

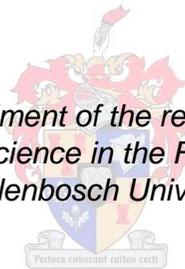
THE RELATIONSHIP BETWEEN TASK COMPLEXITY AND CEREBRAL OXYGENATION IN STROKE PATIENTS

BY

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of Master of Sport Science in the Faculty of Education at
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DECLARATION

I, Bradley James Fryer, hereby declare that the information contained herein is solely my own, original work and that I am the owner of the copyright thereof (unless to the extent explicitly otherwise stated). In no way or form was this work previously submitted in its entirety or in part for obtaining any academic qualification.

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SUMMARY

There are a growing number of men and women world-wide who are suffering strokes due to poor lifestyle-related habits. While there is evidence of the differences in cerebral haemodynamics between stroke patients and both elderly and young healthy individuals, limited evidence has examined the effect of rehabilitation on cerebral haemodynamics. Furthermore, most studies have examined changes in cerebral haemodynamics during cognitive and functional tasks in isolation, with no literature published on them simultaneously.

The primary aim of this study was to examine whether differences in cerebral haemodynamics exist between stroke patients and healthy elderly individuals while performing a simple and complex cognitive task.

Thirty two men and women (age 75 ± 8 years) volunteered to participate in the study and were split into an experimental ($n = 14$) group consisting of stroke patients and a control ($n = 18$) group consisting of healthy individuals. Each participant was required to attend one testing session where measurements of oxyhaemoglobin (O_2Hb), deoxy-haemoglobin (HHb), tissue oxygenation index (TOI) and total haemoglobin index (THI) were obtained. Measurements were obtained with the participants at rest, while performing the Mini Mental State Exam (MMSE) and the modified Stroop Task as cognitive tests, and the Timed Up-and-Go (TuG) and six minute walk test (6MWT) or Toe Taps (TT) as the functional tests. Furthermore, the outcome scores of the various tests were also recorded.

Change in O_2Hb levels were lower in the experimental group than in the control group, especially in the left prefrontal cortex (LPFC) while HHb values were higher in the right

prefrontal cortex (RPFC) ($p > 0.05$). There were almost no differences in TOI between the two groups in either the LPFC or RPFC, however, statistically significant differences were seen in THI in the RPFC during the MMSE ($p = 0.03$), rest period 2 ($p = 0.03$), the first modified Stroop Task ($p = 0.04$), as well as the TuG ($p = 0.02$). Furthermore, significant differences were seen between the two groups with respect to the time taken to complete the TuG, with the experimental group completing it much faster ($p = 0.04$). The experimental group participants who had received regular rehabilitation performed consistently better across most of the testing phases, with a number of practically significant findings.

The results show that definite differences exist between stroke patients and healthy elderly individuals when performing a simple and complex task. The positive effect of low intensity exercise on task performance was clearly seen in both groups, and holds a great deal of practical significance for the development of exercise programmes for healthy individuals, as well as stroke patients. Furthermore, rehabilitation following a stroke has obvious benefits as shown by the positive results of the current study, however, limited research exists to validate these findings, highlighting the need for further research in this area.

OPSOMMING

Daar is 'n wêreld wye toename in die aantal mans en dames wat beroertes ondervind as gevolg van swak lewenstyl-verwante gewoontes. Alhoewel baie navorsing beskikbaar is oor die verskille in serebrale hemodinamika tussen beroerte pasiënte en bejaardes, asook jong gesonde individue, is daar 'n beperkte aantal studies oor die effek van rehabilitasie op serebrale hemodinamika. Meeste van hierdie studies het die veranderinge in serebrale hemodinamika tydens kognitiewe of funksionele take in isolasie ondersoek, met geen literatuur waar die effek van albei gesamentlik gemeet word nie.

Die hoofdoel van hierdie studie was om die verskille in serebrale hemodinamika tussen beroerte pasiënte en gesonde bejaardes, tydens die uitvoering van 'n eenvoudige en komplekse kognitiewe taak, te ondersoek.

Twee-en-dertig mans en vroue (ouderdom 75 ± 8 jaar) het aan die studie deelgeneem. Die eksperimentele groep ($n = 14$) het bestaan uit die beroerte pasiënte en die kontrole groep ($n = 18$) was gesonde bejaardes. Elke deelnemer het een toets sessie bygewoon waartydens oksihemoglobien (O_2Hb), deoksihemoglobien (HHb), weefsel oksigenasie indeks (TOI) en totale hemoglobien indeks (THI) gemeet is. Metings is tydens rus geneem, asook tydens die kognitiewe toetse, die "Mini Mental State Exam" (MMSE) en die gewysigde Stroop taak gemeet, en die funksionele toetse, naamlik die "Timed Up-and-Go" (TuG) en die ses minute loop toets (6MWT) of "Toe Taps" (TT).

Die eksperimentele groep se O_2Hb was laer as die kontrole groep, veral in die linker voor frontale korteks (LPFC), en die eksperimentele groep se HHb waardes was hoër in die regter voor frontale korteks (RPFC) ($p > 0.05$). Daar was geen statisties betekenisvolle

verskille in TOI tussen die twee groepe nie, maar wel in die THI in die RPFC tydens die MMSE ($p = 0.03$), rusperiode twee ($p = 0.03$), die eerste gewysigde Stroop Taak ($p = 0.04$) en die TuG toets ($p = 0.02$). Die kontrole groep was statisties betekenisvol vinniger as die eksperimentele groep in die TuG toets ($p = 0.04$). Deelnemers in die eksperimentele groep wat gereelde rehabilitasie ontvang het, het konsekwent beter gevaar tydens die toets sessie, en 'n aantal prakties betekenisvolle verskille is in sekere veranderlikes gevind.

Die resultate dui aan dat daar wel 'n verskil in serebrale hemodinamika bestaan tussen beroerte pasiënte en gesonde bejaardes terwyl hulle eenvoudige en komplekse take verrig. Die positiewe effek van lae intensiteit oefening op prestasie was duidelike sigbaar van beide groepe. Hierdie resultate is prakties betekenisvol as dit kom by die ontwikkeling van oefenprogramme vir gesonde individue asook beroerte pasiënte. Rehabilitasie na 'n beroerte hou ooglopende voordele in soos aangedui deur die positiewe bevindinge van die huidige studie, hoewel daar beperkte navorsing beskikbaar is om hierdie bevindinge te staaf. Daar is dus 'n behoefte vir verdere navorsing in hierdie gebied.

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LIST OF ABBREVIATIONS AND ACRONYMS

°	:	Degree
Δ	:	Delta (Change of)
\bar{x}	:	Mean
\$:	Dollar
%	:	Percentage
ε	:	Extinction coefficient
β	:	Beta
I_0	:	Light entering
I	:	Light exiting
[C]	:	Micromolar concentration
μMol	:	Micromol
\geq	:	Greater than or equal to
\leq	:	Smaller than or equal to
$>$:	Greater than
$<$:	Smaller than
6MWT	:	Six minute walk test
A	:	Attenuation
ACEIs	:	Angiotensin-converting enzyme inhibitors
ACSM	:	American College of Sports Medicine
AD	:	Alzheimer's disease
ADA	:	American Diabetes Association
ADL	:	Activity of daily living
ADL's	:	Activities of daily living
AF	:	Atrial fibrillation

ARBs	:	Angiotensin receptor blockers
ART	:	Anti-retroviral therapy
ARVs	:	Anti-retrovirals
a.u.	:	Arbitrary units
AV	:	Activation volume
BAT	:	Bilateral arm training
BBB	:	Blood-brain barrier
BFI	:	Blood flow index
BI	:	Barthel index
BMI	:	Body mass index
BOLD	:	Blood oxygen level-dependent contrast
Botox	:	Botulinum toxin A
BP	:	Blood pressure
BWS	:	Body weight-supported
C	:	Celsius
C1	:	Condition one of the modified Stroop Task
C2	:	Condition two of the modified Stroop Task
C3	:	Condition three of the modified Stroop Task
C4	:	Condition four of the modified Stroop Task
CAD	:	Coronary artery disease
CBF	:	Cerebral blood flow
CBV	:	Cerebral blood volume
CIMT	:	Constraint-induced movement therapy
cm	:	Centimetre
cm ²	:	Centimetre squared
CMRO ₂	:	Cerebral metabolic rate of oxygen

CNS	:	Central nervous system
CON	:	Control
CRP	:	C-reactive protein
CSF	:	Cerebrospinal fluid
CVD	:	Cardiovascular disease
CytOx	:	Cytochrome oxidase
DALYs	:	Disability-adjusted life years
DHR	:	Day hospital rehabilitation
DM	:	Diabetes mellitus
DPF	:	Differential pathlength factor
DTI	:	Diffusor tensor imaging
EEG	:	Electroencephalogram
EF	:	Ejection fraction
ERP	:	Event-related brain potential
ES	:	Effect size
EXP	:	Experimental
F3	:	EEG position frontal 3
F4	:	EEG position frontal 4
F7	:	EEG position frontal 7
F8	:	EEG position frontal 8
FBG	:	Fasting blood glucose
FDA	:	Food and drug administration
FES	:	Functional electrical stimulation
FHS	:	Family history of stroke
fMRI	:	Functional magnetic resonance imaging
Fp1	:	EEG position prefrontal 1

Fp2	:	EEG position prefrontal 2
Fpz	:	EEG position mid-line prefrontal
Fz	:	EEG position mid-line frontal
g	:	Gram
GI	:	Glycaemic index
GL	:	Glycaemic load
GLUT4	:	Glucose transporter type 4
GMT	:	Goal management training
Hb	:	Haemoglobin
HbA _{1c}	:	Glycosylated haemoglobin
HbT	:	Total cerebral haemoglobin
Hcy	:	Homocysteine
HDL-C	:	High-density lipoprotein cholesterol
HGF	:	Hepatocyte growth factor
HHb	:	Deoxy-haemoglobin
HR _{max}	:	Maximal heart rate
HRQoL	:	Health-related quality of life
HRR	:	Heart rate reserve
HRT	:	Hormone replacement therapy
HUT	:	Head-up tilt
Hz	:	Hertz
ICG	:	Indocyanine green
ICH	:	Intracerebral haemorrhage
IDDM	:	Insulin-dependent diabetes mellitus
IL-6	:	Interleukin-6
IR	:	Infrared

ISAK	:	International society for the advancement of Kinanthropometry
IV	:	Intravenous
k	:	Scattering constant
K	:	Tissue loss constant
kcal	:	Kilocalories
kg	:	Kilogram
kg.m ⁻²	:	Kilogram per meter squared
L	:	Internal dimension of the cuvette
L	:	Large practical significance
LDL-C	:	Low-density lipoprotein cholesterol
LI	:	Lacunar infarction
LPFC	:	Left prefrontal cortex
LVH	:	Left ventricular hypertrophy
m	:	Metres
M	:	Moderate practical significance
MA	:	Mexican Americans
Mb	:	Myoglobin
MCA	:	Middle cerebral artery
MCI	:	Mild cognitive impairment
MI	:	Myocardial infarction
mm ⁻¹	:	Per millimetre
mmHg	:	Millimetre's mercury
MMSE	:	Mini-mental state exam
MOF	:	Multi-organ failure
MRI	:	Magnetic resonance imaging
MTHRF	:	Methylentetrahydroflolate reductase

n	:	Number
N	:	Negligible practical significance
N/A	:	Not applicable
NHW	:	Non-Hispanic whites
NIDDM	:	Non-insulin dependent diabetes mellitus
NIL	:	Near-infrared light
NIRS	:	Near-infrared spectroscopy
nm	:	Nanometers
NO	:	Nitric oxide
O ₂ Hb	:	Oxyhaemoglobin
Oz	:	EEG position mid-line occipital
p	:	Probability
PCA	:	Posterior cerebral artery
PET	:	Positron emission tomography
PMC	:	Premotor cortex
PNF	:	Proprioceptive neuromuscular facilitation
PSMC	:	Primary sensorimotor cortex
QoL	:	Quality of life
r	:	Correlation coefficient
R1	:	Rest period one
R2	:	Rest period two
R3	:	Rest period three
R4	:	Rest period four
R5	:	Rest period five
rCBF	:	Regional cerebral blood flow
RCT	:	Randomised controlled trial

RHR	:	Resting heart rate
ROM	:	Range of motion
RPE	:	Rating of perceived exertion
RPFC	:	Right prefrontal cortex
RT	:	Reaction time
s	:	Seconds
S	:	Small practical significance
SA	:	Sino-atrial
SAH	:	Subarachnoid haemorrhage
SD	:	Standard deviation
SIS	:	Stroke impact scale
SRS	:	Spatially resolved spectroscopy
ST1	:	Modified Stroop Task one
ST2	:	Modified Stroop Task two
TCD	:	Transcranial Doppler
tDCS	:	Transcranial direct current stimulation
TFA's	:	Trans-fatty acids
THI	:	Total haemoglobin index
TMT	:	Trail making test
TMS	:	Transcranial magnetic stimulation
TOI	:	Tissue oxygenation index
TPS	:	Time post-stroke
TRS	:	Time resolved spectroscopy
TSC	:	Total serum cholesterol
TT	:	Toe taps
TuG	:	Timed Up-and-Go

USA	:	United States of America
VD	:	Vascular dementia
VO _{2max}	:	Maximal oxygen uptake
VO _{2peak}	:	Peak oxygen uptake
VO _{2R}	:	Reserve oxygen uptake
WHO	:	World health organisation
WM	:	Working memory
x	:	Pathlength factor
YLD	:	Years of life lost due to disability
YLL	:	Years of life lost

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CHAPTER ONE

INTRODUCTION

Stroke is the third leading cause of death worldwide after cardiovascular diseases and disorders, and cancer (Poynter *et al.*, 2009). There is an estimated 15 million new cases of stroke diagnosed each year with approximately 30% of stroke survivors requiring permanent assistance with performing their activities of daily living (Carod-Artal & Egido, 2009; Poynter *et al.*, 2009). For research purposes the mechanism of stroke can be classified into two categories. The first, and most common cause of stroke, is cerebral ischaemia resulting from the formation of an embolism or thrombosis. This accounts for approximately 85% of stroke cases. The second and least common cause of stroke that accounts for approximately 15% of stroke cases is cerebral haemorrhage which results from micro-aneurisms in the intracerebral arteries (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000a).

There are a number of modifiable risk factors that place individuals at risk for having a stroke. These include hypertension, diabetes, cardiac dysrhythmias, hyperlipidaemia, substance abuse, as well as physical inactivity (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000a). Hypertension, or high blood pressure, is the greatest risk factor for the occurrence of stroke. Blood pressure is classified into three stages according to the American College of Sports Medicine as outlined in *Table 1.1* below (American College of Sports Medicine, 2010).

Table 1.1. Blood Pressure (BP) Classification for Adults

Classification	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
Optimal	< 120	< 80
Pre-Hypertension	120 – 139	80 – 89
Stage 1 Hypertension	140 – 159	90 – 99
Stage 2 Hypertension	≥ 160	≥ 100

BP, blood pressure; mmHg, millimetres mercury. (Adapted from ACSM's Guidelines for Exercise Testing and Prescription (8th Edition), 2010.)

The incidence of stroke in individuals younger than 45 years is very low (approximately 20 per 1000 population), with the peak incidence occurring in individuals between 60 and 70 years of age (approximately 100 per 1000 population) (Palmer-McLean & Harbst, 2009; Mohr *et al.*, 2004; Hildick-Smith, 2000a). It is believed that men are one and a half times more likely to suffer a stroke than women, although this number equalises after the age of 75 years. A possible reason for this is that women generally tend to live longer than men (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000a).

A stroke has a significant impact on a number of areas of life and in some cases may result in permanent disability (Carod-Artal & Egido, 2009; Palmer-McLean & Harbst, 2009). The area most affected by stroke is motor control and motor functioning which is why there is such a strong emphasis in this area during the post-stroke recovery period (Michael *et al.*, 2009; Hildick-Smith, 2000a). Loss of motor control and functioning usually presents itself in the form of paralysis or weakness that generally affects one side of the body (hemiparesis/hemiplegia). The side of the body affected is usually opposite to the side of the brain where the lesion is located, and the extent of the paralysis is related to both the size and location of the lesion (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000a). The upper extremities are generally affected to a greater extent than the lower extremities, with minimal to no weakness and/or paralysis of the lower limbs (Carod-Artal & Egido, 2009; Hildick-Smith, 2000a). However, depending on the lesion location, there is a possibility that

the lower limbs may be affected to a greater extent than the upper limbs (Hildick-Smith, 2000a). A further complication of loss of motor control is falling due to balance problems. Balance problems can generally be attributed to the hypertonia that accompanies stroke in either a flexor or extensor synergy pattern (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000b).

Losses of spatial and kinaesthetic awareness are further hallmarks of stroke. Patients are often unable to distinguish between a hot and cold object, a blunt and sharp object, and the position of an object relative to themselves (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000b). This is a potentially dangerous occurrence if not recognised and accommodated for (Hildick-Smith, 2000b). Visual disturbances have also been found in some cases with individuals struggling to perform everyday living activities such as putting on clothes, both due to the loss of sight and absence of realisation of their impairment (Hildick-Smith, 2000b). Approximately 25% of all stroke survivors suffer from an inability to read, write, speak, and understand what is being said to them, or any combination thereof, resulting in a great loss of daily functioning and quality of life (Palmer-McLean & Harbst, 2009).

Cognitive decline following stroke is very common and manifests itself in a number of different ways. Short- and long-term memory, attention, calculations, decision-making and problem solving are all areas that are affected by a stroke (Gottesman & Hillis, 2010; Palmer-McLean & Harbst, 2009). Recent research has shown that a certain degree of neuroplasticity does take place following rehabilitation which allows for partial recovery in the above-mentioned areas (Kluding, Tseng, & Billinger, 2011; Bütetfisch, Kleiser, & Seitz, 2006).

Near-Infrared Spectroscopy (NIRS) is an imaging technique first used in 1977 (Jöbsis, 1977) that has since been used extensively in research in a number of different populations, examining the correlation, among others, between brain functioning and cerebral blood flow (CBF). While NIRS is not a direct measure of CBF, it has been shown to be a valid and accurate indirect measure of CBF showing good correlations with O₂Hb ($r = 0.80$), HHb ($r = 0.67$) and THI ($r = 0.74$) (Plichta *et al.*, 2006). Comparative studies with fMRI and other brain imaging techniques have shown a very strong correlation between the two (Kato *et al.*, 2002). Compared to fMRI, NIRS is a relatively simple, non-invasive and inexpensive technique without compromising the validity and accuracy of the measurements (Tausky *et al.*, 2012). NIRS makes use of near-infrared light with a wavelength of between 650 nm and 950 nm, which enables it to pass readily into biological tissue due to the low levels of scatter and absorption by specific chromophores (Hoshi, 2009; Perrey, 2008). The chromophores of interest with NIRS are those of haemoglobin (Hb), myoglobin (Mb) and cytochrome oxidase (CytOx). The differing wavelengths allow for specific constituents of haemoglobin to be examined for the oxygenation states, thus the relative concentrations of oxyhaemoglobin (HbO₂) and deoxy-haemoglobin (HHb) can be measured, providing an indication of cerebral blood flow (Nakahachi *et al.*, 2010; Hoshi, 2009; Perrey, 2008). Research has shown that cerebral blood flow, as well as oxy- and deoxy-haemoglobin values are correlated with brain activity and that higher neural activation results in higher levels of cerebral blood flow as well as oxyhaemoglobin levels, with a concomitant decrease in deoxy-haemoglobin (Hoshi, 2009; Kato *et al.*, 2002). Furthermore, aging and exercise intensity have been shown to have an effect on both cerebral blood flow, as well as oxy- and deoxy-haemoglobin concentrations within the area of interest (Lucas *et al.*, 2012).

The purpose of this study was to investigate whether differences in cerebral haemodynamics exist between stroke patients and healthy elderly individuals while performing a simple and complex cognitive task, and what the effect of low intensity exercise is on task performance. Furthermore, time post-stroke and rehabilitation status were examined for their influence on cerebral haemodynamics and task performance.

CHAPTER TWO

UNDERSTANDING STROKE

A. INTRODUCTION

Stroke is today seen as one of the most devastating neurological conditions world-wide accounting for almost 5.5 million deaths annually, and is the third leading cause of death behind coronary heart disease and cancer (Hisham & Bayraktutan, 2012; Mukherjee & Patil, 2011). It affects men and women of all ages, from young children to the aged, and despite its high incidence, can be prevented to a large extent through the management of a number of risk factors (Long *et al.*, 2011; Mukherjee & Patil, 2011; Rundek & Sacco, 2009). Despite the extensive knowledge on stroke pathophysiology, there are still a number of areas that clinicians and researchers are still unsure of, thus rendering the potential field for further research extremely wide (Mohr *et al.*, 2004).

B. BASIC ANATOMY AND STRUCTURE OF THE BRAIN

The brain is comprised of five major and continuous components, namely the telencephalon (cerebrum), diencephalon, mesencephalon (midbrain), metencephalon (pons) and myelencephalon (medulla oblongata), each with their own constituents (Drake *et al.*, 2005). The telencephalon is the largest of the three components, accounting for approximately 80% of the total brain volume and is comprised of a left and right cerebral hemisphere (Saladin, 2007; Drake *et al.*, 2005). The thalamus, hypothalamus and other related structures comprise the diencephalon which is the most anteriorly positioned part of the brainstem. The metencephalon consists of the cerebellum and pons with the

myelencephalon being the most posteriorly positioned part of the brainstem (Drake *et al.*, 2005).

The cerebral cortex is divided into four lobes that are responsible for a number of different functions. They are the frontal, temporal, parietal and occipital lobe respectively which can be seen in *Figure 2.1* below.

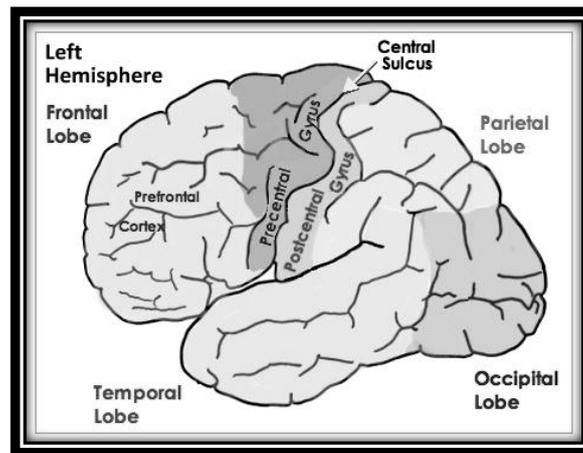


Figure 2.1. Various lobes of the cerebral cortex (Adapted from AMBA, 2012)

The frontal lobe lies posterior to the frontal bone of the skull and is separated from the parietal lobe by the central sulcus. It is primarily responsible for voluntary motor functions, planning and foresight, memory, mood and motivation. The parietal lobe lies underneath the parietal bone of the skull and is separated from the occipital and temporal lobes by the parieto-occipital and lateral sulcus, respectively. It is responsible for receiving and integrating somesthetic (touch, pain, etc.), taste and visual information. The occipital lobe is the most posteriorly located underneath the occipital bone and is the smallest of the lobes. It is primarily responsible for processing information related to vision. The temporal lobe lies on the lateral surface of the cerebral cortex, underneath the temporal bone. Information related to sound, smell, learning, memory and emotional behaviour are processed here (Saladin, 2007; Silverthorn, 2007).

Mapping of the cerebral cortex was introduced to differentiate between the differing functions of the various areas that make up the cerebral cortex. Brodmann divided the cortex of each hemisphere into 46 continuous and often overlapping areas. Due to its high degree of accuracy, the brain mapping classification of Brodmann is often used for reference purposes (Nolte, 1994). A further point to note is that the primary areas have unimodal association areas that function as an integration point between the various parts of the cerebral cortex, shown in *Figure 2.2* below (Silverthorn, 2007; Nolte, 1994).

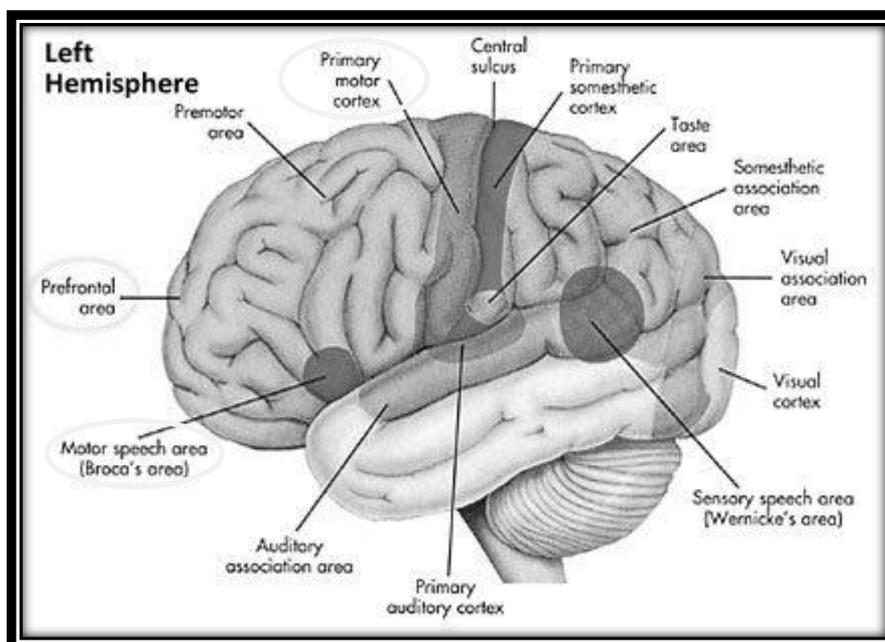


Figure 2.2. Major areas and association areas of the cerebral cortex (Adapted from Seeley, Stephens, & Tate, 2006).

