the University of Leeds and Leeds Teaching Hospitals NHS Trust.

What will happen to the results of the research study?

The anonymised results from the study will be used towards an educational qualification (PhD) by a member of the research team (Helen Chadwick).

Anonymised results may also be presented at conferences and/or in scientific journals. Individuals will not be identifiable from any details in reports, presentations or scientific publications based on the results of the study.

Will I receive anything for taking part?

Upon completion of the study, you will receive a £10 Love2Shop Voucher to compensate you for your time and effort. Your travel expenses will also be reimbursed up to the value of £10.

If I want to take part or get more information what do I do next?

If you have any questions or would like to volunteer to take part in this study, please contact:

Helen Chadwick

PhD Student

Research Psychologist (St James's University Hospital)

Institute of Psychological Sciences

University of Leeds

LS2 9JT

Tel: 0113 343 2275 (Office)

Email: h.k.chadwick@leeds.ac.uk

Other contacts:

Dr Clare Lawton (c.l.lawton@leeds.ac.uk; 0113 XXX XXXX)

Professor Louise Dye (l.dye@leeds.ac.uk; 0113 XXX XXXX)

Appendix Q: RIQ for healthy controls

RECRUITMENT INFORMATION SHEET

Study Title: Cognition in Cystic Fibrosis patients and matched controls

A study investigating the memory, attention and executive function of people with Cystic Fibrosis (CF)

Date of contact: _____ / _____ / _____ Researcher: ....

First Name(s): ....

Surname: ....

Address: ....

....

....

....

Telephone number: ....

Mobile number: ....

Email Address: ....

Date of Birth: .... / ..../.................. Age: ....

Female: ☐ Male: ☐

Level of Education: None ☐ GCSE ☐ GCE O Level ☐ AS/A Level ☐

Diploma ☐ Degree ☐ Masters ☐ PhD/Doctorate ☐

Occupation: Employed: *Full time* ☐ *Part time* ☐

Unemployed ☐ Student: ☐ Housewife/husband ☐

Retired ☐ Other: ....

Have you ever smoked?: No, never smoked ☐

Smoker: ☐ *Roughly, how many a day?* ....

Given up: ☐ *how long ago?*...

If you are a smoker please complete the below questions:

Type of Tobacco used: *Pipe/Cigars* ☐   *Cigarettes* ☐

Switched from cigarettes to pipes and/or cigars ☐

Usual daily consumption: ....

Number smoked so far today: ....   *Representative of daily amount* ☐

Time since last smoke: ....

Occupation: ....

Do you drink high caffeine/stimulant drinks (e.g. Red Bull)?   No ☐

Yes ☐

If YES, what, and how often? ....

....

How many cups of tea &/or coffee do you normally drink in a _day_? Tea: _____ Coffee: _____

How many cups of tea &/or coffee do you normally drink in a _morning_? Tea: ____ Coffee:____

MEASUREMENTS

Height: .... Weight: .... BMI: ....

Do you have Cystic Fibrosis: Yes; ☐   If YES please go to section 1

No; ☐   If NO please go to section 2

SECTION 1:

What type of Cystic Fibrosis mutation do you have? (e.g. F508) ……………………………

Class I: Class II: Class III: Class IV: Class V:

☐   ☐   ☐   ☐   ☐

How would you rate your health today, given your condition?

Not very   1   2   3   4   5   6   7   8   9   10   Extremely
healthy   healthy

Do you have known impaired glucose tolerance, or Cystic Fibrosis Related-Diabetes?

No: ☐

Yes*: Impaired glucose tolerance (IGT); ☐ Cystic Fibrosis Related-Diabetes (CFRD) ☐

*If YES, what date did you get the diagnosis? (Roughly) ……………………………………

*If YES, are you currently being prescribed and taking insulin? No ☐   Yes ☐

Dose & Frequency: ………………………………………………………………………

Have you had a transplant? (E.g. lung)   No ☐

                                                Yes ☐

                     Type(s) and date(s): ……………………………………………………

                     ……………………………………………………………

Do you do regular exercise?   No ☐   Yes ☐

If YES, how many times a week: One to four ☐

                                          More than four ☐

                          What   types   of   exercise   do   you   do?