The vascular system within the brain itself is highly complex and intricate and falls outside of the scope of this study. However, a discussion of the major blood vessels to and from the brain, as well as the blood vessels most indicated in stroke pathophysiology will be carried out below.

The left and right vertebral and internal carotid arteries are the main sources of blood flow to the brain and unite in the arterial circle of Willis at the base of the brain. Further branching occurs from this point where the anterior, posterior and middle cerebral arteries, as well as the anterior, posterior and inferior cerebellar arteries diverge to the various parts of the brain (Drake *et al.*, 2005). Venous return is accomplished through a myriad of smaller venous channels that ultimately empty into the dural venous sinuses, where after they empty into the internal jugular veins en route to the heart (Drake *et al.*, 2005).

C. CLASSIFICATION OF STROKE

Stroke can be generally classified as being ischemic or haemorrhagic in origin, with sub-classifications of each cited in the literature. These two types are in stark contrast to one another, with ischemic stroke occurring as a result of insufficient blood flow to the brain, and haemorrhagic stroke occurring as a result of excessive blood flow in the brain (Mohr *et al.*, 2004; Caplan & Moelter, 2000).

Ischemic stroke is further sub-divided into large artery stenosis occlusion, tandem arterial pathology, lacunar infarction (LI), embolism attributed to cardiac sources and cryptogenic infarction. Haemorrhagic stroke is sub-divided into intracerebral and subarachnoid stroke. Ischemic stroke and its various subtypes are the most commonly occurring stroke with an approximate 70-80% incidence with the remaining 20-30% comprising haemorrhagic stroke (Mohr *et al.*, 2004; Caplan & Moelter, 2000).

Lacunar infarction, embolism attributed to cardiac sources and cryptogenic infarctions constitute the three most common causes of ischemic stroke. Evaluating which of the three is a complex task with an algorithm being used together with diagnostic equipment.

Lacunar infarctions usually occur as a result of occlusion of the small deep arteries that supply the basal ganglia and thalamus, and in some cases the pons. These deep arteries are usually penetrating branches of the cerebral arteries. The mechanisms responsible for LI are microatheroma and/or lipohyalinosis, both caused by chronic hypertension and diabetes mellitus, and generally results in sensorimotor syndromes and movement disorders such as ataxic hemiparesis, hand dysarthria, dystonia and aphasia to name a few (Hisham & Bayraktutan, 2012; Mohr *et al.*, 2004). Emboli are said to account for between 15 and 70% of all ischemic strokes and can be attributable to a number of sources. It has been found that fibrin-platelet emboli, and not calcific plaques, are the main causes of embolitic strokes which mainly occur in the Middle Cerebral Artery (MCA). The exact mechanism and contributing factors are not completely understood, however due to the compressibility, elasticity and instability of these emboli it has been found that a number of occlusions may occur from a single emboli. This was found in a number of patients who initially presented with hemiparesis which dissipated with a concomitant presentation of Wernicke's aphasia (Mohr *et al.*, 2004).

Cryptogenic infarctions are infarcts with no known or diagnosed cause which account for approximately 40% of stroke patients seen in the acute healthcare setting. Three possible reasons are given for a patient being classified as having a cryptogenic infarction. The first reason is that no appropriate laboratory studies are performed and may be attributed to the patient's disease status and severity, age and unwillingness of the patient or physician to undergo or perform such studies. The second possible reason is that laboratory studies were performed at an improper time or not performed sufficiently enough. These cases are generally seen when angiography or MRI scans are performed longer than 48 hours post infarction, however, it must be noted that in some cases where a small lacunar infarct is the cause, neither timing nor the quantity of scans will affect the diagnosis as the lesion is

generally below the limits of resolution of the scan. The third and final reason for a person to be classified as having an infarct of undetermined cause is where ambiguous findings are reached despite appropriate studies and timing and poses a very serious problem for researchers and physicians alike (Mohr *et al.*, 2004).

Intracerebral haemorrhage (ICH) occurs as a result of bleeding into the brain tissue and accounts for between five and 13% of all strokes. Hypertension is the primary risk factor for ICH although other non-hypertensive risk factors include alcohol consumption, cigarette smoking, intracranial tumours, anti-coagulant therapy and vasculitis to name a few. Clinical syndromes and features vary widely depending on the topography of the haemorrhage. Ipsilateral and contralateral motor and sensory deficits as well as behavioural changes have been noted as common features, along with vomiting and severe headaches (Mohr *et al.*, 2004).

Subarachnoid haemorrhage (SAH) is caused in most cases by a rupture of an intracranial saccular aneurysm which causes bleeding into the brain tissue. SAH accounts for between five to 10% of all strokes but is also the most fatal, with a mortality rate of approximately 50%. The danger of SAH manifests itself in the number of complications that occur following the initial rupture with a high percentage of deaths occurring between 24 hours and three months after the event. Common complications include hydrocephalus, recurrent haemorrhage and vasospasm of surrounding arteries resulting in an ischemic stroke. Clinical syndromes for SAH are similar to those of ICH, although psychiatric disturbances and certain palsies are more common with SAH (Mohr *et al.*, 2004).

D. CAUSES OF STROKE

1. Modifiable Risk Factors

There are a host of modifiable risk factors that if controlled for, can significantly reduce the risk and incidence of having a stroke. The following risk factors will be discussed in more detail below: hypertension, diabetes, dyslipidemia, atrial fibrillation and other cardiac disorders, smoking and alcohol use, poor diet, obesity and physical inactivity as well as hyperhomocysteinemia (Rundek & Sacco, 2009; Mohr *et al.*, 2004).

1.1. Hypertension

Hypertension is defined as a blood pressure of 140/90 mmHg and above and is the primary cause of a number of strokes. The level of blood pressure is an independent predictor of stroke risk, with higher levels (stage two and three), carrying a higher risk. However, research has shown that the risk of first incidence is highest in those with stage 1 hypertension (Rundek & Sacco, 2009; Mohr *et al.*, 2004). Furthermore it has been found that those patients who have had a consistently high blood pressure over an extended period of time, even though the absolute blood pressure values may be relatively low, are at greater risk for a stroke. Research has shown that elevated blood pressure over the preceding 10 years of life increases the risk by a factor of 1.68 (Mohr *et al.*, 2004).

Guidelines suggest that lowering of blood pressure to 140/90 mmHg and below for patients without diabetes and 130/80 mmHg for patients with diabetes should be the primary goal in stroke prevention or stroke reoccurrence. A number of studies have shown that lifestyle modifications, as well as pharmacological interventions, lower stroke risk by

35 to 44%. Common anti-hypertensive medications include thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), β -blockers and calcium channel blockers. Current research seems to show that treatment with a combination of the above mentioned medications, as opposed to the medications in isolation, provide the best results, both in preventing an initial event and reducing the risk of a re-infarction following a non-fatal stroke (Hisham & Bayraktutan, 2012; Rundek & Sacco, 2009).

1.2. *Diabetes*

Diabetes has two clinical subtypes, namely type I and II. Type I diabetes, also known as insulin dependent diabetes mellitus (IDDM), is due to the auto-immune destruction of the beta cells of the pancreas and insufficient insulin production resulting in hyperglycaemia. Type II diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM), is caused by high levels of free fatty acids in the blood stream which cause intracellular mutations ultimately leading to reduced GLUT4 translocation which is the cause of hyperglycaemia (Silverthorn, 2007).

Extensive research has shown that the risk of ischemic stroke in diabetic individuals, and specifically type II diabetics, is at least double than that of their non-diabetic counterparts. Interestingly, there was found to be no increase in haemorrhagic stroke amongst diabetics when compared to non-diabetics. A possible reason for this finding was due to the pathophysiology of NIDDM and its causative effects. Hyperglycaemia and dyslipidemia result in atherosclerosis and the formation of atherothrombosis through the up-regulation of pro-inflammatory cytokines as well as pro-thrombotic products. Furthermore, due to the high levels of blood glucose, nitric oxide (NO) action is impaired resulting in endothelial

dysfunction - all pre-disposing an individual to an ischemic event. It is very rare to find NIDDM in isolation, with a host of further risk factors such as hypertension, obesity and dyslipidemia usually being present (Rundek & Sacco, 2009; Laakso & Kuusisto, 2007; Mohr *et al.*, 2004).

To reduce the risk of stroke in diabetics, the American Diabetes Association (ADA) recommends an aggressive and multi-factorial approach to the management of NIDDM and its associated cardiovascular risk factors. The main aims of treatment are to prevent further or reduce current atherosclerosis and to restore endothelial dysfunction. Both lifestyle and pharmacological interventions are used in both cases. Regular participation in light to moderate exercise, reduced dietary fat, and strict glycaemic control have shown to lower the relative risk for stroke by up to 57% with a 42% reduction in the relative risk for all cardiovascular disease (CVD) (Hatzitolios *et al.*, 2009; Rundek & Sacco, 2009). Anti-hypertensive medications such as ACEI's and ARB's, together with statins and oral hypoglycaemic drugs such as metformin have all shown a marked decrease in the relative stroke risk in patients with NIDDM compared to those individuals without diabetes (Hatzitolios *et al.*, 2009; Rundek & Sacco, 2009).

1.3. *Dyslipidemia*

Dyslipidemia is defined as abnormal lipid levels, either in excess or below their normative ranges and includes indices of cholesterol, and all its sub-classifications, as well as triglycerides (Silverthorn, 2007). Research on whether dyslipidemia is actually a modifiable risk factor is conflicting, with a number of researchers only finding a very weak or inconsistent association between ischemic stroke and abnormal lipid levels, while others find a significantly positive relationship between total low-density lipoprotein cholesterol

(LDL-C) and an inverse relationship between high-density lipoprotein cholesterol (HDL-C) and stroke risk (Rundek & Sacco, 2009; Sanossian *et al.*, 2006; Mohr *et al.*, 2004).

Despite conflicting evidence, a number of clinical trials have shown that the use of statins, commonly used cholesterol-lowering medications, significantly reduces the relative risk of non-fatal ischemic stroke by up to 38%, with no reduction seen in fatal stroke, and in some cases an increased incidence seen in haemorrhagic stroke (Caterina *et al.*, 2010; Rundek & Sacco, 2009; Fitchett, Goodman, & Langer, 2008; Mohr *et al.*, 2004). The long-term benefits of statins on stroke risk were verified by Fitchett *et al.* (2008) where they found that the early benefits seen were maintained with prolonged treatment. This is in stark contrast to what is commonly seen in patients who are treated with statins following a myocardial infarction (MI), where early benefits significantly decrease over time. Ihle-Hansen *et al.* (2012) showed that there was a significant association between hyperlipidaemia and lacunar infarction, while a study by Kim *et al.* (2012) suggested that atherogenic dyslipidemia may be a possible causative factor in ischemic stroke and not solely high LDL-C and total serum cholesterol (TSC). Evidence of this has been found in numerous studies where higher levels of HDL-C were associated with a decreased risk of ischemic stroke, however, this seems to be true only in cases where the individual is under the age of 50 years, although further research is needed to verify these findings (Rundek & Sacco, 2009; Sanossian *et al.*, 2006; Mohr *et al.*, 2004). The likelihood of ICH occurring as a result of statin treatment is relatively low (relative risk of 2.3%). When compared to the reduction in coronary events and recurrent stroke seen with statin treatment, it has been said that the benefits far exceed the risks involved (Fitchett *et al.*, 2008). A possible causative mechanism for the increased incidence of ICH seen with lower cholesterol levels is alteration of the cell membrane, thereby weakening the endothelium of the intracerebral arteries (Mohr *et al.*, 2004).

1.4. Atrial Fibrillation and Other Cardiac Disorders

Atrial fibrillation (AF) is a cardiac arrhythmia that results from misfiring of the sino-atrial (SA) node which causes irregular conduction of the impulses to the ventricles ultimately resulting in a significantly reduced ejection fraction (EF) (Drake *et al.*, 2005). It has been shown that patients with AF have between a four- and five-fold increase in the incidence of stroke which is attributable to thromboembolism (Henriksson *et al.*, 2010; Uchiyama *et al.*, 2010; Rundek & Sacco, 2009; Mohr *et al.*, 2004).

Anti-coagulation and anti-thrombotic therapies are the most successful mechanisms for lowering the stroke risk in those individuals with AF. Warfarin is the most commonly used drug in these cases with a reduction in the overall risk of stroke by 68%. Aspirin has also been used due to its limited side-effects; however, it is significantly less effective when compared to Warfarin. Clinical trials are still being conducted on Ximelagatran, a thrombin inhibitor, which is believed to lower stroke risk in a similar range to Warfarin, however, concern exists over the potential side effects such as hepatotoxicity, and is therefore not yet been approved by the Food and Drug Administration (FDA) (Rundek & Sacco, 2009; Mohr *et al.*, 2004).

It has been consistently shown that a previous myocardial infarction (MI) is an independent risk factor for stroke, with most strokes occurring within two weeks following an acute MI. Older age and ventricular dysfunction, as well as diabetes all raise the risk further. The highest incidence of stroke was found in patients who suffered an anterior wall MI where a left ventricle thrombus was the probable cause (Rundek & Sacco, 2009; Witt *et al.*, 2006; Mohr *et al.*, 2004). Furthermore, it was also found that previous MI was a powerful predictor of prognosis following a stroke (Basile *et al.*, 2008). Cardiomyopathy has been implicated as another potential cardiac source for stroke occurrence with once again

thrombus formation as a result of left ventricular hypertrophy (LVH) being the probable cause. It has also been suggested that stroke can act as a “stressor” that induces cardiomyopathy although this still requires further investigation (Lee *et al.*, 2011).

1.5. *Smoking and Alcohol Use*

Smoking in itself is an independent risk factor for stroke as has been confirmed extensively in research, with a relative risk of 3.7 for all types of stroke and 9.8 for subarachnoid haemorrhage (SAH) (Brust, 2008). This can be seen in cases where hypertension was treated pharmacologically in smokers and non-smokers and it was found that the non-smokers had a reduced incidence of stroke, whereas the smokers had no change in stroke incidence (Brust, 2008). Furthermore, women who smoked while they were on oral contraceptives had a 15-fold increased risk for SAH, implicating oral contraceptives as a further possible risk factor for stroke (Brust, 2008; Mohr *et al.*, 2004). The mechanism behind increased stroke risk with smoking is thought to be related to the cerebrovascular changes induced by nicotine that include alterations in the cerebrovascular endothelium, breakdown of the blood-brain barrier (BBB), changes in cerebral blood flow and increased thrombus formation. This risk seems to be transferred to “non-smokers” who are exposed to environmental or passive smoke over a period of time with their risk of stroke almost matching their smoking counterparts. The cessation of smoking has been found to significantly reduce the risk of stroke, however, these levels never match those achieved by individuals who have never smoked or been exposed to environmental smoke over a period of time (Kim *et al.*, 2012; Weng *et al.*, 2011; Rundek & Sacco, 2009; Brust, 2008; Lee & Forey, 2006; Hawkins, Brown, & Davis, 2002).

Alcohol consumption in low to moderate quantities has been found to have a protective effect and lower the risk of stroke incidence when compared to high levels of alcohol consumption, thus exhibiting a J-shaped curve. It was also found that binge drinkers showed a similar risk profile to those that regularly consumed large quantities of alcohol. Extensive research has shown that haemorrhagic stroke risk is increased far more than ischemic stroke by a factor of 2.2 compared to 1.7. The proposed mechanism behind the increased risk of developing ICH or SAH is linked to the elevated fibrinolytic activity and decrease fibrinogen levels seen with high amounts of alcohol consumption (Rundek & Sacco, 2009; Brust, 2008; Mohr *et al.*, 2004; Gill *et al.*, 1991).

1.6. *Poor Diet*

While it is difficult to exactly define malnutrition it describes a deficiency, excess or imbalance in a wide variety of macro- and micro-nutrients that ultimately results in an adverse effect on normal bodily functioning. While high intake of total fat have commonly been implicated in increased stroke risk, recent research has shown that this may not necessarily be the case and it seems that the type of fat consumed might be a better predictor, with trans fatty acids (TFA's) and saturated fatty acids (SFA's) being shown to increase stroke risk (Apostolopoulou *et al.*, 2012; Hankey, 2012; Strazzullo *et al.*, 2004). Carbohydrates with a high glycaemic index (GI) or glycaemic load (GL) such as refined sugar or processed foods have generally been found to increase stroke risk due to the concomitant increase in body weight and insulin dysfunction. Protein in the form of fish, which is high in omega-3 fatty acids has been shown to decrease stroke risk by between six to 17%, while the consumption of poultry and nuts lowered the risk of stroke by 27 and 17%, respectively. However, it must be noted that consumption of red meat has been

found to increase the risk of stroke by up to 24% (Apostolopoulou *et al.*, 2012; Hankey, 2012; Mohr *et al.*, 2004).

Extensive research has shown that with a daily serving of at least five fruits and vegetables, stroke risk can be reduced by between 27 and 55% with recent research showing that for every one serving per day of fruit and vegetables, there is a six percent reduction in stroke risk. The Mediterranean diet which prioritizes a high intake of fruits and vegetables has consistently shown reduced stroke, cardiovascular and all-cause mortality over a number of years. High levels of sodium intake coupled with low potassium intake are a further risk factor for the development of stroke. Once again extensive research has shown that sodium levels lower than 2.3 g per day and potassium levels higher than 4.7 g per day showed a reduced risk of stroke. It is believed that the reduction in stroke risk seen with dietary modifications are as a result of the improvement in blood pressure that accompanies these changes (Apostolopoulou *et al.*, 2012; Hankey, 2012; Rundek & Sacco, 2009; Strazzullo *et al.*, 2004).

1.7. *Physical Activity and Obesity*

Physical activity is defined by the American College of Sports Medicine (2010:2) as:

“Any bodily movement produced by the contraction of skeletal muscles that result in a substantial increase over resting energy expenditure”.

Physical activity has consistently been shown to reduce cardiovascular and all-cause mortality through a number of different physiological pathways (American College of

Sports Medicine, 2010). Moderate to high intensity physical activity has been found to provide the greatest benefit with higher intensities providing slightly greater benefit. The beneficial effects of physical activity are related to its ability to regulate blood pressure, glucose levels and insulin sensitivity as well as blood lipid levels and body weight which ultimately results in a lower risk and incidence in stroke across both genders and all age and ethnic groups (American College of Sports Medicine, 2010; Rundek & Sacco, 2009; Silverthorn, 2007; Mohr *et al.*, 2004).

Regulation of hypertension and the magnitude of the reduction thereof is dependent on the frequency, intensity, time and type of exercise. Those individuals with hypertension are encouraged to exercise five to seven days a week at an intensity of 40% to 60% VO_2R (oxygen consumption reserve) and for longer than 30 minutes, performing a combination of both resistance and aerobic exercise as a general guideline (Gordon, 2009). Reductions in blood pressure vary from 4 mmHg to 11 mmHg for SBP and 2 mmHg to 8 mmHg for DBP (Guzel *et al.*, 2012; Davy & Gentile, 2007; Tsai *et al.*, 2004; Whelton *et al.*, 2002; Fagard, 2001; Hagberg *et al.*, 2000).

The control of glucose and insulin sensitivity in non-insulin dependent diabetes mellitus (NIDDM) is of utmost importance and the role of exercise cannot be understated. A combination of resistance and aerobic exercise is indicated with the mode varying according to co-existing complications. Exercise of a low to moderate intensity (50-80% VO_{2max}) and longer than 30 minutes is indicated. A number of studies have revealed a decrease in glycosylated haemoglobin (HbA_{1c}) by 0.3% to 1.2% over a period of 6 months or more, as well as reductions in fasting blood glucose (FBG) by 0.6 mmol/L to 2.2 mmol/L (Sung & Bae, 2012; Church, 2011; Colberg, 2006; Miller & Dunstan, 2004; Maiorana *et al.*, 2002).

The effect of exercise on blood lipids has received substantial attention over the past few years. It is recommended that those individual's suffering from hyperlipidaemia (high lipid levels) exercise at least four to five days a week for longer than 30 minutes and include both resistance and aerobic exercise. A few published studies have suggested that exercise frequency in this population is of greater importance than intensity, with five days or more being optimal (Durstine *et al.*, 2009; Kim *et al.*, 2001; Wei *et al.*, 1997). Decrease in total cholesterol, triglycerides and LDL-C are reported to be 11 mg/dL to 15 mg/dL, 8 mg/dL to 10 mg/dL and 6 mg/dL to 17 mg/dL respectively with an increase in HDL-C of 3 mg/dL to 6 mg/dL (Guzel *et al.*, 2012; Sung & Bae, 2012).

Obesity is defined as a body mass index (BMI) greater than 30 kg.m⁻² and is an independent risk factor for cardiovascular and all-cause mortality. Android obesity, which is characterized by fat deposition around the abdomen (visceral fat), has been shown to increase the risk of developing hypertension, NIDDM, dyslipidemia, metabolic syndrome, coronary artery disease (CAD) and stroke when compared to individuals who presented with gynoid obesity which is characterized by fat deposition on and around the hip and thigh region (American College of Sports Medicine, 2010; Rundek & Sacco, 2009; Mohr *et al.*, 2004). Obesity increases the relative risk of stroke by a factor of between 1.5 and 2.0, with its mechanism proposed to act through cytokines secreted by the adipose tissue known as adipokines. The adipokine leptin has consistently been shown to be related to stroke risk with adiponectin, resistin and hepatocyte growth factor (HGF) returning conflicting results, thereby necessitating further research into their potential effects on stroke risk and incidence. An interesting observation that has been noted in the literature is that of the "obesity-stroke paradox" where overweight and obese individuals had a significantly lower risk of early and 10 year mortality when compared to their normal weight counterparts. Further research is needed to try and explain this paradox (Katsiki, Ntaios, &

Vemmos, 2011; Savopoulos *et al.*, 2011). With the diagnosis of obesity occurring at very young ages in modern society, the findings of a study conducted by Deutsch *et al.* (2009) are particularly concerning as they found that diet-induced obesity at a young age causes a number of changes in the cerebral vasculature and increases the risk and subsequent damage following an ischemic stroke.

1.8 Homocysteneimia

Homocysteine (Hcy) is a metabolic by-product of methionine metabolism, with high levels being implicated in the risk of developing cardiovascular diseases and disorders, including stroke. Common causes of elevated Hcy include a lack of folic acid and cobalamin, various medications, renal disease and inherited metabolic defects such as genetic mutations. These high levels of Hcy cause endothelial dysfunction, promote atherosclerosis, decrease nitric oxide (NO) levels and impair the action of a number of anticoagulants. Those with high levels of Hcy had a relative risk of 1.82 for strokes when compared to those with low-normal levels of Hcy, with this incidence being supported by a number of further studies. In addition to increasing the risk of stroke it has also been found that high levels of Hcy may lead to brain atrophy coupled with impairment in verbal memory and fine motor speed. Further research is however warranted to corroborate this finding (Dhamija *et al.*, 2009; Rundek & Sacco, 2009; Sachdev, 2004; Deloughery, 2002).

2. Non-Modifiable Risk Factors

2.1. Gender

Research into the differences in stroke risk between men and women is still on-going as there are still a number of 'grey' areas. There seems to be a general consensus, however, that men are at higher risk than women up until a woman starts menopause and after the age of 75 years where the difference in risk diminishes and both genders are equally likely to suffer from a stroke. However, there is some evidence that women above the age of 75 years have a greater risk than men (Mohr *et al.*, 2004). Interestingly, it has been found that men are more likely to have the traditional risk factors of diabetes mellitus (DM), previous cardiovascular event, excessive alcohol consumption and smoking. On the contrary, it was found that women were more likely to have atrial fibrillation, hypertension and obesity. It was further noted that women were at a greater risk for having cardioembolic strokes as well as subarachnoid haemorrhage (SAH), whereas men were more likely to have lacunar infarctions and intracerebral haemorrhages (ICH's) (Sealy-Jefferson *et al.*, 2012; Katsiki *et al.*, 2011; Mohr *et al.*, 2004).

The cardioprotective effects of oestrogens have been proposed as the protective mechanism that lowers the risk of stroke in the pre-menopausal women. Oestrogens aid with the restoration of endothelial dysfunction, enhance vasodilation and have antioxidant and anti-inflammatory properties. Furthermore, oestrogens have neuroprotective properties thereby aiding in neural cell proliferation and axonal regeneration following a brain injury. Progesterone also has antioxidant and neuroprotective properties and has been found to decrease lesion size and improve overall recovery following a brain injury. Interestingly, hormone replacement therapy (HRT) in post-menopausal women carries a

cardiovascular risk that is caused by the proatherogenic response when supra-physiological doses of oestrogens are administered together with progestin (Katsiki *et al.*, 2011; Silverthorn, 2007).

There are a number of changes that occur during menopause that cause the increased risk of stroke in post-menopausal women. These changes include changes in body fat distribution and lipid concentrations (increase in LDL-C and triglycerides with a decrease in HDL-C), increasing blood pressure, increases in fibrinolytic and inflammatory markers as well as the increased prevalence of the metabolic syndrome. This has been corroborated by research conducted by Lisabeth *et al.* (2009) where they found that women with an early onset menopause (<42 years of age) had an increased risk of stroke compared to those who entered menopause at a later age (between 42-54 years). There are a number of hormone-independent mechanisms that provide women with a lower risk for stroke which include a greater resistance to ischemic stress and ischemic cell death, as well as decreased risk of multi-organ failure (MOF) and in-hospital infection following a haemorrhagic stroke when compared to men (Sealy-Jefferson *et al.*, 2012; Katsiki *et al.*, 2011).

2.2. Age

The risk of stroke increases with advancing age, with the relative risk being very low under the age of 45 years. With each advancing decade the risk of stroke almost doubles with the average age of onset being approximately 75 years. As mentioned above there are gender differences between men and women with regards to both risk and age of onset, with men being at higher risk below the age of 75 years, where after women are found to have higher risk from age 75. It has been proposed that the increased risk in women

above 75 years is due to fact that women generally tend to live longer than men, although further research is still needed to clarify this finding (Sealy-Jefferson *et al.*, 2012; Hildick-Smith, 2000a).

Interesting ethnic differences have been found relating to the age of onset of stroke with where African populations have a lower age of onset (between 35 – 65 years) compared to Caucasian, Hispanic and Asian populations (between 65 – 85 years), however recent research has shown that the average age of onset in developed countries is increasing (Shiue, 2011; Mohr *et al.*, 2004).

2.3. *Ethnicity*

The question of whether ethnicity plays a role in stroke risk has been investigated for many years and a number of interesting findings have been made. It appears that there is general consensus that African Americans have a higher overall relative stroke risk (and subsequent mortality) than European Caucasians, American Indians, Hispanics as well as Asians. It has been proposed that the higher levels of obesity, diabetes and hypertension as well as lower socio-economic status in this population account for the increased risk and mortality (Forouhi & Sattar, 2006; Mohr *et al.*, 2004; Caplan & Moelter, 2000). Recent research conducted by Sealy-Jefferson *et al.* (2012) has shown that above the age of 60 years, Mexican Americans (MA) had a higher relative risk of stroke than Non-Hispanic Whites (NHW), which is in agreement with a study conducted by Forouhi and Sattar (2006).

Within the South African context we find similar results with the prevalence of hypertension being highest in the black and coloured populations, with women having a higher

prevalence than men (Hasumi & Jacobsen, 2012). The respective diets of these population groups has been proposed as a possible cause, with high sodium intake being a commonality due to its high levels in bread, margarine and various gravies or soups (Bertram *et al.*, 2012). It has been proposed that the high prevalence of HIV/AIDS in South Africa may contribute to the higher levels of hypertension, however, a recent study by Malaza *et al.* (2012) found that both men and women who received anti-retroviral therapy (ART) had lower SBP and DBP as well as a lower incidence of stage I and stage II hypertension. Two interesting studies by Bell *et al.* (2010) and Mels *et al.* (2012) have implicated a lack of social support and high levels of L-Carnitine and long-chain acylcarnitines in the development of hypertension, with both of these being risk factors in black populations.

Diabetes, both IDDM and NIDDM is on the rise in South Africa and has its highest prevalence amongst black South Africans (Peer *et al.*, 2012). This finding, specifically related to NIDDM, implicates the obesity epidemic that is rife within the black South African population and is a major contributing factor to insulin resistance (Peer *et al.*, 2012). The incidence of diabetes in South Africa is approximately 3.9%, with women being more affected than men. Furthermore, the presence of microalbuminuria, a predisposing factor to the development of diabetes is more prevalent in black populations within South Africa (Kalk *et al.*, 2010; Mbanya *et al.*, 2010). A possible implicating factor in the development of NIDDM within South Africa is the high prevalence of HIV/AIDS and the subsequent use of anti-retrovirals (ARVs) which predispose the individual to development of the metabolic syndrome (Mbanya *et al.*, 2010).

Another recent study examined whether biomarkers that could potentially predict further cardiovascular events were influenced by ethnicity. The study found that biomarker risk

association with cardiovascular disease (CVD) events incidence was significantly influenced by ethnicity with a positive association being found for C-reactive protein (CRP) with Caucasians, interleukin-6 (IL-6) with African Americans, and fibrinogen among Caucasians, African Americans and Hispanics, with no association found in the Asian population. This research provides an interesting platform for physicians when identifying those patients who are at risk of future CVD through the use of biomarkers (Veeranna *et al.*, 2012).

2.4. Family History

Conflicting results have been found when assessing whether a family history of stroke (FHS) is associated with an increased risk of stroke. There is a definite genetic link to stroke risk as has been seen in twin studies that have shown that monozygotic twins have a five times higher risk of stroke occurrence than dizygotic twins. Furthermore, a history of parental death from stroke was associated with a three-fold increase in risk for stroke. While research has been conducted into examining the gene's that could be responsible for this increase in stroke risk, there is conflicting evidence. Concrete evidence has however been found linking the Gln506 allele, G20210A as well as the gene responsible for encoding methyltetrahydrofolate reductase (MTHFR) to ischemic stroke (Choi *et al.*, 2009; Tonk & Haan, 2007).

Hypertension and hypercholesterolemia are conditions most readily transferred from parents to children and are the other possible factors that account for the increased risk of stroke in certain families (Choi *et al.*, 2009). Polychronopoulos *et al.* (2002) showed that there was a strong positive association between FHS and all stroke types, as well as the large and small-artery disease subtypes (lacunar infarctions). The incidence of stroke in

young women is relatively low, however, a number of studies have examined the link between FHS and stroke risk and/or incidence in women between the ages of 18 and 50 years. The results were conflicting, with the study by Kim *et al.* (2004) finding a significant positive correlation, whereas Siegerink *et al.* (2012) only reported a weak correlation. More research is required in this specific population group to provide more definitive.

E. PREVALENCE OF STROKE

1. Global Prevalence

The World Health Organization (WHO) estimated in 2005 that there were an estimated 9 million strokes world-wide of which 5.7 million people died as a result of stroke. This was more than the 5.5 million to have died in 2002. The mortality rate in low- to middle-income countries is significantly higher than that of the higher income countries and has been confirmed by a number of studies (Bennett *et al.*, 2012; Chin, 2012; De Villiers *et al.*, 2011; Mayosi *et al.*, 2009; Strong & Mathers, 2004). On average there are between 151 – 251 deaths per 100 000 people in Eastern Europe, Northern Asia, Central Africa and the South Pacific (considered low- to middle-income regions), compared to an average of between 25 – 50 deaths per 100 000 people in the United States, Western Europe and Australia (considered high-income areas). It is estimated that by the year 2015, first-ever strokes would rise to 10.5 million, with 6.6 million resulting in death, and that by the year 2030 there would be 13.2 million first-ever strokes with 8.2 million deaths as a result (Bennett *et al.*, 2012; Johnston, Mendis, & Mathers, 2009; Strong & Mathers, 2004). A more recent study by Mukherjee and Patil (2011) found that in the absence of any meaningful clinical or public health interventions the number of first-ever strokes would rise to 23 million by 2030, with 7.8 million resulting in death. Alarmingly, the number of stroke deaths in middle

income countries is likely to increase only a fraction, whereas a steep increase in stroke deaths are estimated to occur in low- to middle-income countries by 2030 (Mukherjee & Patil, 2011; Strong & Mathers, 2004).

In cases where stroke does not result in death, disability-adjusted life years (DALYs) are calculated to estimate the burden of stroke. DALYs for a disease or injury are calculated as the sum of the years of life lost (YLL) owing to premature mortality and the years of life lost due to disability (YLD). In essence, one DALY can be thought of as one “healthy” year of life lost. The statistics for DALYs in low- to middle-income countries are alarming when one considers this with between 1041 – 2200 DALYs lost per 100 000 people in comparison to between 160 – 400 DALYs lost per 100 000 people in the high-income countries (Mukherjee & Patil, 2011). The economic impact of stroke in these countries is an area of concern with between \$20 million and \$1 billion dollars of the GDP being lost as a result of vascular diseases. It is estimated that if prevention is not improved this figure will rise to \$84 billion by the year 2015. The WHO’s goal is to reduce death and lost DALYs attributable to chronic disease by two percent over the next 10 years which would equate to 36 million less deaths worldwide, a 75 million cumulative life year gain and an estimated \$8 billion reduction in loss of GDP worldwide. While this seems difficult in theory to achieve in low- to middle-income countries due to poor infrastructure, countries such as Australia, South Korea, Singapore and the United Kingdom have decreased their death rates from chronic disease by more than two percent, indicating that this goal may be attainable (Mukherjee & Patil, 2011).

It is estimated that of the two types of stroke, ischemic and haemorrhagic stroke, ischemic accounts for between 73 to 90% in high income countries and 54 to 85% in low- to middle-income countries, while haemorrhagic stroke accounts for 10 to 29% in high income

countries and 29 to 37% in low- to middle-income countries. The WHO has also calculated the contribution of eight risk factors to DALYs lost, with hypertension and tobacco smoking contributing most in high-income countries and hypertension and diabetes contributing most in low- to middle-income countries (Bennett *et al.*, 2012; Strong & Mathers, 2004).

2. Prevalence in South Africa

The stroke incidence rate in South Africa has been found to match those of more affluent nations with one big difference; that being the number of individuals left disabled after their first stroke. Figures released in 2004 put the prevalence at approximately 300 per 100 000 people with almost 66% of these survivors requiring assistance for at least one activity of daily living (ADL). This is in stark contrast to the higher-income countries where only approximately 20% of survivors require assistance for the ADLs (Hayward, 2004). A study published by Connor *et al.* (2007) illustrated this point clearly when they found that of the 596 stroke survivors, 406 patients required assistance with one or more of their ADLs, a staggering 68%. In comparison, for the same time period, New Zealand had 1697 stroke survivors of which only 344 patients required assistance with one or more of their ADLs. This equates to 20% which is substantially lower and in agreement with the literature.

The chief reason given for the high levels of disability seen following a stroke is the poor standard of post-stroke care and lack of rehabilitation facilities in the rural areas of South Africa. Epidemiological data shows that black South Africans have a higher prevalence of stroke when compared to white South Africans, although there were no differences in stroke severity. However, black South Africans were found to have a higher incidence of haemorrhagic strokes, possibly due to the lower levels of cholesterol seen in black populations in Sub-Saharan Africa. Furthermore, socio-economic status played a major

role in functional outcome three and six months post-stroke with those who had a lower socio-economic status presenting with a poorer functional outcome (De Villiers *et al.*, 2011; Bryer, 2009; Connor, Modi, & Warlow, 2009).

As is the global trend, stroke incidence increases with advancing age, which has been confirmed with South African statistics. During the time period of 1992 to 2006, stroke was found to be one of the leading causes of death in South Africa in both men and women, accounting for up to 20% of total deaths in the 50 – 64 years age category and up to 16% in the above 65 years age category (Mayosi *et al.*, 2009; Tollman *et al.*, 2008).

F. COMMON MANIFESTATIONS OF STROKE

The clinical manifestations following a stroke are largely dependent on the location and size of the lesion, and display a large intra-person variation, even when lesion and location are identical. However, there seems to be certain common symptoms that accompany damage to a particular region of the brain (Caplan & Moelter, 2000). Due to the extensive number of symptoms seen in stroke patients, only four of the most common ones will be discussed briefly further. These are hemiplegia, a motor deficit; agnosia and aphasia, both sensory deficits, and cognitive dysfunction.

1. Hemiplegia

The main cause of disability following a stroke is hemiparesis on the contralateral side of the lesion location and may involve either the upper extremities, lower extremities or both (Hildick-Smith, 2000a). The hypertonicity that accompanies strokes contributes significantly to reduced quality of life as well as activity limitation (Laurent *et al.*, 2011;

Marciniak, 2011). Generally the hypertonicity occurs in the flexors of the arm and the extensors of the leg (Hildick-Smith, 2000a). The positioning of the upper extremity is of concern as the shoulder is in a position of adduction and internal rotation, which over time can result in soft tissue shortening and the formation of a contracture (Namdari *et al.*, 2012; Marciniak, 2011). In some cases hemiplegia is accompanied by anosognosia which is an unawareness of the motor deficit or paralysis following a stroke. More recently the term anosognosia has been used to describe any form of unawareness or lack of insight following injury or illness (Jenkinson, Preston, & Ellis, 2011; Preston, Jenkinson, & Newport, 2010).

There are a number of treatment options for the hypertonicity seen with stroke. In cases where the lower extremities have been involved, recent research has found that immersion of the limbs in water of 41 °C resulted in significant decreases in spasticity that allowed for better quality and ease of movement (Matsumoto *et al.*, 2010). When the upper extremities are involved, two methods are commonly used to improve shoulder functioning. These two methods are muscle release and tendon lengthening, and botulinum toxin A (Botox) which is injected intramuscularly. Both methods have been shown to positively affect shoulder range of motion (ROM), functional ability as well as significantly reducing pain levels (Namdari *et al.*, 2012; Rosales, Kanovsky, & Fernandez, 2011).

Rehabilitation of gait is particularly challenging in the stroke population suffering from hemiparesis due to the presence of a “drop foot” which results from ankle dorsiflexor weakness. Botox, as well as intensive strengthening of the ankle dorsiflexors of the affected limb have been shown to significantly improve performance on the six minute walk test, as well as improve joint mobility and ankle kinematics (Ng & Hui-Chan, 2012; Novak *et al.*, 2009).

2. Agnosia and Aphasia

Agnosia is defined as a partial or complete inability to recognise sensory stimuli that cannot be explained by defects in basic sensation or diminished alertness and can be subdivided into visual, auditory and somatosensory agnosia. Visual agnosia occurs as a result of a lesion in the occipital temporal region which is perfused by the posterior cerebral artery (PCA). Often patients with visual agnosia present with an impairment of visual object recognition. It has an incidence rate of between three and eight percent and may or may not be accompanied by visual field loss (Martinaud *et al.*, 2012; Rowe, 2009; Caplan & Moelter, 2000). Auditory agnosia is characterised by the inability to recognise sounds in the presence of intact hearing and is usually caused by a lesion in the left or right temporal lobe. A person may suffer from verbal or non-verbal auditory agnosia, with right-sided lesions resulting in non-verbal agnosia and left-sided lesions resulting in verbal agnosia (Saygin, Leech, & Dick, 2010; Mendez, 2001; Caplan & Moelter, 2000). Somatosensory agnosia occurs as a result of a lesion in the parietal lobe and is characterized by difficulty in perceiving objects through tactile stimulation despite an otherwise intact somatosensory capacity. Often patients will demonstrate impaired recognition of shape, size (macrogeometrical) and texture (microgeometrical) of objects (Baizabal-Carvallo, Estanol, & Senties-Madrid, 2008; Caplan & Moelter, 2000).

Aphasia is characterized by an impairment of language comprehension or production and has five subtypes. Broca's aphasia occurs as a result of damage to Broca's area in the brain and is characterized by poor articulation and non-fluent output, but reasonable comprehension. Wernicke's aphasia occurs as a result of damage to Wernicke's area in the brain and is characterized by fluent, albeit basic output, with poor comprehension capacity. Individuals with conduction aphasia have a reasonably fluent output and

adequate comprehension, however, struggle with auditory-verbal memory and repetition. Global aphasia is characterized by significant impairment in both expressive and receptive language functions. The last type of aphasia is known as anomia and is characterized by a deficit in word-finding with good language comprehension, fluency and repetition. All aphasia's occur as a result of damage to the left hemisphere and is seen in approximately one third of all stroke patients in the acute phase (Sinanovic, 2010; Caplan & Moelter, 2000). The severity of aphasia at onset is a good predictor of final outcome with only eight percent of those with severe aphasia fully recovering, compared to 74% of those with mild aphasia (Maas *et al.*, 2012; Dobkin, 2011). Speech therapy has always been the traditional method to correct aphasia, however, non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) have shown great promise in enhancing functional recovery of language in patients with aphasia (Hamilton, Chrysikou, & Coslett, 2011).

3. Cognitive Dysfunction

Deficits in cognitive or executive function are common following a stroke and have a prevalence rate of between 19 and 75%. The components that make up executive function include initiation and planning, problem solving and strategy applications, inhibition, self-regulation as well as working memory, attention and insight. Dysfunction in any of the above-mentioned areas has a significant impact on the recovery of function, and rehabilitation thereof, following a stroke (Poulin *et al.*, 2012; Levine *et al.*, 2011; Zinn *et al.*, 2007). Recent research has shown a positive association between the magnitude of executive dysfunction and mortality rate, with the Trail Making Test (TMT)–A and –B, as well as digit span test shown to be accurate measurement tools in this regard (Ihle-Hansen *et al.*, 2012; Wiberg *et al.*, 2012; Tamez *et al.*, 2011). Furthermore, lesion size seem to

play an important role in executive dysfunction following stroke in both adults and children (Long *et al.*, 2011).

Traditional theories suggest that once part of the central nervous system (CNS) has been damaged, it is irreparable. However, recent research has examined the growing evidence of neuroplasticity, i.e. the ability of the CNS to remodel and restore itself as a compensatory mechanism. A number of imaging modalities such as functional MRI (fMRI) and diffusor tensor imaging (DTI) have shown the beneficial effects of TMS, functional electrical stimulation (FES) and other rehabilitative models in driving this process. The most commonly used rehabilitative model used in stroke rehabilitation is constraint-induced movement therapy (CIMT) which involves restraining the unaffected upper extremity for a number of hours during the day while the affected upper extremity is used to complete functional tasks. This method is used to retrain the paretic upper extremity from learned non-use behaviours and has shown great promise in a number of studies. In most studies CIMT has shown to improve functioning of the paretic arm as well as increasing the motor map area in the brain – an indication that neuroplasticity has taken place (Young & Tolentino, 2011; Hodics, Cohen, & Cramer, 2006). Additional treatment modalities include goal management training (GMT), as well as art therapy which have all shown far-reaching and diverse improvements in a number of the variables that comprise executive or cognitive functioning (Reynolds, 2012; Levine *et al.*, 2011).

G. ADDITIONAL REHABILITATION TECHNIQUES FOLLOWING A STROKE

Rehabilitation following a stroke is a complicated and multi-dimensional process that is carefully managed by occupational and physical therapists. Restoration of a certain degree of motor and cognitive functioning are of utmost importance to ensure a better health related quality of life (Muren, Hütler, & Hooper, 2008). Motor and cognitive function recover spontaneously in some cases up to a point, where after further intervention is necessary. Intervention strategies include the use of conventional treadmill and body weight-supported (BWS) treadmill training for the restoration of gait, constraint-induced movement therapy (CIMT) for the restoration of upper extremity functioning, as well as working memory and strategy training for the restoration of a number of the components that comprise executive function or cognition (Poulin *et al.*, 2012; Combs *et al.*, 2010; Langhammer & Stanghelle, 2010; Walker & Pink, 2009).

Retraining of gait is achieved through the use of physical therapy, robotic devices or functional electrical stimulation (FES), or a combination thereof. For the most part, physical therapy using neurophysiological and motor learning techniques has shown the most promise. Miyai *et al.* (2001) showed that when the control of movement of the paretic leg was facilitated by a physical therapist, improvements in both cortical activation and performance were seen compared to a mechanical device. Robotic devices are commonly used to train specific and task-orientated parts of gait, as well as functioning of the upper extremity, and provide more structural stability than a physical therapist can. Furthermore, the intensity of the training is often higher with the use of robotic devices and they provide excellent repeatability. FES is rarely used in isolation and is mostly combined with robotic therapy. The current generated by the FES causes muscle contraction, With FES electrodes can be strategically placed to elicit muscle contraction of the required muscles (Belda-Lois *et al.*, 2011).

Treadmill training has wider-reaching benefits aside from improvements in gait, as was seen in a study by Combs *et al.* (2010). They found that balance, balance confidence and overall health-related quality of life (HRQoL) improved in addition to the improvements in gait and walking performance. Traditional aerobic and resistance training have also been shown to have extensive benefits to a number of different motor areas, as well as cognition. This was documented by Michael *et al.* (2009) as well as Kluding, Tseng and Billinger (2011), where improvements in balance, gait, cardiorespiratory endurance as well as executive function were found. CIMT has been widely used as a rehabilitation technique for upper extremity dysfunction, with a number of studies providing evidence of its effectiveness in restoring a degree of functionality as well as cortical reorganisation (Wu *et al.*, 2011; Lin *et al.*, 2010). Imaging of changes that take place within the brain as a result of rehabilitation are achieved through the use of magnetic resonance imaging (MRI), positron emission tomography (PET), diffusion-tensor imaging (DTI) or transcranial magnetic stimulation (TMS) to name a few (Gottesman & Hillis, 2010).

Long-term outcome following rehabilitation is of utmost importance with two studies suggesting that, if rehabilitation is indicated in patients, and adherence to a rehabilitation programme is good, most of the functionality that is restored is maintained at follow up periods up to two years post-stroke (Olsson & Sunnerhagen, 2007; Musicco *et al.*, 2003).

H. SUMMARY

With the incidence of stroke on the increase, it becomes clear that a cooperative effort between patient and physician is necessary to tackle this debilitating condition. Adequate management of the modifiable risk factors, whether through pharmacological or non-pharmacological methods, or both, as well as education on these risk factors should set the foundation for a reduction in mortality as well as morbidity rates globally. The old antage of prevention is better than cure could not fit more suitably with this disease. However, the realities and challenges that accompany a stroke cannot be ignored and further research on various current, as well as novel treatment modalities should be explored to minimize the global burden of disease and disability that accompanies stroke.

CHAPTER THREE

NEAR-INFRARED SPECTROSCOPY

A. INTRODUCTION

While the science behind near-infrared spectroscopy (NIRS) has not changed significantly, the practical applications and uses have increased exponentially since first being discovered in 1977 (Jöbsis, 1977). NIRS provides both researchers and clinicians with a relatively non-invasive, yet reliable method for assessing and monitoring redox and saturation levels in their respective disciplines (Plichta *et al.*, 2006). While there are still some limitations to NIRS when compared to other traditional imaging methods such as functional magnetic resonance imaging (fMRI) and positron emission topography (PET), work is being done to eliminate these limitations as far as possible. This research is documented in a number of studies where MRI, PET and NIRS have been used as complementary imaging modalities in a clinical setting (Cui *et al.*, 2011; Elissen *et al.*, 2008; Ferrari, Mottola, & Quaresima, 2004; Villringer *et al.*, 1997).

B. PRINCIPLES OF NEAR-INFRARED SPECTROSCOPY

1. Near – Infrared Light

The near-infrared light range (NIL) is between 650 nm and 950 nm and has proven to be a useful technique for determining oxygen saturation levels in various tissues. Within this range, oxyhaemoglobin (O₂Hb), deoxy-haemoglobin (HHb) and cytochrome oxidase (CytOx) concentrations, and changes thereof, can be accurately measured through the

use of tissue oximeters (Ferrari *et al.*, 2004; Rolfe, 2000; Owen-Reece *et al.*, 1999; Madsen & Secher, 1999; McCormick *et al.*, 1992). Research has shown that O₂Hb has its peak absorbance at approximately 850 nm, whereas HHb has its peak absorbance at 760 nm, thereby allowing for a change in either of the two to be clearly seen and calculated (Madsen & Secher, 1999; McCully, Halber, & Posner, 1994). When NIL is propagated into the tissue, the principles of light absorption and scattering determine the degree of attenuation of the NIL, thereby providing information on the oxygen saturation levels of the respective tissue (Owen Reece *et al.*, 1999; McCormick *et al.*, 1992). The relatively high attenuation of NIL seen in biological tissue is due to oxygen-dependent absorption from chromophores of variable concentration, absorption from chromophores of fixed concentration or light scattering (Ferrari *et al.*, 2004).