                          ……………………………………………………………………

                          ……………………………………………………………………

Do you have a cardiac pacemaker fitted?   No ☐

                                            Yes ☐

Can we keep this information on file and contact you about future studies?   Yes / No

SECTION 2:

How would you rate your health?

Not very   1   2   3   4   5   6   7   8   9   10   Extremely
healthy   healthy

Do you have or have you had any medical conditions? (I.e. heart condition, asthma, diabetes)

....
....
....

Do you take any medication (over the counter or prescribed)?   No   ☐

                                                                   Yes   ☐

please give details:

....
....

Do you do regular exercise?   No   ☐

                            Yes   ☐

If YES, how many times a week: One to four   ☐

                                      More than four   ☐

What   types   of   exercise   do   you   do?

....
....

Do you have a cardiac pacemaker fitted?   Yes   ☐   No   ☐

Appendix R: Consent form healthy controls

<u>CONSENT FORM FOR HEALTHY CONTROLS</u>

Study Title: A study investigating the mental performance of people with Cystic Fibrosis (CF)

	Please Initial
1. I confirm I have read and understood the Participant Information Sheet for Healthy Controls dated 09.08.2013 (Version 2) for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
2. 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.	
3. I understand that the testing session will involve completing some questionnaires, tests of mental performance and having my blood sugar and carbon monoxide measured.	
4. I understand that data collected during the study may be looked at by individuals from University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.	
5. I agree to take part in the above study.	

Name of Participant (print name)	Signature	Date

Name of Researcher	Signature	Date

Appendix S: Power calculation for the PRM test

Parameter	Difference	Average Control Group	N per group, Two sided	N per group, One sided
Spatial Span (De Luca et al., 2003)	5%	6.5	261	205
	10%		64	51
	20%		17	14
Pattern Recognition Memory, Immediate Recall Correct Responses (Lasselin et al., 2012)	5%	92	42	33
	10%		14	11
	20%		5	4
Pattern Recognition Memory, Delayed Recall Correct Responses	5%	74	186	147
	10%		42	33
	20%		12	9
Pattern Location Associative Learning, Total trials (Collie et al., 2012)	Taken from paper (5.6)	6.4	13	11
Pattern Location Associative Learning, Total Errors	Taken from paper (18)	13	12	10
Pattern Location Associative Learning, List Memory	Taken from paper (4)	9	10	8

Appendix T: 'Cognitive Failures Questionnaire for others'
(Broadbent, Cooper, FitzGerald & Parkes, 1982)

The questions given below are about mistakes and difficulties which everybody has from time to time. We want to know how often, in your opinion, your relative or partner has shown any of these troubles during the **last 6 months**. After each question, please **circle only one of the five possible answers**.

Please make sure you read them carefully because for some of the questions, 'very often' is on the left side of the page, and 'never' is on the right, but for others, 'never' is on the left and 'very often' is on the right.

How are you related to the patient? Partner: ☐ Relative: ☐ Other:

During the last six months, has your relative or partner seemed to be:

1. **Absent-minded, that is making mistakes in what he/she is doing because he/she is thinking of something else?**

Very Often	Quite Often	Occasionally	Very Rarely	Never

2. **Finding it difficult to concentrate on anything because his/her attention tends to wander from one thing to another?**

Never	Very Rarely	Occasionally	Quite Often	Very Often

3. **Forgetful, such as forgetting where he/she has put things, or about appointments, or about what he/she has done?**

Very Often	Quite Often	Occasionally	Very Rarely	Never

4. **Busy thinking about his/her own affairs, and so not noticing what is going on around him/her?**

Never	Very Rarely	Occasionally	Quite Often	Very Often

5. **Clumsy, for example, dropping things or bumping into people?**

Very Often	Quite Often	Occasionally	Very Rarely	Never

6. **Having difficulty in making up his/her mind?**

Never	Very Rarely	Occasionally	Quite Often	Very Often

7. Disorganised, that is, getting into a muddle when doing something because of lack of planning or concentration?

Very Often	Quite Often	Occasionally	Very Rarely	Never

8. Getting unduly cross about minor matter?

Never	Very Rarely	Occasionally	Quite Often	Very Often

Appendix U: Cognitive Difficulties Scale Items (McNair & Kahn, 1983)

Below are statements describing everyday inefficiencies, lapses of attention of memory, and related functions that people often notice about themselves.