2. Reflection, Absorption and Scattering of Light

When light is propagated into biological tissue, the transmission thereof is dependent on the reflectance, absorption and scattering effects of the specific tissue. Reflectance is defined as a function of the angle of a light beam relative to the tissue surface. Both absorption and scattering are wave-length dependent, with the degree of absorption being determined by the molecular properties of the tissue and the degree of scattering being determined by the wavelength of the Infrared (IR) light. Research has shown that scattering decreases with increasing wavelengths (Jöbsis, 1977). In a simple cuvette model, the degree of light lost after passing through a homogenous medium, is due to absorption only due to the fact that the distance the light travels is constant (Owen-Reece *et al.*, 1999). While this may be true of extremely simplified optical experiments, biological tissue is both complex and heterogeneous and therefore this principle cannot be applied (Rolfe, 2000).

The physical principle of reflection is often explained through the use of mirrors and lenses where the angle of reflection is equal to the angle of incidence, however, mirrors and lenses are not tissues capable of absorption of light and energy, thus this theory cannot be applied to biological tissue. When light is propagated into a tissue the angle is approximately 90 degrees, therefore the contribution of light lost to reflection is extremely low. This has been corroborated by Madsen and Secher (1999) suggesting that absorption and scattering account for the vast majority of light lost (Giancoli, 2005).

Absorption of light varies according to the type and molecular make-up of tissue and occurs at varying wavelengths of light. This was alluded to in the section on Infrared Light (B.1) where the difference in oxy- and deoxy-haemoglobin absorption were seen at differing wavelengths (Jöbsis, 1977). In the human head, the grey matter of the brain has the highest absorption coefficient with a value of between 0.025 mm^{-1} and 0.036 mm^{-1} , with the scalp accounting for the next highest absorption capabilities (Hoshi *et al.*, 2005; Okada & Delpy, 2003; Okada *et al.*, 1997).

Scattering in biological tissue takes place as a result of the difference in the refractive index of two adjacent tissues and can be either elastic or inelastic. Scattering accounts for the greatest proportion of light lost (Rolfe, 2000; Madsen & Secher, 1999). Refraction of light in biological tissues can be explained by Snell's Law which states that when light passes from one medium to another with a different index of refraction, part of the light is refracted or bent at the boundary or surface (Giancoli, 2005). Inelastic scattering occurs when the incident energy of the photon is absorbed by the scatter and then emitted at a different wavelength and energy. With elastic scattering, there is no change or loss of photon energy or wavelength. The photon energy merely moves in a different direction to that of the incoming energy (Rolfe, 2000).

In biological tissue there are three possible scattering patterns. Firstly, the possibility exists that the photon will remain essentially unscattered and passes through the tissue in a linear fashion, where the optical path length is the same as the distance between the entry and exit points. Secondly, photons may be scattered but maintain the same net direction which is termed forward scatter. Lastly, photons may exhibit a net direction of 180 degrees which is known as back scatter. Both forward and backward scatter cause the photon to travel distances that are far greater than that of the linear distance between the entry and exit points. The actual distance travelled by the photon in the tissue is expressed via the differential pathlength factor (DPF), which in a normal human head is 6.3. That is to say, light travels 6.3 times further than the straight line path between the entry and exit point, or the source and detector (Rolfe, 2000; Owen-Reece *et al.*, 1999).

3. Variables Measured

The variables that are measured by NIRS can be accurately measured due to a continuous wave light between 600 nm and 1000 nm, in combination with the modified Beer-Lambert Law as well as spatially and time resolved spectroscopy (SRS/TRS) (Ferrari *et al.*, 2004). The Beer-Lambert Law (*Equation 3.1*) is often used in physics to determine the chemical concentration of compounds or solutions:

$$A = \epsilon[C]L \quad (3.1)$$

Equation 3.1. Beer-Lambert Equation for calculating differences in concentrations of chemical compounds or solutions where A is defined as the attenuation, ϵ is the extinction coefficient, $[C]$ is the micromolar concentration, and L is the internal dimension of the cuvette (Rolfe, 2000).

In biological compounds, however, light is attenuated due to scattering from the various tissues. Therefore, the modified Beer-Lambert Law (*Equation 3.2*) was devised to account for this change:

$$A = \log \left[\frac{I_0}{I} \right] = \epsilon[C]Lx + K \quad (3.2)$$

Equation 3.2. Modified Beer-Lambert Equation for calculating differences in concentrations of chemical compounds or solutions where light scatter is taken into account where A is defined as the attenuation, I_0 is the light entering, I is the light exiting, ϵ is the extinction coefficient, $[C]$ is the micromolar concentration, L is the linear distance, x is the pathlength factor and K is the tissue loss constant (Hamamatsu Photonics Deutschland, 2012).

It has been extensively reported that absolute O_2Hb and HHb values cannot be calculated using traditional NIRS methods and formulae, therefore relative changes has been proposed as an accurate measurement of the changing physiological environment. The relative changes are mathematically represented by *Equation 3.3*:

$$\Delta A = (A_2 - A_1) = \Delta[C]\epsilon Lx \quad (3.3)$$

Equation 3.3. Calculation used for determining changes in concentration where tissue loss is accounted for where A_1 and A_2 are defined as the attenuation of light at two different time points, $[C]$ is the micromolar concentration, ϵ is the extinction coefficient, L is the linear distance and x is the pathlength factor (Hamamatsu Photonics, Deutschland, 2012).

With the advent of time or spatially resolved spectroscopy (TRS or SRS), absolute quantification of saturation levels via NIRS has been made possible. A strong correlation between tissue saturation and tissue oxygenation index (TOI) has been found by some authors (Ferrari *et al.*, 2004; Quaresima, Komiyama, & Ferrari, 2002). Due to the relative placement of the light emitter and detector adjacent to one another, the levels of scattering

(k) in the tissue are relatively similar at both sites; therefore the attenuation of light is as a result of the absorptive properties of the tissue only (Ferrari *et al.*, 2004; Rolfe, 2000).

Tissue oxygenation is calculated by *Equation 3.4*:

$$TOI = \frac{kO_2Hb}{kO_2Hb+kHHb} \quad (3.4)$$

Equation 3.4. Formula for calculating tissue oxygenation where k is the constant for scattering, O₂Hb is oxyhaemoglobin and HHb is deoxy-haemoglobin (Hamamatsu Photonics, Deutschland, 2012).

Due to the short distance the light has to travel, the effect of scattering on the attenuation of light in the tissue is minimal, therefore, the simplified formula for calculating tissue oxygenation where the scattering constant is mathematically removed, is *Equation 3.5*:

$$TOI = \frac{O_2Hb}{O_2Hb+HHb} \quad (3.5)$$

Equation 3.5. Simplified formula for calculating tissue oxygenation where the scattering constant is mathematically removed, where O₂Hb is oxyhaemoglobin and HHb is deoxy-haemoglobin (Hamamatsu Photonics, Deutschland, 2012).

The total haemoglobin index (THI) is also calculated through the use of SRS and is a measure of the total haemoglobin content within the tissue being measured. Once again, the effect of light attenuation due to scattering is minimal due to the instrumentation set-up, however the scattering constant remains as it is not possible to mathematically simplify the formula. THI is calculated by the formula indicted below (*Equation 3.6*):

$$THI = kO_2Hb+kHHb \quad (3.6)$$

Equation 3.6. Formula for calculating the total haemoglobin index within the tissue where k is the constant for scattering, O₂Hb is oxyhaemoglobin and HHb is deoxy-haemoglobin (Hamamatsu Photonics, Deutschland, 2012).

Aside from the direct measurement of O₂Hb, HHb and oxygen saturation, NIRS has been used extensively as an indirect measure of both muscle and cerebral blood flow as well as cerebral blood volume (Ferrari *et al.*, 2004; Owen-Reece *et al.*, 1999). Both these measurement variables will be covered in a later section.

4. Validity and Reliability of NIRS

NIRS is a non-invasive techniques and has been clinically shown to be a reliable and valid measurement tool for determining changes in oxygenation in both cerebral and muscle tissue (Madsen & Secher, 1999). Research has shown that both the temporal and spatial sensitivity of NIRS are comparable to more traditional imaging modalities such as fMRI and PET (Strangman, Boas, & Sutton, 2002; Villringer *et al.*, 1997). Furthermore, both clinical and physiological validation have been published across various conditions (Cui *et al.*, 2011; Madsen & Secher, 1999). Although TOI is rarely reported in the literature, a number of studies have shown that it has high spatial sensitivity and specificity, which would allow for the results to be interpreted with a greater degree of certainty (Yoshitani & Ohnishi, 2008; Al-Rawi, Smielewski, & Kirkpatrick, 2001). NIRS has also been shown as a reliable measure for tracking changes that result from rehabilitation following stroke, both in the short- and long-term (Strangman *et al.*, 2006).

C. USES OF NIRS

1. Indications

As mentioned previously, traditional imaging modalities such as MRI and PET have often been used in both healthy and diseased populations to quantify various parameters, but

with the advancement of NIRS technology, more clinical indications for NIRS have emerged (Ferrari & Quaresima, 2012). Most commonly, NIRS is used for foetal, neonatal and infant cerebral oxygenation monitoring as most other neuroimaging methods are not feasible in this population (Strangman *et al.*, 2002; Rolfe, 2000). Research into changes in muscle oxygenation during both acute and prolonged exercise, as well as adaptive changes that take place as a result of long-term resistance and aerobic training have been studied extensively with NIRS (Neary, 2004; Rolfe, 2000). A further research area that is common to NIRS is that of psychology, specifically anxiety, schizophrenic and personality disorders where differences regarding cerebral activation patterns as well as cerebral haemodynamics are investigated (Ferrari & Quaresima, 2012; Strangman *et al.*, 2002). Chronic diseases such as Alzheimer's Disease, Parkinson's Disease and stroke have also been studied extensively (Ferrari & Quaresima, 2012; Strangman *et al.*, 2002; Rolfe, 2000). In healthy populations, NIRS is used to examine gender differences regarding brain activation patterns during various cognitive tasks as well as cerebral haemodynamic differences during periods of low and high cortical activation (Ferrari & Quaresima, 2012).

2. Cerebral Blood Flow and Cerebral Blood Volume at Rest

There are two common methods for measuring both cerebral blood flow (CBF) and cerebral blood volume (CBV) via NIRS. The first method is to use indocyanine green (ICG) as an intravascular tracer, and by applying the Fick principle, determine quantitatively CBF and CBV as the tracer enters into the circulation within the brain (Pellicer & Bravo, 2011; Ferrari *et al.*, 2004; Madsen & Secher, 1999). The Fick principle states the following:

“The amount of substance taken up by an organ per unit time is equivalent to the difference between the rate of the arrival of the substance and the rate of departure of the substance from the organ”

(Pellicer & Bravo, 2011:44).

The rate of arrival of the substance is calculated as the product of blood flow through the organ and arterial concentration of the substance, while the rate of departure is calculated as the venous concentration of the substance (Pellicer & Bravo, 2011). The second method is to use 100% oxygen as an intravascular tracer, once again using the Fick principle. Importantly with both methods is that measurements must be taken within four seconds after the application of the tracer as venous outflow is considered to be zero, therefore any accumulation of the tracer or oxygen in the brain is assumed to be entirely as a result of arterial inflow. Changes in total cerebral haemoglobin (HbT) have also been shown to be a good indicator of changes in CBV (Pellicer & Bravo, 2011; Ferrari *et al.*, 2004; Madsen & Secher, 1999; Owen-Reece *et al.*, 1999). A final method used to measure both CBF and CBV is transcranial Doppler measurements, although this method does have a limitation in that the observed changes in the CBF velocity may be caused by changes in the integrity of the insonated vessel (Owen-Reece *et al.*, 1999).

3. Cerebral Blood Flow and Cerebral Blood Volume during Neural Activation

Brain activation, otherwise known as cortical activation, causes a number of changes to cerebral haemodynamics and varies according to the type of activity (Villringer & Chance, 1997). Typically, with increased brain activity, an increase in oxyhaemoglobin (O₂Hb) and a decrease in deoxy-haemoglobin (HHb) are seen which correspond with the increase in cerebral blood flow. There is also a concomitant increase in total cerebral haemoglobin

(HbT), or Total Haemoglobin Index (THI) which corresponds with the increase in cerebral blood volume (Ferrari *et al.*, 2004; Villringer & Chance, 1997; Obrig *et al.*, 1996). These findings have been corroborated by a number of authors. Schroeter *et al.* (2004) found that when children performed a cognitive task, there was a significant increase in O₂Hb together with a significant decrease in HHb. Similar patterns have been observed in the adult population with the application of basic arithmetic and simulation games (Sakatani *et al.*, 2006; Villringer *et al.*, 1993).

While there is general consensus that there is an increase in O₂Hb and HbT, there is evidence to suggest that HHb does not always follow the same pattern. A number of authors have reported that during cortical activation in healthy adults, HHb may increase, decrease or not change significantly at all (Ehlis *et al.*, 2005; Meek *et al.*, 1995; Villringer *et al.*, 1994). An interesting finding by Toichi *et al.* (2004) was that tasks that require higher cognitive processing, produced the typical haemodynamic response, which is an increase in O₂Hb and HbT and decrease in HHb, whereas tasks of attention saw an increase in both O₂Hb and HHb without the increase in HbT.

4. Cerebral Blood Flow and Cerebral Blood Volume during Exercise

Cerebral haemodynamics during exercise are slightly different than at rest, with low level exercise ($\leq 30\%$ VO_{2max}) causing a slight decrease or no change in deoxy-haemoglobin (HHb) levels with a concomitant increase in oxyhaemoglobin (O₂Hb) levels and total haemoglobin levels (HbT). Higher intensity exercise ($\geq 60\%$ VO_{2max}) cause a greater increase in O₂Hb and HbT compared to low intensity exercise, together with an increase in HHb levels (Ide & Secher, 2000; Ide, Horn, & Secher, 1999). Interestingly, maximal exercise (all-out effort) that is performed with a large muscle mass cause a slight decrease

in cerebral oxygen saturation which, if prolonged, may lead to central fatigue. This was clearly demonstrated when two groups of rowers, one with supplemental oxygen and one without, performed a six minute all out row. Those who did not receive oxygen supplementation showed a significant drop in cerebral oxygen saturation, whereas those who received supplementation maintained their cerebral oxygen saturation as well as increasing power output (Madsen & Secher, 1999; Nielsen *et al.*, 1999). This finding is further corroborated by Perrey (2008) where it was found that a reduction in cerebral oxygenation precedes muscular fatigue, thereby acting as a potential protective mechanism to prevent irreversible damage to organs and tissues.

Ageing was proposed as a factor which may alter cerebral haemodynamics during exercise with Lucas *et al.* (2012) finding that younger individuals (24 ± 5 years) showed a decrease in O₂Hb at low intensity exercise (30% heart rate reserve - HRR), with an increase in HHb, whereas in older individuals (62 ± 3 years) O₂Hb was unchanged at low intensity exercise. However, at higher intensity exercise (70% HRR), both groups had an increase in O₂Hb and HHb.

5. Factors Affecting the NIRS Measurements

5.1. Skin Blood Flow

Due to the NIRS probes being placed directly on the scalp, there is a high likelihood that blood flow to the skin may affect the measurements. Increases in skin temperature or redistribution of blood will cause changes to the various haemodynamic variables. This has been documented in muscle physiology by Davis *et al.* (2006) where he found that increased total and localized body heat caused an increase in tissue oxygenation. There is

conflicting evidence about the effect of blood flow to the scalp on NIRS measurements. When scalp blood flow is controlled via a tourniquet, several authors have found that scalp blood flow has no to minimal effect on the NIRS measurement parameters (Owen-Reece *et al.*, 1996; Elwell *et al.*, 1994). However, recent research has shown that when performing a verbal fluency task, changes in scalp blood flow were a major contributing factor to the change in oxyhaemoglobin (O₂Hb) concentration (Takahashi *et al.*, 2011).

5.2. Skull Thickness and Cerebrospinal Fluid (CSF) Area

There is extreme variability between individuals with respect to skull or cranial thickness, as well as the area between the skull and the grey matter of the brain which is occupied by cerebrospinal fluid (CSF) (Okada & Delpy, 2003). As mentioned earlier, the skull has a relatively small absorption coefficient, but a moderate scattering coefficient which contributes to the effect on NIRS measurements (Okada *et al.*, 1997). Skull thickness varies between four to 20 millimetres in humans with only small differences found between men and women (Yoshitani *et al.*, 2007; Lynnerup, 2001). Hagemann *et al.* (2008) found that skull thickness had minimal effect on EEG activity and proposed that individual differences in brain activity accounted for the change. Contrary to this, Yoshitani *et al.* (2007) found that cranial thickness had a significant impact on regional cerebral saturation, however, TOI was not affected. The area occupied by the CSF varies between 0.25 cm² and 0.52 cm² and generally has the lowest scattering and absorption coefficient. Despite this, numerous authors have suggested that the CSF may affect the NIRS measurements, and therefore needs to be controlled for where possible (e.g. through the use of SRS or TRS) (Yoshitani *et al.*, 2007; Okada & Delpy, 2003; Dehghani & Delpy, 2000).

5.3. *Other Factors*

There are a number of additional variables that may have an influence on the NIRS measurement if not controlled for (where possible). These variables include position of the frontal sinus in the skull, position of the temporalis muscle, changes in blood pressure during the measurement, as well as haemoglobin concentration (Minati *et al.*, 2011; Okada *et al.*, 2010; Perrey, 2008; Yoshitani *et al.*, 2007).

The frontal sinus is located superior to the bridge of the nose and extends bilaterally within the frontal bone. It is one of the paranasal sinuses and is lined with a mucous membrane and filled with air (Saladin, 2007). Okada *et al.* (2010) showed that the frontal sinus may impact the sensitivity of the NIRS measurements, thereby highlighting the importance of correct optode placement. The authors did, however, recommend that further studies be carried out due to their limited sample size. In a similar manner, placement of the optodes over the temporalis muscle of the lateral aspect of the forehead has shown to influence the sensitivity and reliability of the NIRS measurements (Perrey, 2008). Changes in blood pressure during a measurement period have been implicated in lowering the reliability of NIRS measurements for both cerebral and muscle oxygenation. Minati *et al.* (2011) showed that when blood pressure was increased when performing a cognitive task, the NIRS measurement parameters exhibited a large pressure-related response while the changes resulting from the performance of the cognitive task were absent. Finally, Yoshitani *et al.* (2007) found that haemoglobin concentration, which is significantly different between men and women, may have an effect of regional cerebral saturation (American College of Sports Medicine, 2010).

D. NIRS AND THE STROKE PATIENT

The mechanisms of stroke themselves allow for NIRS to be explored as a potential monitoring tool, both during the acute phase following a stroke, as well as during the chronic phase during which rehabilitation takes place (Belda-Lois *et al.*, 2011; Terborg *et al.*, 2009). Monitoring of ischemic stroke is usually achieved via the intravenous administration of indocyanine green (ICG). Middle cerebral artery (MCA) occlusion is most commonly reported in the literature with significant differences in bolus transit time and concentration within the affected hemisphere. Furthermore, time to peak concentration increased and blood flow index (BFI) decreased in stroke patients when compared to controls with the tissue oxygenation index (TOI) being lower on the affected side (Durduran *et al.*, 2009; Terborg *et al.*, 2009; Terborg *et al.*, 2004). Subarachnoid haemorrhage (SAH) provides a slightly more complex challenge due to the presence of cerebral vasospasms. While traditional methods such as Transcranial Doppler (TCD) are often used in conjunction with NIRS, recent research has shown that by using TOI as a measurement variable, cerebral perfusion and blood flow can be accurately and reliably measured in haemorrhagic stroke patients (Vasdekis *et al.*, 2011; Poon, Wong, & Ng, 2010; Zweifel *et al.*, 2010). While monitoring during the acute stages following a stroke is extremely useful, researchers have questioned whether NIRS can be effectively used to predict prognosis following a stroke. No conclusive evidence yet exists to support the theory that NIRS is able to accurately predict prognosis, however, it has been shown to predict perioperative neurological outcome well in patients undergoing antegrade cerebral perfusion (Palazzo *et al.*, 2010; Olsson & Thelin, 2006).

Cerebral haemodynamics in stroke patients during neuronal activation is slightly different from their healthy matched counterparts. In patients with cerebral ischemia, the contralateral hemisphere to the lesion showed a typical response, i.e. an increase in

oxyhaemoglobin (O₂Hb) and total cerebral haemoglobin (HbT) with a decrease in deoxyhaemoglobin (HHb). However, the affected hemisphere presented with an increase in all three variables although the increase in O₂Hb was far greater than the increase in HHb. Furthermore, activation volumes as determined by fMRI were lower on the lesion side (Murata *et al.*, 2006; Murata *et al.*, 2002). Differences in cerebral oxygenation were also found between aphasic and non-aphasic patients, where aphasic patients demonstrated increases in O₂Hb, HHb and HbT during a speech task, providing evidence that the aphasic patients utilize more oxygen than the non-aphasics and healthy controls during the task (Sakatani *et al.*, 1998).

A simulation study where cerebral blood flow was occluded, showed that attention levels decreased in proportion to the magnitude and duration of the occlusion, indicating the possible loss of brain functioning that is seen immediately prior to and following a stroke (Marshall *et al.*, 2001). Depression following stroke is a commonly occurring phenomenon with research in elderly patients suggesting that O₂Hb is lower and HHb slightly higher in those with depression during a verbal fluency task when compared to those without depression (Matsuo *et al.*, 2000). Further research on stroke patients is needed to investigate whether similar results are found.

Changes in activation and cerebral haemodynamics as a result of rehabilitation following a stroke have been researched extensively over the past 10 years with a number of interesting findings. Feedback while performing exercises has been shown to be particularly beneficial in promoting motor recovery, as activation of the premotor cortex increased when compared to those who did not receive any feedback (Lin *et al.*, 2012). In patients suffering from hemiparesis, motor activation areas in the sensorimotor cortex shifted from bilateral activation within the acute phase of stroke, to unilateral activation one month or more following stroke, which is the typical or expected activation pattern when

compared to healthy controls (Takeda *et al.*, 2007). These finding are suggestive of the neuroplasticity that has been extensively reported in stroke patients.

Gait abnormalities and cerebral haemodynamic responses have been studied in patients by using a treadmill, while a number of participants were studied under partial body weight support (BWS) conditions (Belda-Lois *et al.*, 2011). In most cases, there was an increase in activation of the unaffected hemisphere's prefrontal and premotor cortex which corresponded with an increase in O₂Hb. Interestingly, during steady state gait, high levels of O₂Hb decreased in healthy individuals. while in those with severe gait abnormalities it remained elevated (Belda-Lois *et al.*, 2011; Obrig & Steinbrink, 2011). Consistent rehabilitation of gait may, however, assist in improving the asymmetry (Arenth, Ricker, & Schultheis, 2007).

E. SUMMARY

NIRS is fast becoming a commonly used imaging modality in clinical and research settings to assess changes in the brain. While there are still a number of questions regarding its ability to quantify absolute changes, numerous authors consider it to be an essential component of neuroimaging in both healthy and diseased populations. With continued methodological and technical developments and improved standardization NIRS will potentially allow for more effective and accurate therapeutic interventions to aid those suffering with or recovering from chronic conditions such as stroke.

CHAPTER FOUR

PROBLEM STATEMENT

A. SUMMARY OF THE LITERATURE

There is a marked increase in the global incidence of stroke making it one of the leading causes of death and disability world-wide (Carod-Artal & Egido, 2009; Hildick-Smith, 2000a). For most individuals it is a life-long disability (Carod-Artal & Egido, 2009; Palmer-McLean & Harbst, 2009), although some would recover their pre-stroke abilities to a certain degree (Carod-Artal & Egido, 2009; Palmer-McLean & Harbst, 2009). Mostly, a person's activities of daily living (ADL's) are affected, with between 55% and 80% of all stroke survivors unable to properly care for themselves independently (Medée *et al.*, 2010; Salbach *et al.*, 2004).

Unfortunately the exact underlying cause of stroke amongst the global population cannot be pinpointed due to the extensive probable causes and overlapping conditions (Palmer-McLean & Harbst, 2009). There are a number of risk factors for stroke that, in isolation, have the potential to significantly impact on the health of a person. The most common of these risk factors, irrespective of the type of stroke, are hypertension, hypercholesterolemia, diabetes and obesity (Mohr *et al.*, 2004). Other risk factors include family history of previous stroke, high levels of the methionine pre-cursor homocysteine, as well as elevated levels of fibrinogen, clotting factors and inflammation (Mohr *et al.*, 2004).

There is a growing need for non-invasive neuroimaging techniques that will enable medical practitioners to monitor cerebral blood flow (CBF), as well as neuronal activation in

patients with brain injuries both while at rest and during movement (Eliassen *et al.*, 2008). Near-infrared spectroscopy (NIRS) is a viable and relatively inexpensive option that has been shown to be both reliable and valid and which correlates very well with other more common neuroimaging techniques such as fMRI and PET (Tausky *et al.*, 2012; Strangman *et al.*, 2006).