Please circle the number to rate the degree to which each statement describes your typical or usual behaviour during the <u>past week</u>.

	Very Often	Often	Sometimes	Rarely	Not at all
I have trouble recalling frequently used phone numbers.	4	3	2	1	0
I put things down (glasses, keys, wallet, purse, papers) and have trouble finding them.	4	3	2	1	0
When interrupted while reading, I have trouble finding place again.	4	3	2	1	0
I need a written list when I do errands to avoid forgetting things.	4	3	2	1	0
I forget appointments, dates or classes.	4	3	2	1	0
I forget to return phone calls.	4	3	2	1	0
I have trouble putting my keys into the lock.	4	3	2	1	0
I forget errands I planned to do on my way home.	4	3	2	1	0
I have trouble recalling the names of people I know.	4	3	2	1	0
I find it hard to keep my mind on a task or job.	4	3	2	1	0

I have trouble describing a program that I just watched on television.	4	3	2	1	0
I don't quite say what I mean.	4	3	2	1	0
I fail to recognise people I know.	4	3	2	1	0
I have trouble getting out information that is at the tip of my tongue.	4	3	2	1	0
I have trouble thinking of the names of objects.	4	3	2	1	0
I find it hard to understand what I read.	4	3	2	1	0
I forget the names of people soon after being introduced.	4	3	2	1	0
I lose my train of thought as I listen to somebody else.	4	3	2	1	0
I miss the point of what other people are saying.	4	3	2	1	0
I forget steps in recipes I know well, or have to look them up.	4	3	2	1	0
I forget what day of the week it is.	4	3	2	1	0
I forget to button or zip my clothing.	4	3	2	1	0
I need to check or double check whether I locked the door, turned off the stove etc.	4	3	2	1	0
I make mistakes in writing, typing or operating a calculator.	4	3	2	1	0
I cannot keep my mind on one thing.	4	3	2	1	0
I need to have instructions repeated several times.	4	3	2	1	0
I leave out ingredients when cooking.	4	3	2	1	0
I have trouble manipulating buttons, fasteners, scissors or bottle caps.	4	3	2	1	0
I misplace my clothing.	4	3	2	1	0
I have trouble sewing or mending.	4	3	2	1	0
I find it hard to keep my mind on what I'm reading.	4	3	2	1	0
I forget right away what people say to me.	4	3	2	1	0

When walking or riding, I forget how I've gotten from one place to another.	4	3	2	1	0
I have trouble deciding if I have received the correct change.	4	3	2	1	0
I forget to pay my bills, record checks or mail letters.	4	3	2	1	0
I have to do things very slowly to be sure I'm doing them right.	4	3	2	1	0
My mind goes blank at times.	4	3	2	1	0
I forget the date of the month.	4	3	2	1	0
I have trouble using tools (hammers, pliers, etc) for minor household repairs.	4	3	2	1	0

Appendix V: Debriefing questionnaire for follow-up study

Study Title: A Follow-up study investigating cognition in patients with cystic fibrosis- related diabetes (CFRD)

A study investigating the memory, attention and executive function of people with cystic fibrosis (CF)

ID Number: _____   **Date:** _____/_____/ 201____

Recruitment and Time between testing sessions

1. Why did you decide to take part in the follow-up study?

………………………………………………………………………………………………………

………………………………………………………………………………………………………

2. Did you have any concerns taking part in the follow-up study?

…………………………………………………………………………………………..……

………………………………………………………………………………………………

3. Have you thought about or noticed any changes in your memory and/or attention since the last testing session?   *If so, please explain.*

…………………………………………………………………………………………..……

………………………………………………………………………………………………

4. Do you think your memory and/or attention may have declined since the last testing session? W*hy?*

…………………………………………………………………………………………..……

………………………………………………………………………………………………

Study Procedures

5. Where did you complete the follow-up study? (Place a tick or cross in the box)

As an inpatient: ☐   Hospital Appointment: ☐   At home: ☐

Came to the ward (not in conjunction with an appointment): ☐

6. Based on your answer to question 5, was this convenient for you? Or would you have preferred a different location- which one, and why?

………………………………………………………………………………………………

7. Was there any part of the study you were unhappy with?

………………………………………………………………………………………………………

Questions about the Cognitive Tests (Those on the tablet/computer)

8. What was your experience of completing the tests for a second time?

The same difficulty: ☐   Harder: ☐   Easier: ☐

9. Based on your answer to question 8, why do you think this?

…………………………………………………………………………………………………

…………………………………………………………………………………………………

10. Which test(s) did you find particularly hard today? (Place a tick or cross in the boxes)

PAL *(6/8 white boxes and locating the patterns in each box)* …………. : ☐

VRM *(Remembering the list of words and recognising them)*………….. : ☐

PRM *(Recognising the patterns from a choice of two)*…………….….. : ☐

RVP *(Finding Number sequences 357, 246, 468)*………………..…… : ☐

SSP *(9 white boxes changing colour and remembering the order)*........ : ☐

AST *(Arrow test with direction and side)*…………………………..…… : ☐

11. Based on your answer to question 10, can you think why you found them hard? *(Duration of test? Pace of the test – too fast/slow? Lost concentration halfway through? etc)*

…………………………………………………………………………………………………

12. Which test(s) did you find particularly easy today? (Place a tick or cross in the boxes)

PAL *(6/8 white boxes and locating the patterns in each box)* ………... ☐

VRM *(Remembering the list of words and recognising them)*………….. ☐

PRM *(Recognising the patterns from a choice of two)*……………...... ☐

RVP *(Finding Number sequences 357, 246, 468)*……………………… : ☐

SSP *(9 white boxes changing colour and remembering the order)*....... : ☐

AST *(Arrow test with direction and side)*………………………………… : ☐

13. Based on your answer to question 12, can you think why you found them easy? (Pace of test was slow? Something to do with the colour/shape of patterns? etc)

…………………………………………………………………………………………………

…………………………………………………………………………………………………

14. Did you try your best in all the tests? (Please be honest)

……………………………………………………………………………………

……………………………………………………………………………………

15. During the study, was there anything in your personal life (e.g. work stress, health, relationships, testing situation) which may have affected your performance (e.g. concentration) on any of the tests?

……………………………………………………………………………………

……………………………………………………………………………………

<u>In General</u>

13. Is there anything else you would like to tell us?

……………………………………………………………………………………

……………………………………………………………………………………

……………………………………………………………………………………

………………………………………………………………………

……………………………………………………………………………………

……………………………………………………………………………………

……………………………………………………………………………………

……………………………………………………………………………………

FOR CHIEF INVESTIGATOR:

<u>ADDITIONAL NOTES ABOUT TEST SESSION</u>

Appendix W: Participant Information Sheet for the follow-up study

A follow-up study investigating cognition in patients with cystic fibrosis-related diabetes (CFRD)

We would like to invite you to take part in our follow- up research study. Before you decide we would like you to understand why the study is being done and what it would involve for you. Please take your time to decide whether or not you wish to take part. Please ask if anything is unclear or if you would like more information.

What is the research about?

This follow-up study has been designed to investigate the mental performance (e.g. memory, attention, reaction time) of diabetic patients with cystic fibrosis after a 18 (+/- 6) month period (i.e. since you last completed the memory and attention tests).