The practical application of neuroimaging in stroke patients has been examined in recent years. For instance fMRI is considered the preferred technique for tracking the effects of a rehabilitation program, however, NIRS is now being used in a number of studies with stroke patients due to its practicality (Hodics *et al.*, 2006; Strangman *et al.*, 2006).

The current study will be the first to examine whether differences in neural activity exist in stroke patients who have, and those who have not received regular treatment following a stroke. Regular rehabilitation was defined as exercise with a health professional on at least two days a week of at least 30 minutes in duration, for a period of two months or more after hospital discharge. Significant findings in this area may highlight the necessity for continuous rehabilitation following a stroke for both physical and cognitive improvements. This may reveal more about the timing and frequency of physical training and whether this has any obvious health benefits.

B. SHORTCOMINGS OF THE EXISTING LITERATURE

While there has been a steady increase in the number of NIRS and stroke-related studies, there is still a large degree of variation amongst the results. No studies exist that have compared the time following a stroke and changes in cerebral haemodynamic variables using NIRS, nor have any studies been published that show whether rehabilitation has any

significant benefit over no rehabilitation regarding cerebral haemodynamic changes. Furthermore, there is still conflicting evidence regarding the typical deoxy-haemoglobin pattern during cortical activation in both healthy individuals and stroke patients.

C. RESEARCH QUESTIONS

The following research questions were addressed with the outcome variables and respective measurements selected to try and answer them:

1. Is there a difference in cerebral haemodynamics between stroke patients and healthy age-matched individuals when performing a simple and complex cognitive task, before and after exercise?
2. Does low intensity exercise have an influence on task performance?
3. Does time post-stroke have an influence on cerebral haemodynamics or task performance?
4. Does regular rehabilitation following a stroke have an influence on cerebral haemodynamics and task performance?

CHAPTER FIVE

METHODOLOGY

A. STUDY DESIGN

An experimental study design was used with the participants being divided into an experimental group consisting of stroke patients and a control group consisting of age-matched healthy individuals. The outcome variables were measured prior to the commencement of the various test components in order to establish baseline data for comparison. Thereafter, outcome variables were measured continuously during the testing procedure.

B. PARTICIPANTS

1. Participant Selection

Participants were recruited through advertisements in the local newspapers and Stellenbosch Biokinetics Centre, old age homes, as well as through consultation with specialist physicians and cardiologists in the Stellenbosch, Somerset West and Paarl areas. Fourteen stroke patients (men and women), aged between 53 and 83 years, and eighteen healthy elderly men and women, aged between 52 and 85 years volunteered to participate in the study. All participants were informed of the purpose of the study and gave full consent to participate.

1.1. *Inclusion and Exclusion Criteria*

Participants were included in the study if they were above the age of 50 years and were able to walk at least a distance of 20 meters, with or without the aid of a walking device. They needed to be able to stand from a sitting position without assistance and not be suffering from severe cognitive impairment as determined by the Mini-Mental State Exam (MMSE) (Appendix E). Stroke patients needed to have had one or more clinically diagnosed strokes between two months and two years prior to the commencement of the study. Participants were excluded if it was found that they would be unable, due to physical limitations, to perform any of the tasks required, if they were colour-blind or suffered from visual agnosia, or if they were exclusively left-handed.

2. **Assumptions**

It is assumed that cerebral oxygenation will be similar for both groups at rest and that there will be no differences between men and women, as well as different ethnic groups. Furthermore, it is assumed that the cognitive task will be comprehended in a similar way by both groups.

3. **Delimitations**

This study will be limited to healthy elderly individuals and stroke patients in the Boland and/or Overberg region and will be specifically looking at pre-frontal cortex activation.

4. Limitations

Medication may have an effect on blood viscosity which may have an effect on cerebral blood flow (e.g. Warfarin, Aspirin, Ecotrin and Plavix). Unfortunately, due to the dangers of cessation of medication, even for a short period of time, this cannot be controlled for. Furthermore, some of the NIRS variables are only measured as the changes relative to baseline values and therefore does not give absolute values, with the exception of the variables measured by spatially resolved spectroscopy (SRS).

C. EXPERIMENTAL DESIGN

All data collection sessions took place in the Motor Learning Laboratory at the Department of Sport Science, Stellenbosch University. The participant was required to make only one visit to the laboratory as the first visit was conducted at the participant's place of residence. Testing sessions lasted between 90 to 120 minutes, depending on the time required to perform the various components of the testing procedure. No feedback regarding performance during the various testing components was given.

1. Laboratory Visits

1.1. First Visit

The first visit took place at the participant's place of residence where the aims and outline of the study, as well as consent form (Appendix A) were explained to them in their preferred language, and they were allowed the opportunity to ask questions pertaining to the study. Thereafter, a full screening took place which included a comprehensive medical

history, activity profile, current medications (including dosage and frequency), as well as identifying those individuals who could not be included in the study by virtue of severe cognitive or physical impairments, colour-blindness or handedness (Appendix B).

1.2. *Second Visit*

During the second visit, the participant's anthropometric measurements were taken which included height and body mass, as well as cardiovascular measurements of heart rate and blood pressure. If a participant had a resting blood pressure of greater than or equal to 200/110 mmHg the testing day was rescheduled due to safety concerns, and as recommended by the American College of Sports Medicine. Following completion of the anthropometric measurements, the positioning of the NIRS probes was obtained by using the international 10-20 EEG electrode placement system (Jurcak, Tsuzuki, & Dan, 2007), where after they were attached to the respective areas on the participant's forehead. The participant was then asked to remain seated quietly, with their eyes closed for a period of five minutes as baseline data was obtained (this constituted rest period 1). Following the initial baseline period, the following components of the testing procedure, in chronological order took place: Mini Mental State Exam (MMSE), rest period 2 (R2), modified Stroop Task 1 (ST1), rest period 3 (R3), timed up-and-go (TuG), rest period 4 (R4), six minute walk test (6MWT) or toe taps (TT), modified Stroop Task 2 (ST2) and finally rest period 5 (R5). The participant was requested to remain quiet and close their eyes for the duration of the rest periods. Furthermore, the TT were used in conjunction with the 6MWT as a control test. The data capturing sheet for the testing session can be seen in Appendix C and a schematic representation of the testing procedures in chronological order can be seen in *Figure 5.1*.

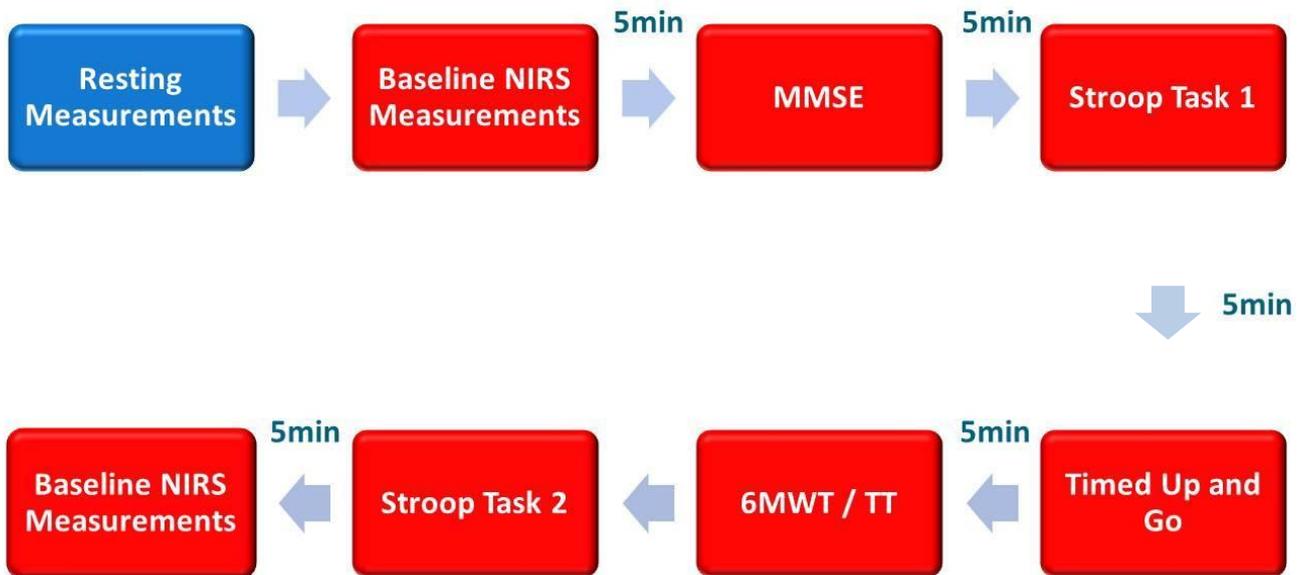


Figure 5.1. Schematic representation of the testing procedures in chronological order. All blocks that are in red indicate that the various NIRS variables were being measured.

2. Ethical Aspects

The study protocol was approved by the Ethics Committee of Research Subcommittee A of Stellenbosch University (Reference number HS784/2012). The study did not use any invasive procedures and participants were informed that their participation was completely voluntary and that they could withdraw from the study at any time without any penalty, financial or other. The informed consent form was explained verbally in full, and any questions answered before being completed by the participants. The dignity of the participants was held in the highest regard at all times. No adverse reactions were reported following completion of the testing procedures. The ethical clearance document can be seen in Appendix D.

D. MEASUREMENTS AND TESTS

The primary dependent (outcome) variables include oxyhaemoglobin (O₂Hb), deoxyhaemoglobin (HHb), tissue oxygenation index (TOI), total haemoglobin index (THI), cognitive test performance and functional testing performance. Secondary outcome variables include anthropometric measurements as well as cardiovascular measurements.

1. Anthropometric Measurements

For both anthropometric measures, participants stood barefoot, and dressed in light weight clothing, with body mass evenly distributed as much as possible. The guidelines outlined by the International Society for the Advancement of Kinanthropometry (ISAK) were used in both measurements.

1.1. Height (Standing Height)

Participants stood with feet together, and heels, buttocks, and the upper back touching the stadiometer (SECA 220, Hamburg, Germany). The participant was placed in the Frankfort Plane with the lower edge of the eye socket (Orbitale) and the notch above the tragus of the ear (Tragion) in the same horizontal plane. During the measurement the participant was asked to take a deep breath in while the headboard was lowered to the highest point of the skull (Vertex). Measurements were taken to the nearest 0.1 centimetre (cm).

1.2. *Body Mass*

Body mass was measured on a calibrated standing sliding scale (Detecto 439 Eye-Level Physician Scale, Web City, USA). Participants were instructed to stand in the middle of the scale with weight evenly distributed and looking straight ahead. Body mass was calculated to the nearest 0.1 kilogram (kg).

2. **Cardiovascular Measurements**

Measurements of the cardiovascular variables were performed according to the guidelines set out by the American College of Sports Medicine (ACSM). Blood pressure was measured only prior to the commencement of the testing session, whereas heart rate was monitored continuously.

2.1. *Blood Pressure*

Participants were instructed to sit quietly with both feet flat on the floor for a period of five minutes prior to blood pressure being taken. All participants had not ingested caffeine or smoked cigarette(s) for at least 3 hours prior to the measurement. Blood pressure was measured with a wall-mounted mercury sphygmomanometer (Phillips M4565B, Eindhoven, Netherlands) and measurements were taken to the nearest 1 millimetre mercury (mmHg). Following the five minute resting period an adult size cuff (27.5 – 36.5 centimetres) was placed on the upper arm, ensuring that the bladder of the cuff encircled at least 80% of the upper arm. The head of the stethoscope (Hi-Care, South Africa) was placed over the antecubital space while the cuff pressure was inflated. The first and last Korotkoff sounds were used to determine the participant's systolic blood pressure (SBP)

and diastolic blood pressure (DBP), respectively. Blood pressure measurements were taken twice with a one minute recovery period between measurements, with the average of the two measurements being used as the final reading.

2.2. Heart Rate

Heart rate was taken following the blood pressure measurements with the participant seated and both feet flat on the floor. Baseline heart rate as well as heart rate monitoring during the testing period was measured with a Suunto heart rate monitor (Suunto Team System, Vantaa, Finland).

3. Cerebral Oxygenation Measurements

Cerebral oxygenation and changes thereof were measured with the NIRO-200NX oximeter (Hamamatsu Photonics, Tokyo, Japan). Prior to any measurements being taken, the participant's forehead was cleaned with alcohol swabs to avoid misrepresentation of the results due to make-up, or other potential substances on the skin surface. The positioning of the measurement probes was calculated using the international 10-20 system for EEG electrode placement (Jurcak *et al.*, 2007). The light emitters were placed at Fp1 and Fp2 for the left and right side respectively, with the detectors being placed between positions F3 and F7 on the left side, and F4 and F8 on the right side. These positions correspond to Brodmann Area 10 and Brodmann Area 46 in the left and right prefrontal cortex. The respective EEG positions were calculated according to the following method, with the areas of interest shown in *Figure 5.2* and *Figure 5.3* respectively:

1. The nasion (bridge of the nose) and inion (occipital protuberance) were located via palpation of the bony anatomy of the skull.
2. The distance between these two anatomical landmarks were measured with a flexible steel anthropometry tape (Rosscraft, Canada). A mark of 10% of the total distance between the two points was marked on the anterior and posterior aspect of the skull which corresponded to Fpz (Anterior) and Oz (Posterior).
3. A mark of 20% of the total distance was then made on the anterior aspect of the skull which corresponded to Fz.
4. A circumference measurement was then taken around Fpz and Oz in order for the remaining EEG positions to be calculated.
5. Five percent of the total circumference around Fpz and Oz was calculated with marks to the left and right of Fpz corresponding to Fp1 and Fp2 respectively.
6. An additional 10% to the left and right of Fp1 and Fp2 were measured and marked which correspond to F7 and F8.
7. The distance between F7 and F8 was calculated and the intersection of half the distance with the first Fz mark was the true Fz.
8. A measurement was then made between F7 and Fz, as well as F8 and Fz, with half the distance between these two measurements corresponding to F3 and F4.

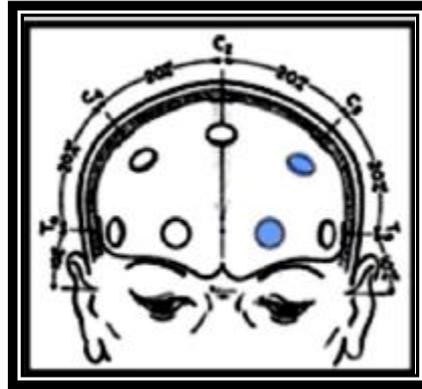


Figure 5.2. Electrode positioning of Fp1 (inferior) and Fp3 (superior) from an anterior view according to the 10-20 international classification system for EEG placement (Reproduced with permission from Perrey, 2008).

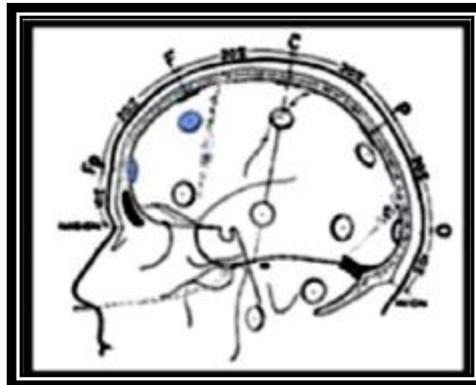


Figure 5.3. Electrode positioning of Fp1 (inferior) and Fp3 (superior) from a lateral view according to the 10-20 international classification system for EEG placement (Reproduced with permission from Perrey, 2008).

The light emitters and detectors were contained within a rubber holder that sets the distance between the emitter and detector at four centimetres. The probes were fixed to the scalp by means of double-sided adhesive tape supplied by the manufacturer, with additional intravenous (IV) stickers (IV3000, Smith & Nephew, Hull, England) placed over the rubber holder to ensure that the probes remained in constant contact with the skin. Furthermore, a white Velcro headband was placed around the head to ensure that the wires of the two measurement channels did not obstruct the participant in any way. Measurements were carried out at wavelengths set at 735 nm, 810 nm, and 850 nm as determined by the manufacturer, with the sampling time set at five hertz (Hz). Channel one

provided measurements of oxyhaemoglobin (O_2Hb), deoxy-haemoglobin (HHb), tissue oxygenation index (TOI) and total haemoglobin index (THI) over the left prefrontal cortex, while channel two provided the same measurements over the right prefrontal cortex. Continuous measurements were obtained from the participants during the five rest periods of five minutes, during the mini-mental state exam (MMSE), during the first and second modified Stroop Task (ST1 and ST2), during the timed up-and-go test (TuG), and during the six minute walk test (6MWT) or toe taps (TT). Markers were placed, and time was recorded at the beginning and end of each event in the testing procedure to ensure accuracy of start and end times during the data analysis. An example of a NIRS graph can be seen in Appendix G while a real-time capture of the NIRS measurement during testing is shown in *Figure 5.4*.



Figure 5.4. Real-time NIRS measurement (Photograph taken by Bradley Fryer)

4. Cognitive Measurements

Two well-known cognitive tests were used to assess cognitive ability, as well as executive function in both groups. The Mini Mental State Exam (MMSE) is a widely used assessment tool in both healthy and diseased populations, while the modified Stroop task has been used extensively in neuropsychological research.

4.1 *Mini Mental State Exam*

The MMSE is comprised of a number of different components and assesses an individual's orientation, attention, calculation, recall, language and motor skills and is often used as a screening tool for Alzheimer's disease (AD) or Dementia and can be seen in Appendix E. An individual scores one point for every correct answer with a maximum of 35 points possible. A score below 20 usually indicates a degree of cognitive impairment. Participants were asked to answer all the questions in English in order to eliminate any confusion. Marker 3 on the NIRO-200NX was placed at the commencement of the first question of the MMSE, while marker 4 was placed after completion of the answer to the last question of the MMSE. The questions that required the participant to write or draw were performed with the participant's dominant or non-affected hand.

4.2 *Modified Stroop Task*

The modified Stroop task is a computer-based task that assesses executive function. It specifically assesses cognition responsible for selective attention to specific information and inhibition of prepotent responses during tasks that require decision making based on stimuli. The traditional Stroop task involves presenting colour words (e.g. Blue) displayed

in either the congruent (blue) or incongruent (red) colours, as well as control trials where the word is presented in a neutral colour (black) or colour blocks without words. The modified Stroop task used in this study consisted of four blocks of increasing difficulty. Each block consists of 24 trials during which the participant had to respond to a pre-determined command given at the beginning of the block. The stimulus was presented on the centre of a laptop screen with the two responses situated at the bottom left and right of the screen. The participant pressed either the “,” or “/” key on an external keyboard, corresponding to the left (,) and right (/) response when responding to the stimulus. During the first block, the easiest condition, the participant was required to identify the word written in a neutral colour (black), thus in effect testing their ability to read. During the second block the participant was required to identify the colour of a rectangle with the choices written in a neutral colour, thus requiring them to differentiate between the four colours (red, green, blue and yellow). The third block required the participant to identify the colour of the text, while inhibiting the response to the word name, with the choices once again written in a neutral colour. The fourth and most difficult block required the participant to identify the colour of the text, while inhibiting the response to the word name, with the choices now written in a colour that may, or may not be congruent with the stimuli word itself. The four blocks ran concurrently, with no rest period between the blocks, except for the time period between completion of the respective blocks and the beginning of the following one. Instructions at the beginning of each block were presented for a period of 15 seconds. There was no time limit for each trial, as it was self-determined by their response time to the stimuli. Both reaction time and accuracy were measured and participants were instructed to press the buttons with their right hand only or non-affected hand in the case of the stroke patients. Furthermore, participants were given the option of completing the task in their language preference (English or Afrikaans), considering that reaction time may be affected by unfamiliarity. Participants were also afforded the opportunity to

familiarize themselves with the testing procedure by performing one trial from each block prior to the test part commencing. The task was programmed in MatLab (Version 7.9.0.529, MathWorks Inc, USA). Event markers seven and 17 were placed on the NIRO-200NX when the instructions for the first block were displayed which corresponded to the beginning of the Stroop task. Event markers eight and 18 were placed after the participant had responded to the last condition and the program had closed. Examples of the different modified Stroop Task conditions can be seen in Appendix F.

5. Functional Measurements

Two functional tests were used to assess functional ability in both the healthy and stroke groups. The timed up-and-go (TuG) test has been widely used as a functional test in diseased and elderly populations due to the similarity to functional activities of daily living (ADL's). The six minute walk test (6MWT) is the most widely used walk test described in the literature and has also been found to be extremely reliable in elderly and chronic disease populations. The toe-tapping exercise was used as a control test to examine the effect of exercise on the haemodynamic response as well as task performance.

5.1 Timed Up-and-Go Test

The TuG test is an accurate predictor of functional mobility and is also widely used as a testing measure amongst the stroke population (Salbach *et al.*, 2004). The participant began the test in a seated position. Following a countdown, they were required to stand-up, walk forward three meters around a pre-measured beacon, turn around, and return to the seated position as quickly as possible. The time taken to complete this entire sequence of events was recorded on a standard stopwatch (BondiBlu B102151-01,

Honeydew, South Africa) to the nearest one hundredth of a second (s). If necessary, participants could perform the test with the use of a walking aid. Event markers 11 and 12 were placed on the NIRO-200NX when the person was instructed to begin the test, and when the person returned to the seated position, respectively.

5.2 Six Minute Walk Test

The aim of the 6MWT was to determine the distance the participant could walk for six continuous minutes at their fastest walking speed and is the most commonly used test for functional capacity amongst stroke patients (Eng *et al.*, 2004). Two beacons were spaced 10 meters apart forming a straight line. The participant was instructed to walk around each beacon in a lap fashion in order for total walking distance to be computed. A chair was provided for the individual to rest should they require it during the test, although the time still continued. Prior to the commencement of the test, the participant's resting blood pressure and heart rate were taken using a wall-mounted mercury sphygmomanometer (Phillips M4565B, Eindhoven, Netherlands) and Suunto heart rate monitor (Suunto Team System, Vantaa, Finland). Measurements were taken to the nearest one millimetre mercury (mmHg) and beat per minute, respectively. The Karvonen formula (*Equation 5.1*) was used to calculate 75% of the individual's maximal heart rate which is a standard procedure required when administering the test.

$$[(220-\text{age}-\text{RHR}) \times I] + \text{RHR} \quad (5.1)$$

Equation 5.1. Karvonen formula for calculating heart rate reserve (HRR), where RHR is the individuals resting heart rate and I is the intensity required.

Seventy-five percent of the individual's maximal heart rate is deemed the threshold for a submaximal test. The modified Borg Rating of Perceived Exertion (RPE) scale was

explained to the individual prior to the commencement of the test and acted as an additional screening tool during the test as well as a monitoring tool to determine whether the participant exercised within the low intensity limit of two to four on the RPE scale (American College of Sports Medicine, 2010). Heart rate was also monitored as an indicator of exercise intensity. Furthermore, if an individual is on any medication that alters their heart rate response to exercise (e.g. β -blockers), the RPE scale is used as a test termination criteria. A RPE of between seven and eight corresponds to 75% HR_{max} which is used as a termination point for a submaximal test. Heart rate and RPE readings were recorded after the first, third and fifth minute, as well as at the completion of the test. Following completion of the test, the individual was required to sit quietly for 3 minutes before their blood pressure and heart rate were measured again. Event markers 15 and 16 were placed on the NIRO-200NX which corresponded to the beginning and end of the 6MWT.

6. Additional Measurements

The time post-stroke, as well as whether a stroke patient had received regular rehabilitation following their stroke or not, was additional outcome variables. The time post-stroke was obtained from the participant and expressed as the number of months post-stroke. A person was deemed to have had regular rehabilitation if they attended any out-patient rehabilitation programme at least twice a week, and at least 30 minutes in duration for a period of two months or more following hospital discharge.

E. STATISTICAL ANALYSIS

Statistical analysis of the data was performed using Microsoft Excel 2010 (Windows[®], 2010, USA) and STATISTICA[®] 10.0 (Statsoft, 2010, USA). All descriptive statistics are reported as means (\bar{x}) and standard deviations (\pm SD), unless otherwise stated. Unpaired t-tests were used to compare the differences between the experimental and control group across the various outcome variables with the level of significance set at $p < 0.05$ for all analyses. Pearson's correlation (r) was calculated to determine if any relationship existed between the outcome variables with r values of between 0 to 0.24 considered a weak correlation, between 0.25 and 0.49 considered a moderate correlation, between 0.50 and 0.74 considered a moderate-good correlation and between 0.75 and one considered a strong correlation.

Cohen's effect sizes (ES) were calculated for the haemodynamic changes between baseline and the various testing procedures to determine practical significance. An effect size of greater than 0 and less than or equal to 0.15 is considered a negligible practical effect, greater than 0.15 and less than or equal to 0.4 is considered a small practical effect, greater than 0.4 and less than or equal to 0.75 is considered a moderate practical effect, greater than 0.75 and less than or equal to 1.10 is considered a large practical effect, greater than 1.10 and less than or equal to 1.45 is considered a very large practical effect, while greater than 1.45 is considered a huge practical effect (Thalheimer & Cook, 2002).