The study will be carried out under the supervision of Dr Daniel Peckham and Dr Michael Mansfield (Leeds Teaching Hospitals Trust) and Professor Louise Dye and Dr Clare Lawton (University of Leeds).

Why have I been asked to take part?

You have been invited to take part because you completed the original study 18 (+/- 6) months ago.

It is up to you to decide whether or not to take part. Your decision will not affect the standard of care you receive in any way.

If you do decide to take part you will be given this information sheet to keep and asked to sign a consent form. Even if you decide to take part you are still free to withdraw at any time without having to give a reason.

What will I have to do?

There is only one study session (lasting about 1.5 hours). To minimise inconvenience to you, you can either complete it whilst you're an inpatient, incorporate it into your routine health appointment on the ward *(at St James's Hospital)* or at outpatient's clinic *(Seacroft Hospital)*, or it can arranged to be completed in your own home between now and your next appointment *(this is something which may not have been available when you initially completed the study)*.

You will need to fast for two hours (i.e. no food, or drink, except water) before the start of testing. Your blood sugar has to be below 12 mmol/L in order for the testing session to go ahead. If you are a smoker, we also ask that you do not smoke within these two hours.

The follow- up study will follow the same procedure as the original study. If you are willing to participate, you will be asked to sign a consent form and complete a questionnaire to state if any of your details have changed e.g. occupation, health etc. We will obtain other information from your medical records with your permission.

You will then be asked to complete several short questionnaires about your sleep quality last night and the past week, perceived stress over the past week and month, and your mood over the past week and right at that moment in time.

We will measure your carbon monoxide levels using a Smokerlyzer i.e. take a deep breath, hold for 15 seconds, and then blow it all out into the machine. We will also measure your blood sugar level using a finger prick diabetic kit.

Following this, we will ask you to complete the same 7 tests on the tablet, which usually take around 45 minutes. We will then ask you to complete 4 short questionnaires asking about the tests you have just completed, about minor mistakes which may have happened in your daily life within the past 6 months *(your relative or partner may also complete a similar questionnaire, which asks them if they have noticed you having any troubles, with your permission),* about minor mistakes which may have happened in your daily life within the past week and finally, about your experience of taking part in the follow-up study.

Once you have completed the last questionnaire, you will be free to ask any questions about the study. You will be paid a £25 Love2Shop voucher and if applicable, your car parking charges too. You will also get to know how you performed in the tests last time.

Below is a summary of what will happen during the study:

Test session incorporated into either your inpatient stay, appointment <u>OR</u> in your own home

↓

Still want to take part after questions have been answered: Sign the Consent Form

↓

Complete Recruitment Information sheet

↓

<u>Complete 6 Questionnaires:</u> Sleep quality last night [1] & last week [2], perceived stress over the past week[3] & month[4], Anxiety and depression levels [5], mood and mental alertness [6]

↓

Blood sugar level and carbon monoxide level measured

↓

Tests of Mental Performance on a touch screen tablet/computer

↓

<u>Complete 4 questionnaires:</u> About the tests of mental performance you have just finished [1], Minor mistakes which may have happened in daily life in the past 6 months [2] and past week [3], Experiences about taking part in the study [4]

↓

Debriefed and compensated with a £25 Love2Shop Voucher. Car parking charges will also be paid, if applicable.

With your permission, your partner or relative may also complete a similar questionnaire to this one which asks them if they have noticed you having any troubles in the past 6 months.

What are the tests of mental performance?

All of the tests which you completed in the original study will be repeated. The tests are not designed to trick you; we just ask that you complete them to the best of your ability.

The tests are administered on a touch-screen tablet/computer, although some tests will require you to push a button instead of touching the screen. As in the original study, Helen will be in the room with you guiding you through the tests.

What are the benefits of taking part?

Taking part will contribute to the growing research on cystic fibrosis. It will help contribute to the limited research into whether people with cystic fibrosis who develop diabetes have any problems with mental performance. Previous research has shown that people with type 1 and

type 2 diabetes develop problems with mental performance, but this is unknown in the cystic fibrosis population. We will also investigate whether there is any difference in mental performance after an 18 (+/-6) month period in patients who have received a transplant.