CHAPTER SIX

RESULTS

A. PARTICIPANTS

Thirty nine participants (22 healthy elderly individuals and 17 stroke survivors) volunteered to participate in the study. Those who met the inclusion criteria were invited to participate in the study and split into a stroke (experimental) and healthy (control) group. Four of the volunteers could not be included in the study as they did not comply with the inclusion criteria. One volunteer withdrew prior to testing due to travel restrictions and two volunteers suffered cardiac events prior to testing and were therefore no longer eligible for participation. A total of 32 participants completed the testing (19 women and 13 men), with the experimental group comprising of 14 participants and the control group 18 participants. *Table 6.1* contains the physical characteristics of the participants, with only standing height being statistically significant between the two groups.

Table 6.1. Physical characteristics (mean \pm SD, range) of the experimental (EXP) and control (CON) groups.

Characteristic	EXP (n = 14)				CON (n = 18)				p value
	Mean	\pm	SD	Range	Mean	\pm	SD	Range	
Age (years)	68.8	\pm	18.5	53 – 83	76.2	\pm	8.47	52 - 85	0.30
Height (cm)	169.6	\pm	8.9	155 - 182	161.6	\pm	10.9	142 - 185	0.03*
Body Mass (kg)	80.9	\pm	18.4	60 – 118	74.5	\pm	18.3	51 - 108	0.33
BMI (kg.m ⁻²)	27.8	\pm	4.2	24 – 36	28.3	\pm	5.6	22 - 40	0.77
SBP (mmHg)	132.9	\pm	14.1	110 - 162	132.4	\pm	11.5	112 - 146	0.92
DBP (mmHg)	77.0	\pm	13.5	58 – 104	70.9	\pm	8.3	56 - 88	0.12
TPS (months)	14.8	\pm	6.0	6 – 24	N/A	\pm	N/A	N/A	N/A

* Significant differences ($p < 0.05$). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TPS, time post-stroke

B. NEAR-INFRARED SPECTROSCOPY (NIRS) MEASUREMENTS

1. Global Changes in NIRS Measurements

The changes in oxyhaemoglobin (O₂Hb), deoxy-haemoglobin (HHb), tissue oxygenation index (TOI) and total haemoglobin index (THI) in both the left and right prefrontal cortex (LPFC and RPFC) are reported as means and standard deviations across all the test conditions and are shown in *Figures 6.1 to 6.8*. The figures represent the changes relative to when the measurement period was started on the NIRO200-NX oximeter. Additionally, Cohen's Effect Sizes (ES) for practical significance were calculated and are displayed in *Table 6.2 to Table 6.5*.

1.1. Oxyhaemoglobin

With respect to changes in O₂Hb (*Figure 6.1 and Figure 6.2*), the experimental and control group showed similar patterns in both the LPFC and RPFC, with increases of no significance during the Mini Mental State Exam (MMSE), and both of the modified Stroop Tasks (ST1 and ST2). Slight decreases relative to the preceding resting period were seen when performing the Timed Up-and-Go Test (TuG), as well as the Six Minute Walk Test (6MWT) or Toe Taps (TT), but once again these differences were not statistically significant ($p > 0.05$). The only statistically significant difference was seen between the two groups during the fourth rest period (R4) ($p = 0.02$) O₂Hb levels in the LPFC were 22%, 33%, 49%, and 86% lower in the experimental group during S1, S2, TuG and the 6MWT / TT respectively when compared to the control group but showed no statistical significance ($p > 0.05$). Differences of moderate practical significance were found in the LPFC and RPFC during R3 (ES = -0.62; ES = 0.49) and R4 (ES = 0.72; ES = 0.56) respectively (*Table 6.2*).

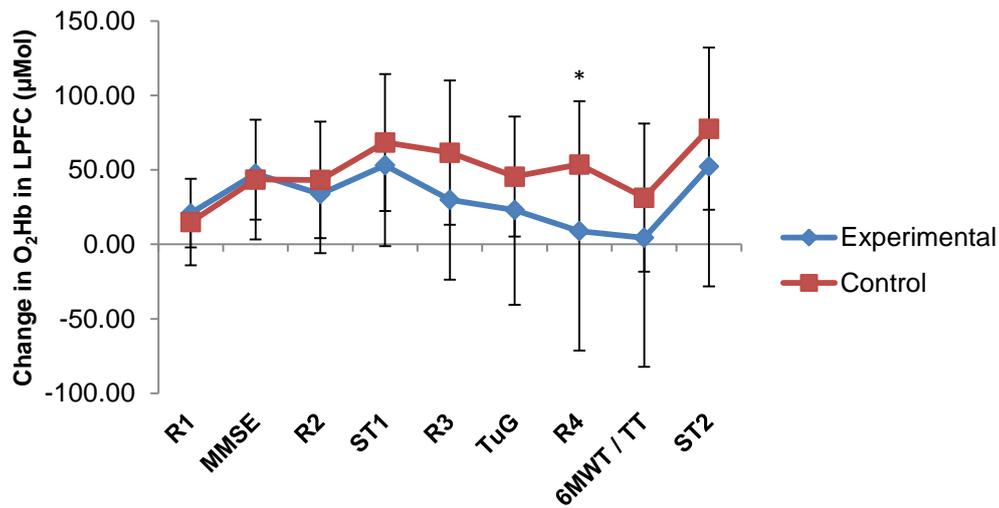


Figure 6.1. Change in Oxyhaemoglobin (O₂Hb) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

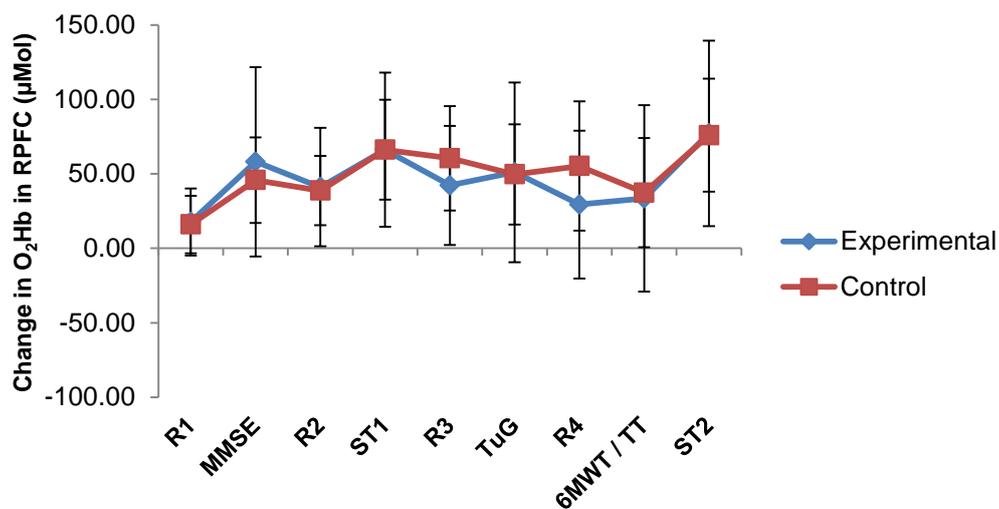


Figure 6.2. Change in Oxyhaemoglobin (O₂Hb) concentration in the Right Prefrontal Cortex (RPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

Table 6.2. Effect Sizes for changes in Oxyhaemoglobin (O₂Hb) from the beginning of the measurement period

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
R1	0.22	-0.48 ; 0.92	S	0.08	-0.62 ; 0.78	N
MMSE	0.11	-0.59 ; 0.81	N	0.26	-0.44 ; 0.96	S
R2	-0.24	-0.94 ; 0.46	S	0.07	-0.62 ; 0.77	N
ST1	-0.31	-1.01 ; 0.40	S	0.00	-0.70 ; 0.70	N
R3	-0.62	-1.34 ; 0.09	M	-0.49	-1.20 ; 0.22	M
TuG	-0.43	-1.14 ; 0.27	M	0.03	-0.67 ; 0.73	N
R4	-0.72	-1.44 ; 0.00	M	-0.56	-1.27 ; 0.15	M
6MWT	-0.39	-1.10 ; 0.31	S	-0.08	-0.78 ; 0.62	N
ST2	-0.38	-1.08 ; 0.33	S	0.02	-0.67 ; 0.72	N

R1, Rest period one; MMSE, Mini Mental State Exam; R2, Rest period two; ST1, modified Stroop Task 1; R3, Rest period three; TuG, Timed Up-and-Go; R4, Rest period four; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate

1.2. Deoxy-haemoglobin

Changes in Deoxy-haemoglobin (HHb) concentration (*Figure 6.3* and *Figure 6.4*) in both the LPFC and RPFC was higher across all the testing phases in the experimental group, however, no statistically significant differences were found compared to the control group ($p > 0.05$). Both groups displayed a decrease in HHb during the MMSE, ST1 and ST2, with an increase in HHb during the TuG and 6MWT / TT. It must be noted that although the experimental group's HHb concentrations were higher, the pattern across the various testing phases was very similar between the two groups. The ES for differences in HHb are shown in *Table 6.3* and contain only differences of small to moderate practical significance. There were differences of moderate practical significance in the LPFC and RPFC for R3 (ES = 0.43; ES = 0.46), R4 (ES = 0.44; ES = 0.53), TuG (ES = 0.57; ES = 0.48) and 6MWT / TT (ES = 0.49; ES = 0.44).

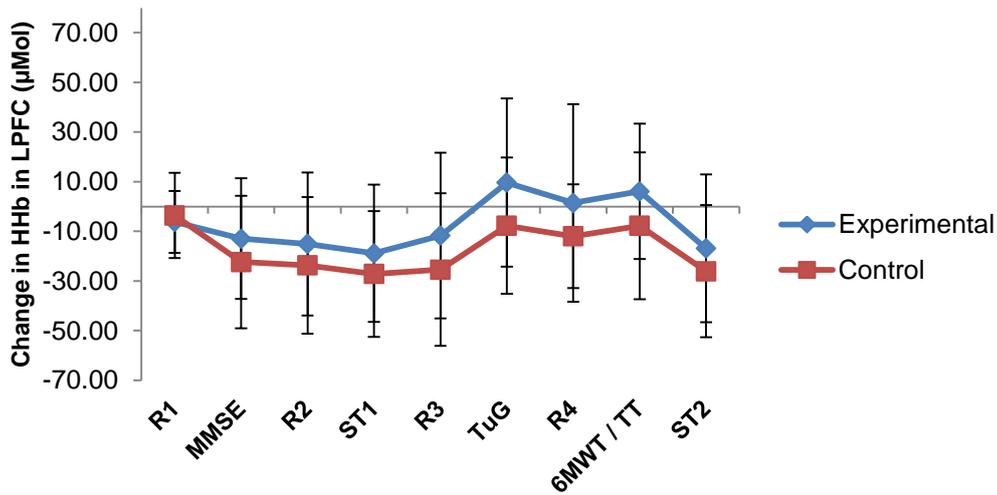


Figure 6.3. Change in Deoxy-haemoglobin (HHb) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

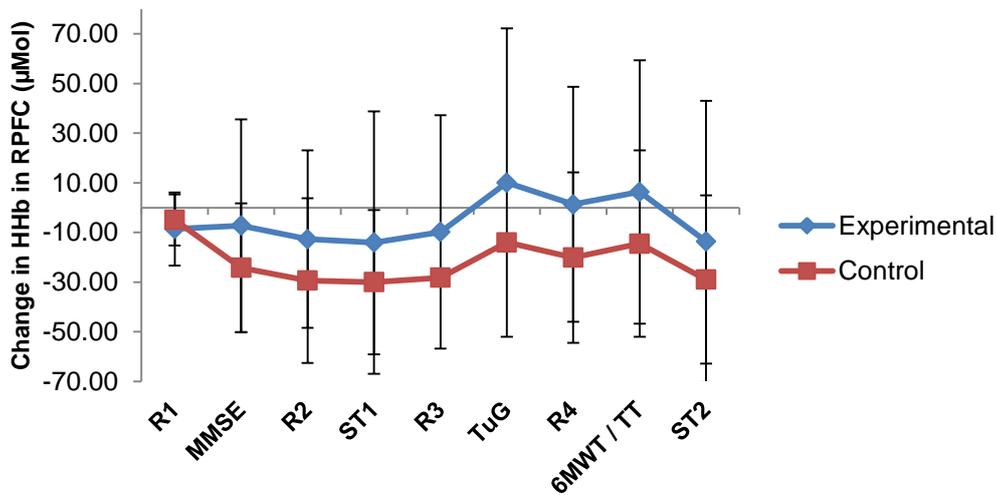


Figure 6.4. Change in Deoxy-haemoglobin (HHb) concentration in the Right Prefrontal Cortex (RPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

Table 6.3. Effect Sizes for changes in Deoxy-haemoglobin (HHb) from the beginning of the measurement period

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
R1	-0.17	-0.87 ; 0.53	S	-0.30	-1.00 ; 0.41	S
MMSE	0.37	-0.34 ; 1.07	S	0.49	-0.21 ; 1.20	M
R2	0.31	-0.40 ; 1.01	S	0.49	-0.22 ; 1.19	M
ST1	0.31	-0.39 ; 1.02	S	0.39	-0.32 ; 1.09	S
R3	0.43	-0.28 ; 1.14	M	0.46	-0.25 ; 1.16	M
TuG	0.57	-0.14 ; 1.28	M	0.48	-0.22 ; 1.19	M
R4	0.44	-0.27 ; 1.15	M	0.53	-0.18 ; 1.24	M
6MWT	0.49	-0.22 ; 1.19	M	0.44	-0.27 ; 1.15	M
ST2	0.33	-0.37 ; 1.03	S	0.33	-0.37 ; 1.03	S

R1, Rest period one; MMSE, Mini Mental State Exam; R2, Rest period two; ST1, modified Stroop Task 1; R3, Rest period three; TuG, Timed Up-and-Go; R4, Rest period four; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; S, small; M, moderate

1.3. Tissue Oxygenation Index

Tissue Oxygenation Index (TOI) percentages for the LPFC and RPFC are shown in *Figure 6.5* and *Figure 6.6*, respectively. TOI in the LPFC was almost identical between the two groups with the experimental group presenting with slightly lower values in the RPFC, however, the differences were not statistically significant ($p > 0.05$). TOI remained relatively constant throughout the testing period with an average of 64% and 63% in the LPFC and an average of 63% and 65% in the RPFC for the experimental and control group, respectively. There were only differences of negligible practical significance found in the LPFC with respect to TOI and can be seen in *Table 6.4*. The RPFC showed mostly differences of small practical significance, with the only difference of moderate practical significance seen during R4 (ES = -0.41).

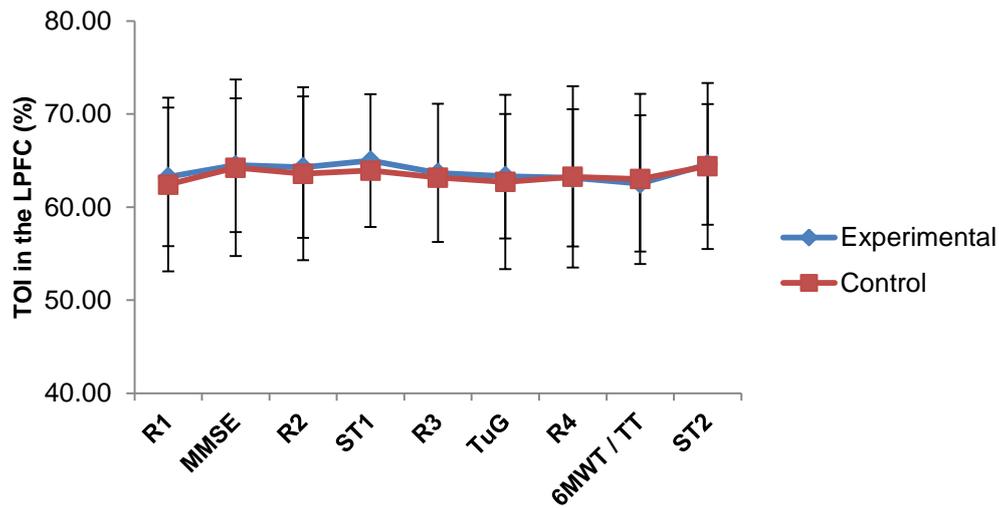


Figure 6.5. Tissue Oxygenation Index (TOI) in the Left Prefrontal Cortex (LPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

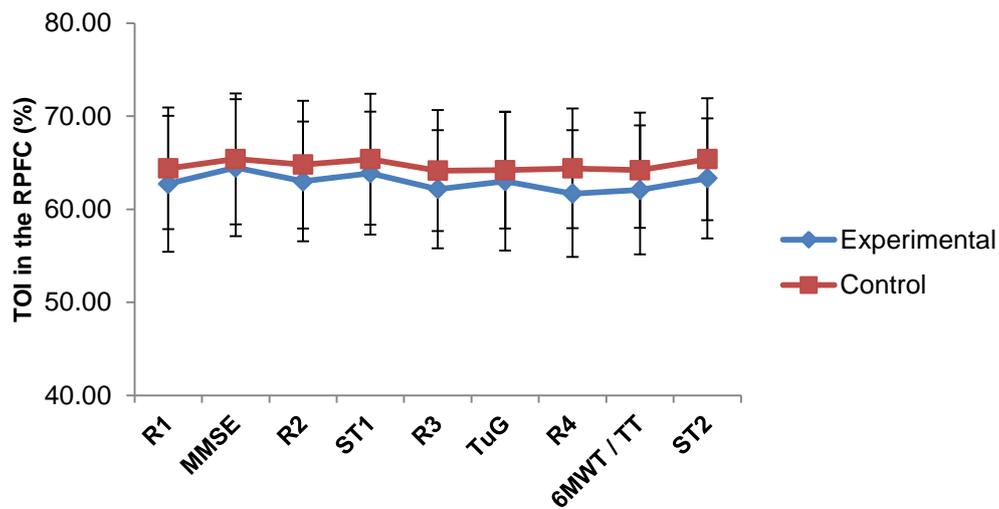


Figure 6.6. Tissue Oxygenation Index (TOI) in the Right Prefrontal Cortex (RPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

Table 6.4. Effect Sizes for changes in Tissue Oxygenation Index (TOI) from the beginning of the measurement period

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
R1	0.10	-0.60 ; 0.80	N	-0.24	-0.94 ; 0.46	S
MMSE	0.03	-0.67 ; 0.73	N	-0.13	-0.83 ; 0.57	N
R2	0.08	-0.62 ; 0.78	N	-0.27	-0.97 ; 0.43	S
ST1	0.13	-0.57 ; 0.83	N	-0.22	-0.92 ; 0.48	S
R3	0.06	-0.64 ; 0.76	N	-0.31	-1.01 ; 0.39	S
TuG	0.08	-0.62 ; 0.78	N	-0.17	-0.87 ; 0.53	S
R4	-0.01	-0.71 ; 0.68	N	-0.41	-1.12 ; 0.30	M
6MWT	-0.06	-0.76 ; 0.64	N	-0.33	-1.03 ; 0.38	S
ST2	0.02	-0.68 ; 0.72	N	-0.32	-1.02 ; 0.39	S

R1, Rest period one; MMSE, Mini Mental State Exam; R2, Rest period two; ST1, modified Stroop Task 1; R3, Rest period three; TuG, Timed Up-and-Go; R4, Rest period four; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate

1.4. Total Haemoglobin Index

Total Haemoglobin Index (THI) values for the LPFC and RPFC are displayed in *Figure 6.7* and *Figure 6.8*, respectively. There were no statistically significant differences in THI in the LPFC between the experimental and control group with an average of 1.03 ± 0.01 a.u. and 1.01 ± 0.02 a.u., respectively ($p > 0.05$). THI in the RPFC, however, revealed statistically and large practically significant differences (*Table 6.5*) between the experimental and control group during the MMSE ($p = 0.03$; ES = 0.82), R2 ($p = 0.03$; ES = 0.81), ST1 ($p = 0.04$; ES = 0.76) and the TuG ($p = 0.02$; ES = 0.87). While no statistically significant differences were found between the two groups and the remaining testing phases ($p > 0.05$), the experimental group have a markedly higher THI relative to the control group in the RPFC. The average THI in the RPFC for the experimental group across all the testing phases was 1.11 ± 0.05 a.u., while the average for the control group was 1.00 ± 0.01 a.u., a difference of 9.9%. An interesting point to note is the fluctuations in THI in the experimental group in the RPFC when performing the relevant tasks while THI in the control group remained relatively constant.

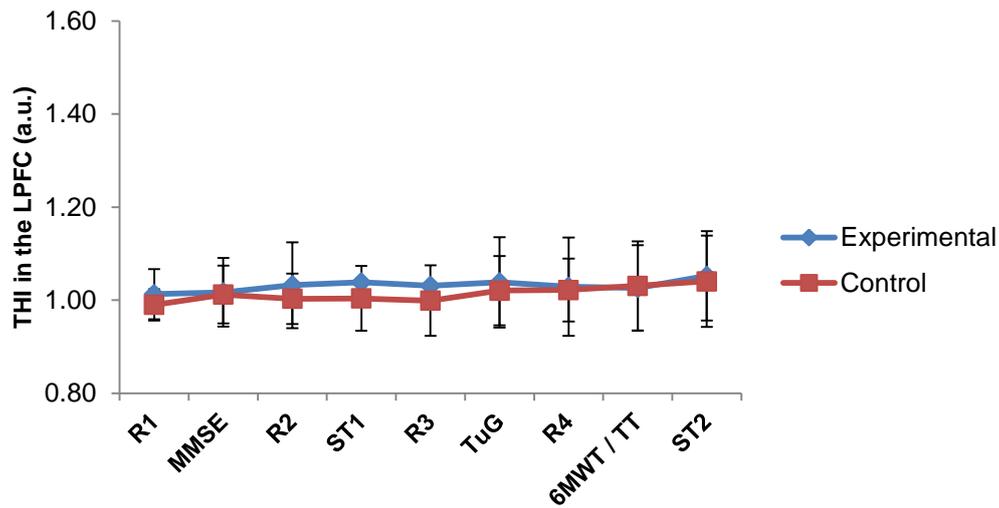


Figure 6.7. Total Haemoglobin Index (THI) in the Left Prefrontal Cortex (LPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2.

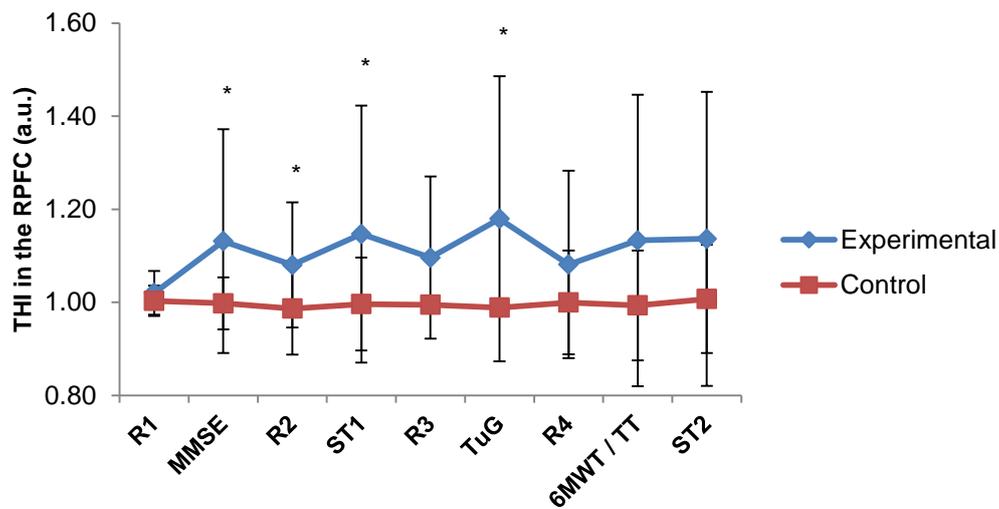


Figure 6.8. Total Haemoglobin Index (THI) in the Right Prefrontal Cortex (RPFC) during the various testing phases. R1, Rest Period 1; MMSE, Mini Mental State Exam; R2, Rest Period 2; ST1, Modified Stroop Task 1; R3, Rest Period 3; TuG, Timed Up-and-Go; R4, Rest Period 4; 6MWT, Six Minute Walk Test; TT, Toe Taps; ST2, Modified Stroop Task 2. * Statistically significant differences between experimental and control group ($p < 0.05$).

Table 6.5. Effect Sizes for changes in Total Haemoglobin Index (THI) from the beginning of the measurement

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
R1	0.52	-0.19 ; 1.23	M	0.44	-0.27 ; 1.15	M
MMSE	0.07	-0.62 ; 0.77	N	0.82	0.09 ; 1.54	L
R2	0.40	-0.31 ; 1.10	S	0.81	0.08 ; 1.54	L
ST1	0.42	-0.29 ; 1.12	M	0.76	0.04 ; 1.49	L
R3	0.35	-0.35 ; 1.06	S	0.71	-0.01 ; 1.43	M
TuG	0.22	-0.48 ; 0.92	S	0.87	0.14 ; 1.60	L
R4	0.09	-0.61 ; 0.78	N	0.51	-0.19 ; 1.22	M
6MWT	-0.05	-0.75 ; 0.65	N	0.61	-0.10 ; 1.33	M
ST2	0.13	-0.57 ; 0.83	N	0.55	-0.16 ; 1.26	M

R1, Rest period one; MMSE, Mini Mental State Exam; R2, Rest period two; ST1, modified Stroop Task 1; R3, Rest period three; TuG, Timed Up-and-Go; R4, Rest period four; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate; L, large

2. Relative Changes in NIRS Measurements

All comparative analyses between the two groups were performed with the first resting period (R1) as the baseline measurement and relative changes between the various testing phases were calculated. Relative change was calculated between R1 and the MMSE (A), R1 and ST1 (B), R1 and the TuG (C), R1 and the 6MWT (D) as well as R1 and ST2 (E). Additionally, Cohen's Effect Sizes (ES) for practical significance were calculated for the relative changes in NIRS variables

2.1 Oxyhaemoglobin

Changes in O₂Hb in the LPFC and RPFC are shown in *Figure 6.9* and *Figure 6.10*, respectively. The control group had an increase in O₂Hb in both the LPFC and RPFC with all of the tests performed, with the modified Stroop Tasks causing an increase of 78% and 81% respectively for ST1 (B) and ST2 (E) in the LPFC, and an increase of 77% and 80%

for ST1 (B) and ST2 (E) in the RPF. Furthermore, the magnitude of the change in the LPFC and RPF in the control group was similar. This was not the case with the experimental group, where smaller changes in O₂Hb were seen across all testing phases in the LPFC and in three of the five testing phases in the RPF. Similarly to the control group, the modified Stroop Tasks caused the greatest increase in O₂Hb with an increase of 61% and 59% respectively for ST1 (B) and ST2 (E) in the LPFC and an increase of 69% and 74% for ST1 (B) and ST2 (E) in the RPF in the experimental group.

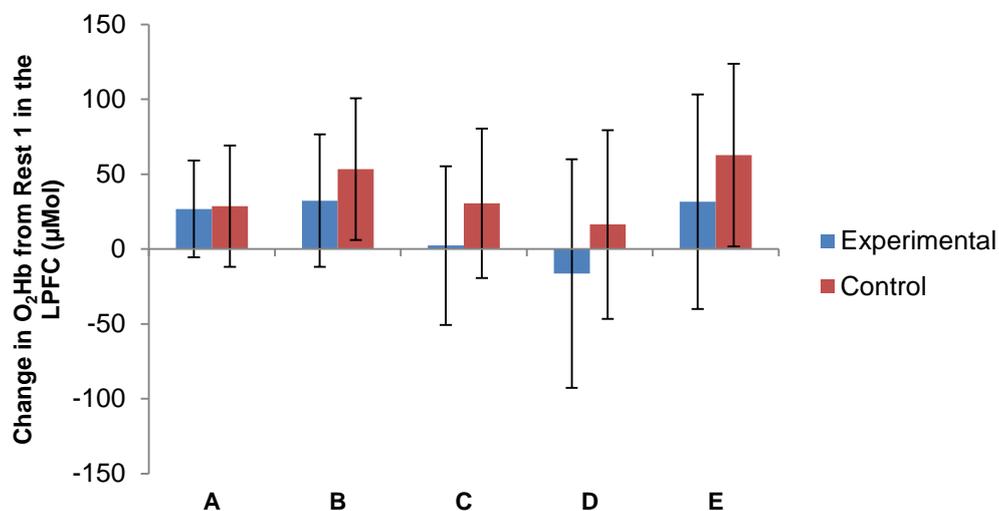


Figure 6.9. Change relative to resting period 1 (baseline) of Oxyhaemoglobin (O₂Hb) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

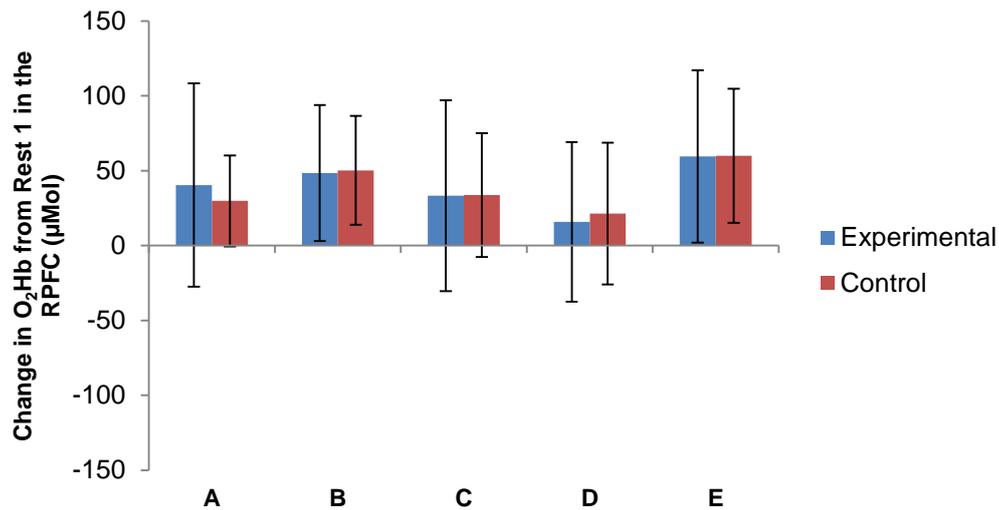


Figure 6.10. Change relative to resting period 1 (baseline) of Oxyhaemoglobin (O_2Hb) concentration in the Right Prefrontal Cortex (RPFPC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

No statistically significant differences were found between the two groups in either the LPFC or RPFPC across the various testing phases ($p > 0.05$). In practical terms, the differences in the relative changes of the RPFPC between the two groups were mostly negligible, however, large practical significant differences were observed for the TuG (C) ($ES = -0.76$), the 6MWT (D) ($ES = -0.89$) and ST2 (E) ($ES = -0.85$) in the LPFC (*Table 6.6*). During the 6MWT (D), O_2Hb values were 27% lower than resting in the experimental group in the LPFC, while in the RPFPC it showed an increase similar to that of the control group. Furthermore, the magnitudes of the changes were greater in the RPFPC in the experimental group, while the TuG (C) and 6MWT (D) caused the smallest increase in O_2Hb for both the experimental and control group in both the LPFC and RPFPC.

Table 6.6. Effect Sizes for changes in Oxyhaemoglobin (O₂Hb) relative to Rest 1 (Baseline)

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
MMSE	-0.05	-0.77 ; 0.67	N	0.22	-0.64 ; 1.08	S
ST1	-0.57	-1.48 ; 0.33	M	-0.04	-0.68 ; 0.61	N
TuG	-0.76	-1.79 ; 0.26	L	-0.01	-0.86 ; 0.84	N
6MWT	-0.89	-2.30 ; 0.52	L	-0.12	-0.89 ; 0.66	N
ST2	-0.85	-2.19 ; 0.49	L	-0.01	-0.82 ; 0.79	N

MMSE, Mini Mental State Exam; ST1, modified Stroop Task 1; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate; L, large

2.2. Deoxy-haemoglobin

Changes in HHb for the LPFC and RPFC are shown in *Figure 6.11* and *Figure 6.12*, respectively. The control group showed decreases in HHb in both the LPFC and RPFC across all the testing phases, with the magnitude of the decrease slightly higher in the RPFC during the TuG (C) and 6MWT (D), while the remaining phases were relatively similar. Conversely to the O₂Hb pattern during the modified Stroop tasks, HHb decreased the most in both groups in the LPFC and RPFC, although the decrease in the experimental group was 46% and 53% lower for the LPFC during ST1 (B) and ST2 (E), respectively, and 78% and 79% lower for the RPFC during ST1 (B) and ST2 (E), when compared to the control group. Interestingly, the experimental group displayed an increase in HHb of similar magnitude in the LPFC and RPFC, although the differences relative to the control group were not statistically significant ($p > 0.05$).

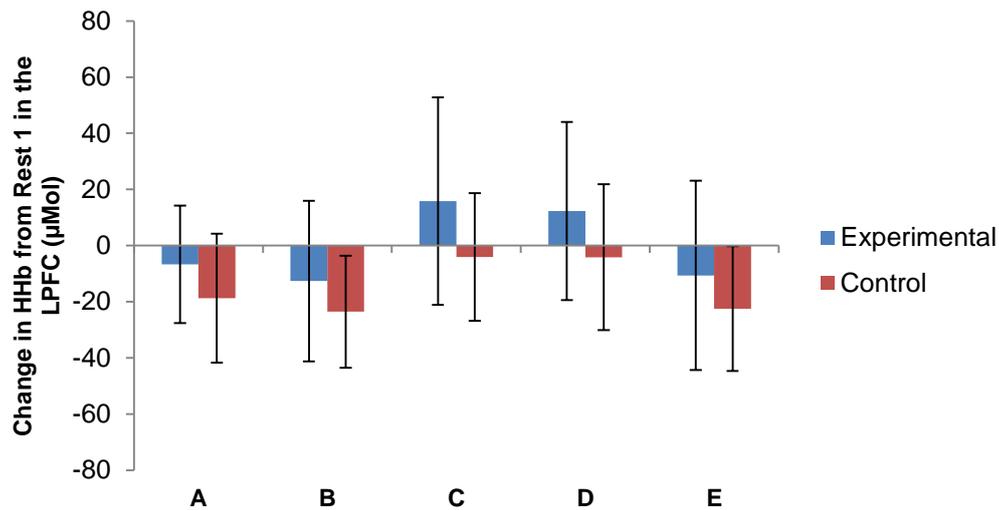


Figure 6.11. Change relative to resting period 1 (baseline) of Deoxy-haemoglobin (HHb) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

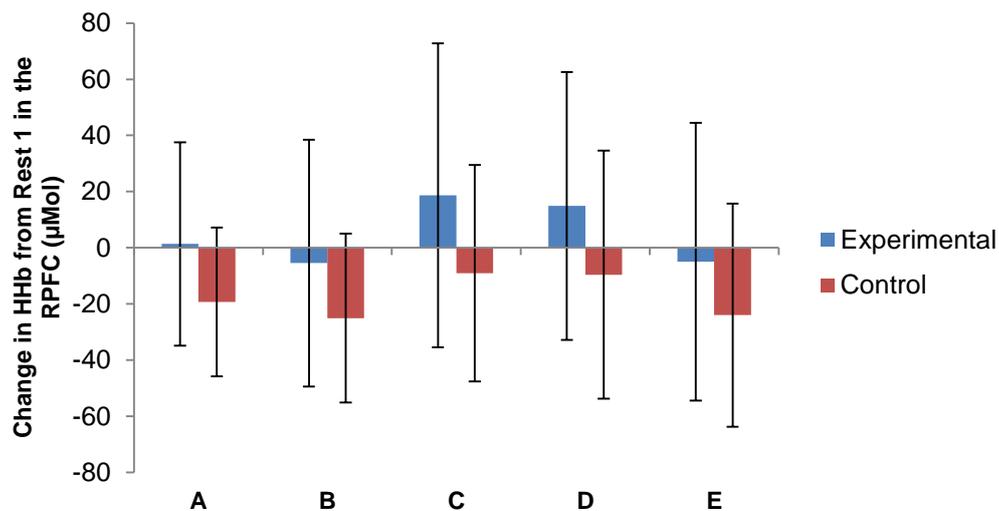


Figure 6.12. Change relative to resting period 1 (baseline) of Deoxy-haemoglobin (HHb) concentration in the Right Prefrontal Cortex (RPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

No statistically significant differences were found in the relative changes between the groups across any of the testing phases ($p > 0.05$). The patterns of practically significant differences between the two groups were identical in the LPFC and the RPFC (Table 6.7).

Moderate practical significant differences were found with the MMSE (A), ST1 (B), 6MWT (D) and ST2 (E) for both the LPFC and RPFC. Differences in the relative changes in HHb of large practical significance were seen in the LPFC and RPFC for the TuG (C), with similar scores (ES = 0.76; ES = 0.78).

Table 6.7. Effect Sizes for changes in Deoxy-haemoglobin (HHb) relative to Rest 1 (Baseline)

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
MMSE	0.46	-0.15 ; 1.06	M	0.58	-0.09 ; 1.24	M
ST1	0.41	-0.29 ; 1.12	M	0.55	-0.25 ; 1.35	M
TuG	0.76	-0.13 ; 1.65	L	0.78	-0.22 ; 1.77	L
6MWT	0.63	-0.19 ; 1.45	M	0.69	-0.26 ; 1.63	M
ST2	0.45	-0.37 ; 1.27	M	0.53	-0.40 ; 1.47	M

MMSE, Mini Mental State Exam; ST1, modified Stroop Task 1; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate; L, large

2.3. Tissue Oxygenation Index

Changes in the TOI for the LPFC and RPFC are displayed in *Figure 6.13* and *Figure 6.14*, respectively. The groups responded in a similar manner to the MMSE (A) and modified Stroop Tasks (B and E), where increases in TOI were seen in both the LPFC and RPFC. While the experimental group had a lower relative change in the LPFC during the MMSE (A), they had a higher relative change in the RPFC compared to the control group. Furthermore, the magnitude of the change for both groups in the RPFC was lower than the LPFC during the modified Stroop Tasks (1.07% and 0.79% for ST1 (B) and ST2 (E) in the RPFC and 1.63% and 1.67% in the LPFC). The control group had a marginal increase in TOI in the LPFC when performing the TuG (C) as well as the 6MWT (D), with a concomitant decrease in the RPFC. The experimental group, on the other hand, had a

non-significant increase ($p > 0.05$) in TOI in both the LPFC and RPFC while performing the TuG (C), and a decrease in TOI while performing the 6MWT (D) in the LPFC and RPFC.

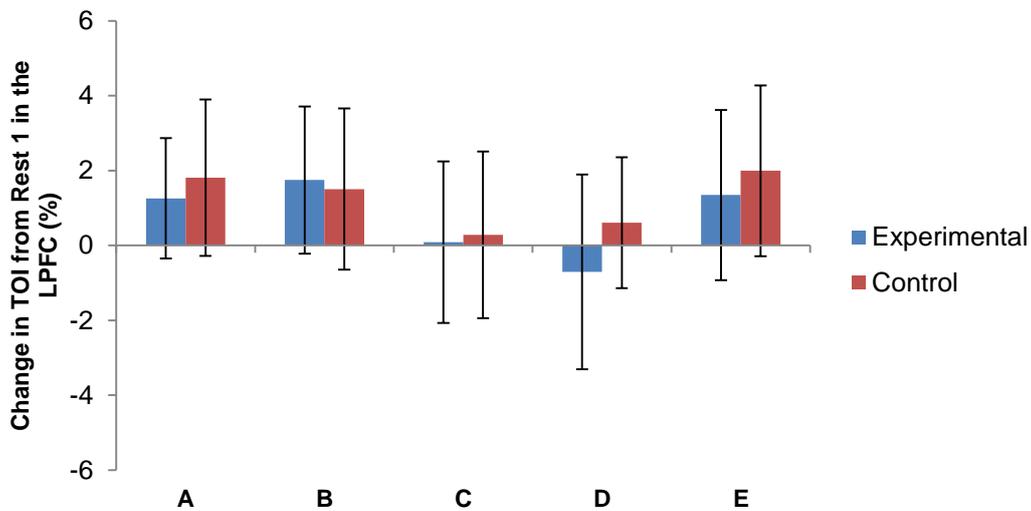


Figure 6.13. Change relative to resting period 1 (baseline) of Tissue Oxygenation Index (TOI) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

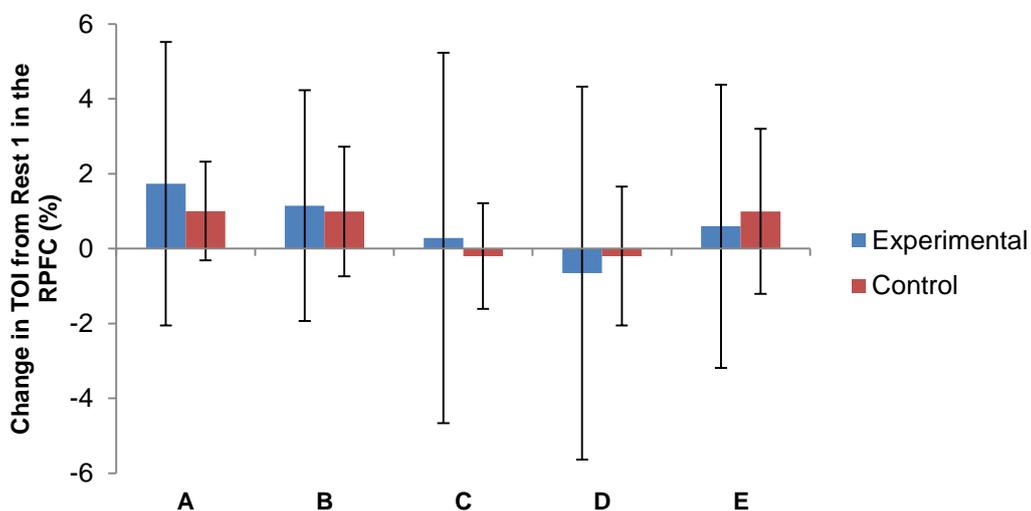


Figure 6.14 Change relative to resting period 1 (baseline) of Tissue Oxygenation Index (TOI) concentration in the Right Prefrontal Cortex (RPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

None of the relative changes in TOI were statistically significant between the two groups ($p > 0.05$). Furthermore, these differences were also of negligible practical significance during most phases for both the LPFC and the RPFC (*Table 6.8*). The only exception was the 6MWT (D) in the LPFC which showed a change of small practical significance (ES = -0.15).

Table 6.8. Effect Sizes for changes in Tissue Oxygenation Index (TOI) relative to Rest 1 (Baseline)

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
MMSE	-0.06	-0.22 ; 0.09	N	0.10	-0.21 ; 0.41	N
ST1	0.03	-0.15 ; 0.20	N	0.02	-0.24 ; 0.29	N
TuG	-0.02	-0.21 ; 0.16	N	0.07	-0.34 ; 0.47	N
6MWT	-0.15	-0.35 ; 0.04	S	-0.06	-0.47 ; 0.35	N
ST2	-0.08	-0.27 ; 0.12	N	-0.05	-0.38 ; 0.27	N

MMSE, Mini Mental State Exam; ST1, modified Stroop Task 1; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate; L, large

2.4. Total Haemoglobin Index

THI changes in the LPFC and RPFC between the groups are displayed in *Figure 6.15* and *Figure 6.16*, respectively. THI increased slightly in the LPFC in both groups and across all the testing phases, with the largest increase during ST2 (E). A slightly different pattern was seen in the RPFC with the control group presenting with a decrease in THI in all of the testing phases, except for a miniscule increase during ST2 (E). The experimental group still maintained the positive increase in THI seen in the LPFC, however, the magnitude of the increase was substantially higher in the RPFC across all the testing phases with a 105% greater increase on average when compared to the control group.

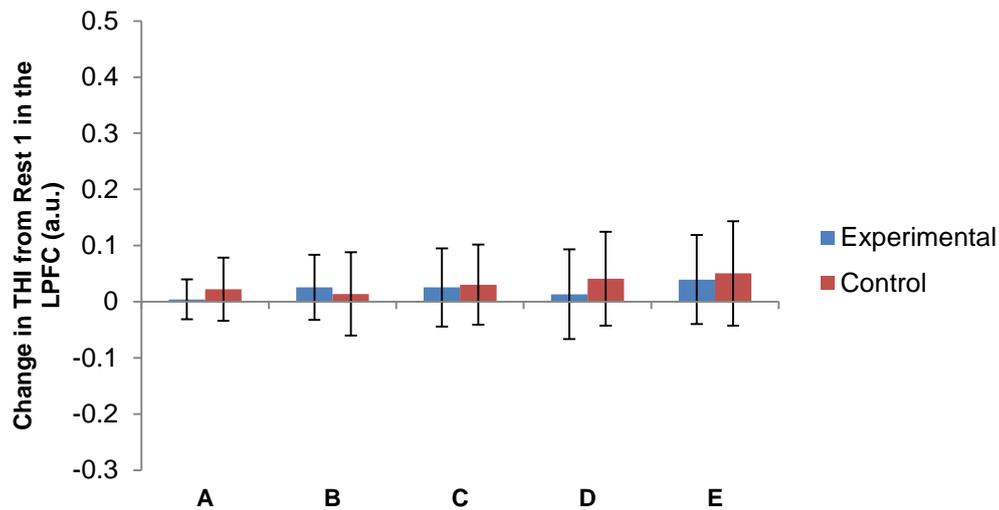


Figure 6.15. Change relative to resting period 1 (baseline) of Total Haemoglobin Index (THI) concentration in the Left Prefrontal Cortex (LPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2.

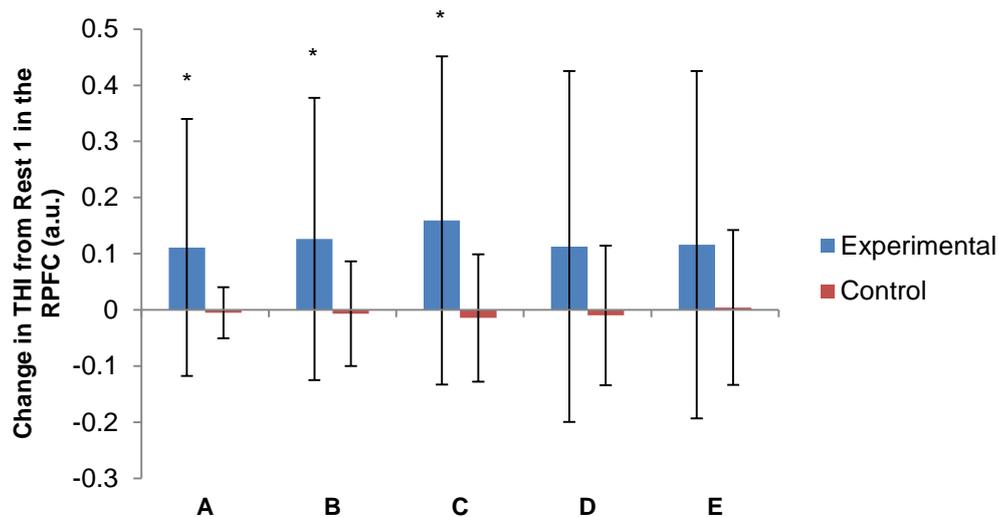


Figure 6.16. Change relative to resting period 1 (baseline) of Total Haemoglobin Index (THI) concentration in the Right Prefrontal Cortex (RPFC) during the various testing phases. A, difference between R1 and MMSE; B, difference between R1 and ST1; C, difference between R1 and TuG; D, difference between R1 and 6MWT; E, difference between R1 and ST2. * Statistically significant differences between experimental and control group ($p < 0.05$).

There were no statistically significant differences between the groups in the LPFC ($p > 0.05$) and the differences in the relative changes were mostly of small to negligible practical significance (*Table 6.9*). There were, however, statistically significant differences in THI between the groups in the RPFC during the MMSE (A; $p = 0.04$), ST1 (B; $p = 0.05$), and the TuG (C; $p = 0.02$), but not during the 6MWT (D) and ST2 (E) ($p > 0.05$). In terms of Cohen's effect sizes, these differences were of medium to large practical significance (ES = 0.62 to 0.97).

Table 6.9. Effect Sizes for changes in Total Haemoglobin Index (THI) relative to Rest 1 (Baseline)

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
MMSE	-0.26	-0.76 ; 0.23	S	0.65	-0.10 ; 1.40	M
ST1	0.17	-0.53 ; 0.87	S	0.74	-0.10 ; 1.58	M
TuG	-0.07	-0.83 ; 0.68	N	0.97	-0.01 ; 1.95	L
6MWT	-0.40	-1.28 ; 0.47	M	0.68	-0.36 ; 1.73	M
ST2	-0.16	-1.08 ; 0.76	S	0.62	-0.42 ; 1.67	M

MMSE, Mini Mental State Exam; ST1, modified Stroop Task 1; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test; ST2, modified Stroop Task 2; N, negligible; S, small; M, moderate; L, large

3. Changes in NIRS Measurements and Task Complexity

The modified Stroop Task consist of four stages (conditions) of increasing complexity, with stage 1 (condition 1 – C1) being the easiest and stage 4 (condition 4 – C4) being the most difficult. The task was completed once before exercise and once following exercise.