If you are completing the testing at a hospital appointment, it gives you an activity to complete whereas otherwise you may be waiting around.

What are the disadvantages of taking part?

The time taken to complete the study has been kept to a minimum. There is only one testing session, which can be in the morning or afternoon. We will arrange your test session to be either at the same appointment as your clinic visit, or completed in your own home, to minimise inconvenience to you.

The risks associated with blood sampling include bruising and discomfort. Researchers are fully trained in blood sampling and first aid and will take every step to minimise any of the risks associated.

Who has reviewed this study?

This study has been reviewed by an independent group of people and given a favourable opinion by Yorkshire & the Humber – Leeds West NHS Research Ethics Committee (reference: 13/YH/0219; Follow-up study approved 15/05/2015).

Will my taking part in the research be kept confidential?

The study is subject to ethical guidelines set out by the British Psychological Society and the NHS. All information that is collected from you during the course of the study will be treated in the strictest of confidence at all times and will only be used for the purposes of this research.

Your data will be recorded safely using the unique study identity code which you were given in the original study. The link between your name (and other personal data) and your study code will be maintained and stored securely at the School of Psychology, University of Leeds or at St James's University Hospital and will only be accessible to the research team.

Who is organising and funding the research?

This research is funded by the Medical Research Council and NHS. It is collaboration between the University of Leeds and Leeds Teaching Hospitals NHS Trust.

What will happen to the results of the research study?

The anonymised results from the study will be used towards an educational qualification (PhD) by a member of the research team (Helen Chadwick).

Anonymised results may also be presented at conferences and/or in scientific journals. Individuals will not be identifiable from any details in reports, presentations or scientific publications based on the results of the study.

Will I receive anything for taking part?

Upon completion of the study, you will receive a £25 Love to Shop Voucher to compensate you for your time and effort. We will also pay your car parking charges whilst you are at clinic.

If, for whatever reason, we cannot combine the testing session with your routine health assessment, and testing cannot be completed in your home, we will reimburse your travel expenses up to the value of £20.

If I want to take part or get more information what do I do next?

If you have any questions or would like to volunteer to take part in this study, please contact:

Helen Chadwick

Research Psychologist (St James's University Hospital, Leeds)

PhD Student (School of Psychology, University of Leeds)

Tel: 0113 343 2275 (Office)

Email: h.k.chadwick@leeds.ac.uk

Other contacts:

Dr Daniel Peckham	Dr Michael Mansfield
Clinical Lead for Cystic Fibrosis	Consultant for Diabetic patients
Tel: 0113 XXX XXXX	Tel: 0113 XXX XXXX

Appendix X: Participant consent form for the follow-up study

FOLLOW- UP STUDY CONSENT FORM

Study Title: A Follow-up study investigating cognition in patients with cystic fibrosis- related diabetes (CFRD)

A study investigating the memory, attention and executive function of people with cystic fibrosis (CF)

	Please Initial
1. I confirm I have read and understood the Follow-Up Study Participant Information Sheet for Patients with Cystic Fibrosis dated 01.03.2015 (Version 1) for the above study. I have had the opportunity to consider the information, ask questions, and have had these answered satisfactorily.	
2. 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.	
3. I understand that the testing session will involve completing some questionnaires, tests of mental performance and having my blood sugar and carbon monoxide measured.	
4. I agree that my partner or relative can complete the questionnaire which asks their opinion about troubles I may have had in the past 6 months.	
5. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Leeds, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
6. I agree to take part in the above study.	

Name of Participant (print name)	Signature	Date

Name of Researcher	Signature	Date

Appendix Y: RIQ for the follow-up study

<u>**FOLLOW-UP RECRUITMENT INFORMATION SHEET**</u>

Study Title: A Follow-up study investigating cognition in patients with cystic fibrosis- related diabetes (CFRD)

A study investigating the memory, attention and executive function of people with cystic fibrosis (CF)

Baseline test: _____ / _____ / _____   AM: ☐ PM: ☐   Tx: ☐

Follow-up date: _____ / _____ / _____   AM: ☐ PM: ☐   Time since baseline: _____ months

First Name(s): ....

Surname: ....

Address: ....

....

....

....

Telephone number: ....

Mobile number: ....

Email Address: ....

Date of Birth: .... / ..../ ....   Age: ....   Female: ☐ Male: ☐

CLINICAL INFORMATION

Cystic Fibrosis Mutations: ..../..

Class I: ☐   Class II: ☐   Class III: ☐   Class IV: ☐   Class V: ☐

EDUCATION

Previous Level of Education: None: ☐ GCSE: ☐   GCE O Level: ☐   AS/A Level: ☐

Diploma: ☐   Degree: ☐   Masters: ☐   PhD/Doctorate: ☐

Current Level of Education: Same: ☐   New highest level of education: ....

OCCUPATION

Previous Occupation: *Employed* Full Time: ☐   *Unemployed:* ☐   *Housewife/husband* : ☐

Employed Part Time: ☐   *Retired:* ☐   *Other:* ....

Student: ☐

Current Occupation: Same: ☐   New Occupation: ....

MEASUREMENTS

Previous measurements: Height: .... Weight: .... BMI: ....

Current measurements: Height: .... Weight: .... BMI: ....

SMOKING

Previous Smoking Status: Never: ☐   Given up: ☐ Duration: .... Smoker: ☐ Approx. daily: ....

Current Smoking Status: Same: ☐   New Status: ....

If you are a smoker, please complete the below questions:
Tobacco used: Cigarettes: ☐   Pipe/Cigars: ☐   Switched cigarettes pipes &/or cigars: ☐

Usual daily consumption: ....   *No. smoked so far today:* ....   Representative? ☐

Time since last smoke: ....   Occupation: ....

HIGH CAFFEINE/ STIMULANT CONSUMPTION

Previous consumption: No: ☐   Yes: ☐   *What & how often:* ....

Current Consumption of high caffeine/stimulant drinks: Same: ☐   OR   No: ☐   Yes: ☐

What & how often: ....

TEA AND/OR COFFEE CONSUMPTION

Previous consumption of tea/coffee (cups) daily: Tea: _____   Coffee: _____

Current consumption of tea/coffee (cups) daily: Same: ☐   OR Tea: _____   Coffee: _____

Previous consumption of tea/coffee (cups) in the morning: Tea: _____   Coffee: _____

Current consumption of tea/coffee (cups) in the morning: Same: ☐ OR Tea: _____ Coffee: _____

EXERCISE

Previous weekly no. of regular exercise: No: ☐   Yes (1-4): ☐   Yes (4+): ☐

                                         Types of exercise: ....

                                         ....

Current weekly no. of regular exercise: Same: ☐   No: ☐   Yes (1-4): ☐   Yes (4+): ☐

                                         Types of exercise: ....

                                         ....

HEALTH RATING

Previous Health Rating: 1 2   3   4   5   6   7   8   9   10

Current/Today's health rating (given your condition):

Not very   1   2   3   4   5   6   7   8   9   10   Extremely
healthy/Well   healthy/ Well

DIABETES

Are you still diagnosed as diabetic?   Yes: ☐   No: ☐

Are you still being prescribed and taking insulin?   Yes: ☐   No: ☐

If   **YES**:   What   Type,   Dose,   Frequency   of   insulin:

…………………………………………………………………………………………………

……………………………………………….

TRANSPLANT

Previous Transplant status: Non-Transplant: ☐   Post Transplant: ☐

Current Transplant status: Same: ☐   Different Status: *On Transplant register:* ☐
                                                            Post-Transplant: ☐

Post-Transplant but Further Transplant Needed: ☐

If   Post-Transplant,   the   Type(s)   and   date(s)   of   operation:

………..…………………………………………..……………….…

Can we keep this information on file and contact you about future studies?   Yes / No

ADDITIONAL NOTES