3.1. Oxyhaemoglobin

Changes in O₂Hb in the LPFC and RPFC between the two groups are displayed in *Figure 6.17*. Both groups presented with an increase in O₂Hb when performing C4 in comparison to C1. O₂Hb values were higher in the control group for both the LPFC and RPFC. There was an increase of 35% and 25% for the experimental and control group in the LPFC from C1 to C4 and an increase of 28% and 18% in the RPFC respectively. Despite this difference no statistically significant difference was found between the two groups across the two tasks ($p > 0.05$), although differences of small to moderate practical significance were seen (*Table 6.10*).

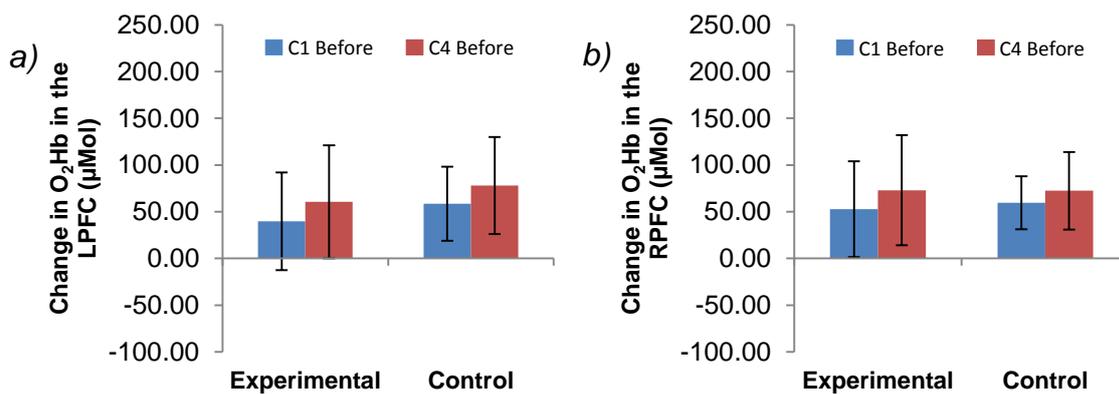


Figure 6.17. Changes in Oxyhaemoglobin (O₂Hb) between an easy (C1) and difficult (C4) cognitive task before exercise. *a)* Changes in the LPFC *b)* Changes in the RPFC. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

Table 6.10. Cohen’s Effect Sizes for changes in Oxyhaemoglobin (O₂Hb) during an easy and difficult cognitive task before a bout of exercise.

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
Experimental	0.37	-0.38 ; 1.12	S	0.36	-0.30 ; 1.02	S
Control	0.42	-0.24 ; 1.08	M	0.37	-0.38 ; 1.11	S

C1, condition one (easiest); C4, condition four (most difficult); S, small; M, moderate

3.2 Deoxy-haemoglobin

Changes in HHb in the LPFC and RPFc for both groups are shown in *Figure 6.18*, with both groups showing a similar pattern, reciprocal to the pattern seen for O₂Hb. The control group displayed consistently lower HHb values across both C1 and C4 with the magnitude of the difference being greater between the two groups in the RPFc, however, no statistically significant difference was found ($p > 0.05$). There was a 35% and 14% decrease in HHb in the LPFC for the experimental and control group respectively with a 45% and 23% decrease seen in the RPFc. From a practical perspective, only differences of negligible to small practical significance were found (*Table 6.11*).

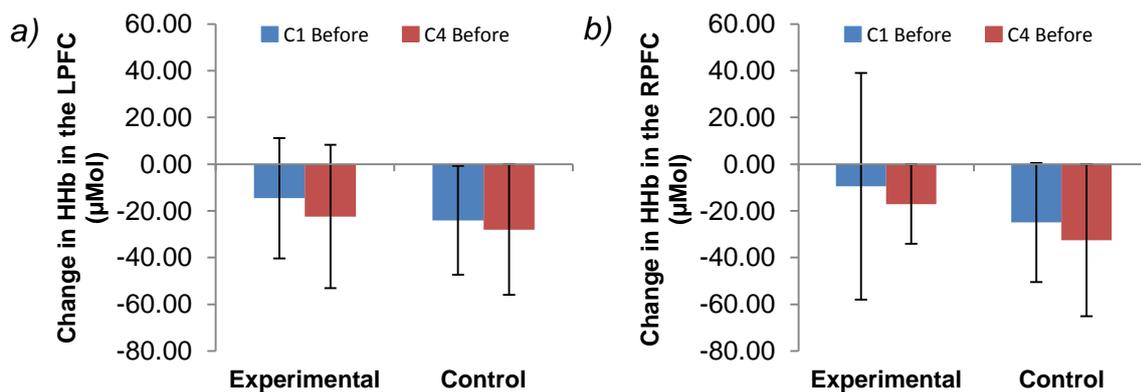


Figure 6.18. Changes in deoxy-haemoglobin (HHb) between an easy (C1) and difficult (C4) cognitive task before exercise. *a)* Changes in the LPFC *b)* Changes in the RPFc. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

Table 6.11. Cohen's Effect Sizes for changes in Deoxy-haemoglobin (HHb) during an easy and difficult cognitive task before and after a bout of exercise.

Condition	LPFC			RPFc		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
Experimental	-0.28	-1.02 ; 0.47	S	-0.15	-0.89 ; 0.60	N
Control	-0.15	-0.81 ; 0.50	N	-0.26	-0.91 ; 0.40	S

C1, condition one (easiest); C4, condition four (most difficult); N, negligible; S, small

3.3. Total Haemoglobin Index

Changes in THI in both the LPFC and RPFC between both groups are shown in *Figure 6.19*. A statistically significant difference was found in the RPFC between the groups during C4 before exercise ($p = 0.04$) and a borderline statistically significant difference was found during C1 before exercise ($p = 0.07$). The increases in THI in the LPFC and RPFC, as well as the two groups were minimal ($\pm 1\%$) with no further statistically or practically significant differences found (*Table 6.12*).

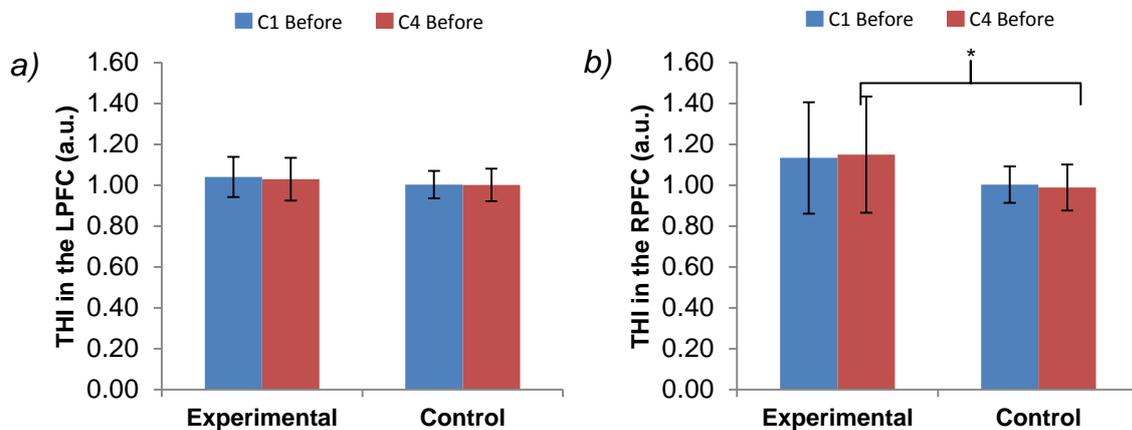


Figure 6.19. Changes in total haemoglobin index (THI) between an easy (C1) and difficult (C4) cognitive task before exercise. a) Changes in the LPFC b) Changes in the RPFC. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition). * Statistically significant difference between the groups for C4 ($p < 0.05$).

Table 6.12. Cohen's Effect Sizes for changes in Total Haemoglobin Index (THI) during an easy and difficult cognitive task before and after a bout of exercise.

Condition	LPFC			RPFC		
	ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
Experimental	-0.10	-0.84 ; 0.65	N	0.07	-0.67 ; 0.81	N
Control	0.00	-0.65 ; 0.65	N	-0.10	-0.75 ; 0.55	N

C1, condition one (easiest); C4, condition four (most difficult); N, negligible; S, small; M, moderate; L, large

4. Changes in NIRS measurements and exercise

Changes before exercise (pre-exercise) were compared to changes after exercise (post-exercise) for both the experimental and control group during C1 and C4 and are displayed below. Additionally, Cohen's Effect Sizes (ES) for practical significance were calculated and reported for the changes in NIRS variables as a result of exercise.

4.1. Oxyhaemoglobin

Changes pre- to post-exercise in O₂Hb in the LPFC and RPFC are shown in *Figure 6.20* and *Figure 6.21*, respectively. The magnitude of the change was greater in the LPFC for the experimental group for both pre- and post-exercise, whereas the magnitude of the change for the control group was similar in both the LPFC and RPFC. No statistically significant differences were found between the two groups pre- or post-exercise in either C1 or C4 ($p > 0.05$). There was an increased change of 83% between C1 and C4 for the control group in the LPFC, while the experimental group increased by 46%. In the RPFC O₂Hb increased by 90% between C1 and C4 for the control group, and by 36% in the experimental group, thereby further illustrating that the magnitude of the change was higher in the LPFC for the experimental group whereas the control group remained relatively similar. Differences of practical significance were negligible for the most part (*Table 6.13*), however, the change in C4 had moderate practical significance in the LPFC (ES = 0.44).

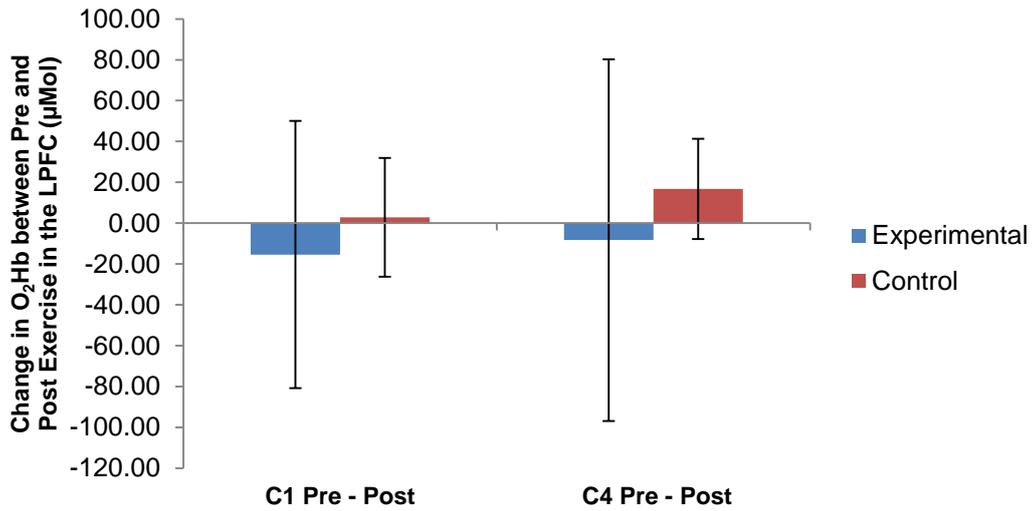


Figure 6.20. The effect of exercise on Oxyhaemoglobin (O₂Hb) in the LPFC after completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

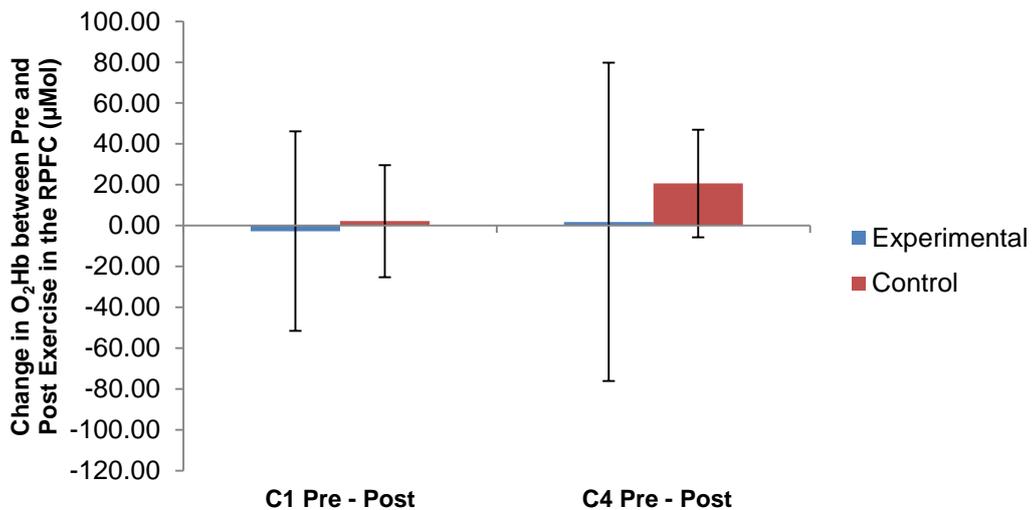


Figure 6.21. The effect of exercise on Oxyhaemoglobin (O₂Hb) in the RPFC after completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

4.2. Deoxy-haemoglobin

Changes in HHb, pre- to post-exercise for C1 and C4 in the LPFC and RPFc are shown in *Figure 6.22* and *Figure 6.23*, respectively. The magnitude of the change was greater in the experimental group for C1 and C4 in both the LPFC and RPFc ($6.34 \pm 19.75 \mu\text{mol}$ and $8.21 \pm 15.70 \mu\text{mol}$ versus $5.32 \pm 15.61 \mu\text{mol}$ and $-2.87 \pm 13.24 \mu\text{mol}$ in the LPFC and $2.71 \pm 26.31 \mu\text{mol}$ and $2.33 \pm 22.86 \mu\text{mol}$ versus $-0.10 \pm 23.51 \mu\text{mol}$ and $-2.18 \pm 14.81 \mu\text{mol}$ in the RPFc), although the change was less in the RPFc. No statistically significant differences were found between the two groups in either the LPFC or RPFc, or between C1 and C4 ($p > 0.05$). There was an increased change of 23% from C1 to C4 in the LPFC for the experimental group, while the control group saw a decrease of 154% from C1 to C4. In the RPFc the experimental group had a slight decrease of 16% from C1 to C4, while the control group had a 95% decrease from C1 to C4. Furthermore, only negligible to small differences of practical significance were seen (*Table 6.13*).

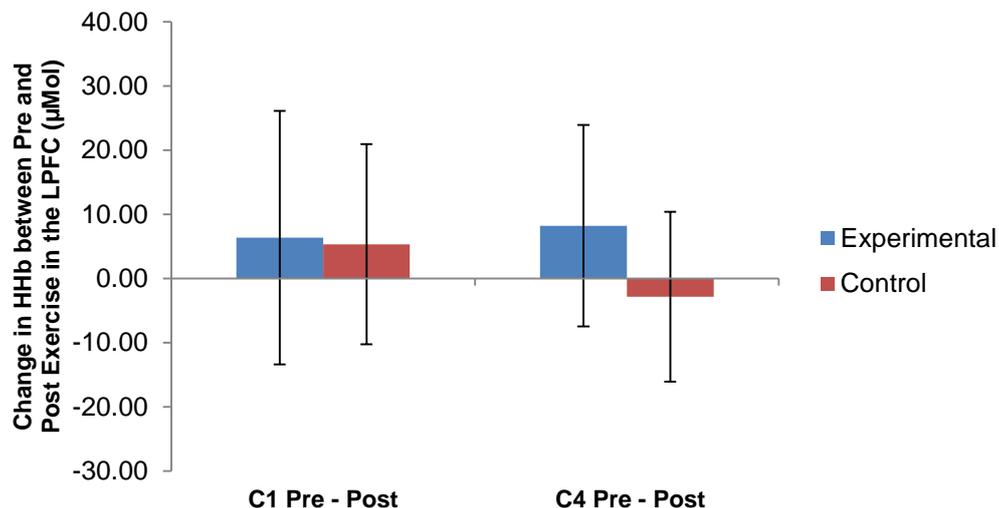


Figure 6.22. The effect of exercise on Deoxy-haemoglobin (HHb) in the LPFC when completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

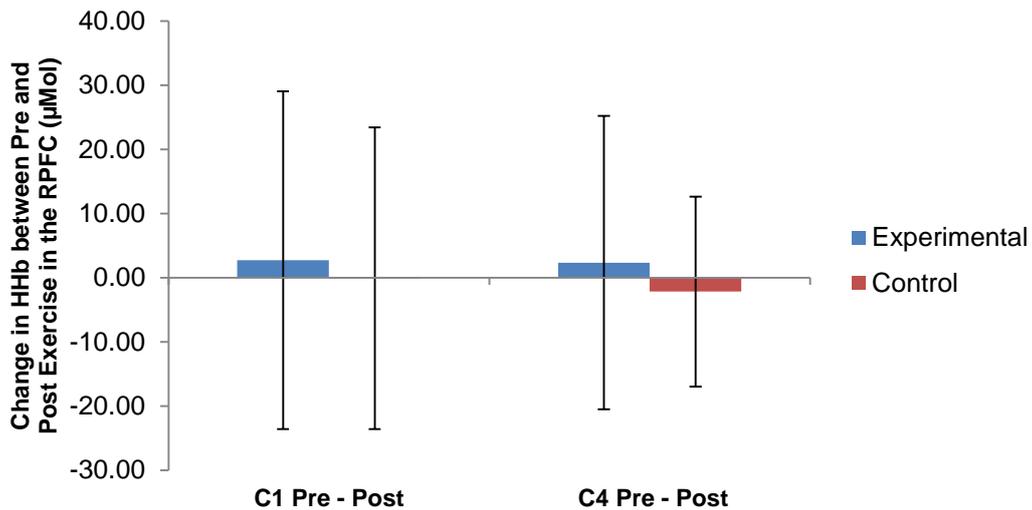


Figure 6.23. The effect of exercise on Deoxy-haemoglobin (HHb) in the RPFC when completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

4.3. Total Haemoglobin Index

Changes between C1 and C4, pre- to post-exercise, in THI in the LPFC and RPFC are shown in *Figure 6.24* and *Figure 6.25*. The magnitude of the change was far greater for the control group than the experimental group in the LPFC and RPFC as well as C1 and C4 (0.05 a.u. and 0.04 a.u. in the LPFC and 0.01 a.u. and 0.03 a.u. in the RPFC), although the change was less pronounced in the RPFC. No statistically significant differences were found between the two groups in the LPFC and RPFC, as well as C1 and C4 ($p > 0.05$), although a difference of moderate practical significance was found during C1 in the LPFC (ES = 0.48; *Table 6.13*). Interestingly, the experimental group had an increased change in C1 and C4 in the LPFC, while there was a decrease in both conditions in the RPFC. In the LPFC there was an increase of 90% between C1 and C4 for the experimental group, while the control group saw a decrease of 25% between C1 and C4. In the RPFC there was an increase of 24% for the experimental group between C1 and C4, although the overall

change was still negative, while the control group had an increase of 67% between C1 and C4.

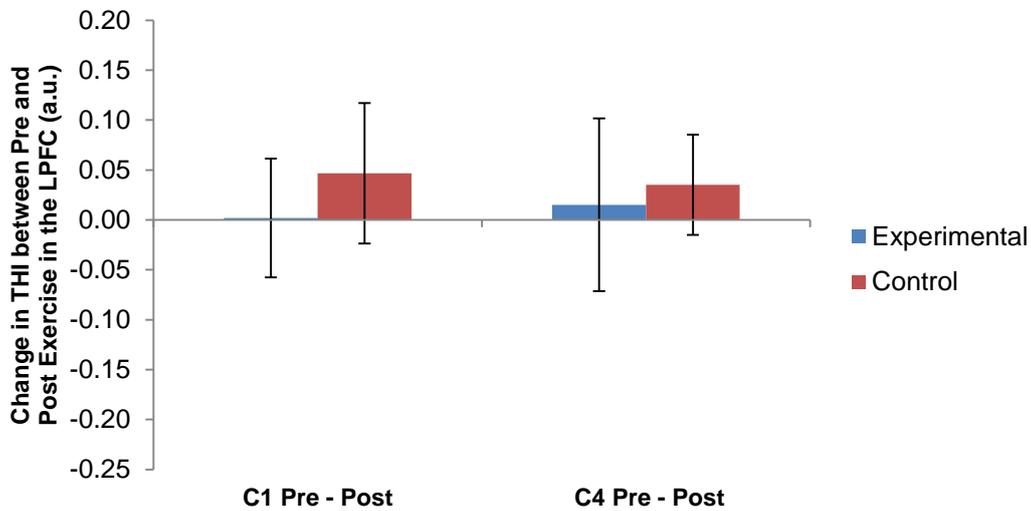


Figure 6.24. The effect of exercise on Total Haemoglobin Index (THI) in the LPFC when completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

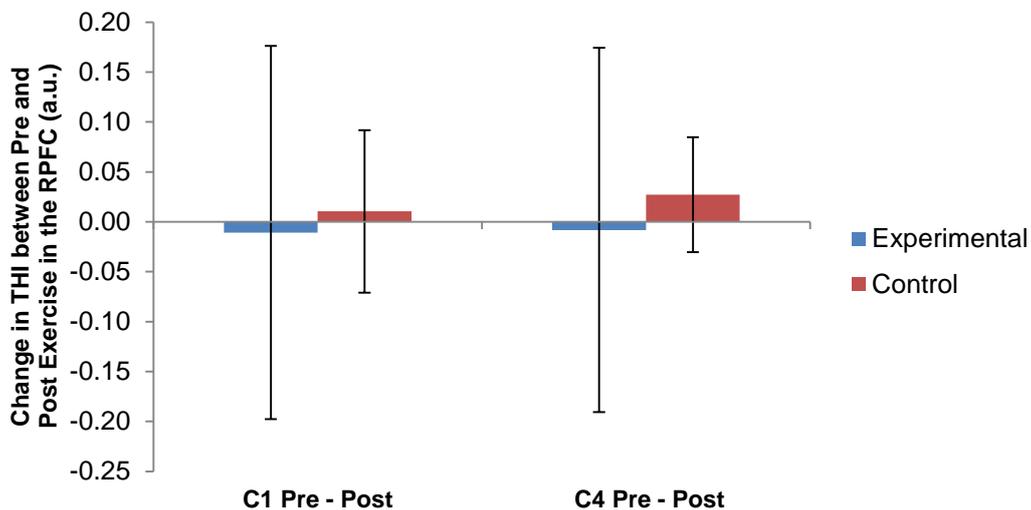


Figure 6.25. The effect of exercise on Total Haemoglobin Index (THI) in the LPFC when completing an easy (C1) and difficult (C4) cognitive task. C1, condition one of the modified Stroop Task (easiest condition); C4, condition four of the modified Stroop Task (most difficult condition).

Table 6.13. Effect Sizes for Changes in NIRS variables during an easy and difficult cognitive task pre- and post-exercise.

NIRS Variable	Condition	LPFC			RPFC		
		ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
O ₂ Hb	C1 B – A	0.32	-0.38 ; 1.02	S	0.10	-0.51 ; 0.71	N
	C4 B – A	0.44	-0.48 ; 1.36	M	0.38	-0.55 ; 1.30	S
HHb	C1 B – A	-0.03	-0.48 ; 0.42	N	-0.06	-0.47 ; 0.34	N
	C4 B – A	-0.38	-0.74 ; -0.01	S	-0.10	-0.42 ; 0.22	N
THI	C1 B – A	0.48	-0.03 ; 0.98	M	0.10	-0.41 ; 0.60	N
	C4 B – A	0.21	-0.37 ; 0.79	S	0.16	-0.32 ; 0.64	S

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; C1, condition one (easiest); C4, condition four (most difficult); B, before exercise; A, after exercise; N, negligible; S, small; M, moderate; L, large

5. Changes in NIRS Measurements: Rehabilitation versus No Rehabilitation

NIRS variables were compared within the experimental group among stroke patients who underwent regular rehabilitation following a stroke (n = 8; Rehab) and those who did not (n = 6; No Rehab). These variables were compared during a cognitive task (MMSE) and a functional task (TuG). Changes relative to resting period 1 (baseline) were calculated for O₂Hb, HHb and THI in the LPFC and RPFC.

5.1. Oxyhaemoglobin

Changes in O₂Hb between the two groups in the LPFC and RPFC are shown in *Figure 6.26* and *Figure 6.27*, respectively. The no rehab group showed a similar pattern of change in the LPFC and RPFC for the cognitive and functional task, with the magnitude of change in the RPFC being 32% higher than the LPFC. The rehab group showed increases in O₂Hb during the MMSE in both the LPFC and RPFC (13.73 μ Mol and 22.41 μ Mol), however, had a decrease during the TuG in the LPFC (-7.32 μ Mol) and an increase in the RPFC (22.82 μ Mol). The magnitude of the increase was greater for the no rehab group

when compared to the rehab group, however, the differences were not statistically significant ($p > 0.05$). Practically, moderate to large differences were seen during the MMSE in the RPFC (ES = -0.63), during the TuG in the LPFC (ES = -0.68) and during the MMSE in the LPFC (ES = -0.92; $p = 0.08$) respectively, and are displayed in *Table 6.14*.

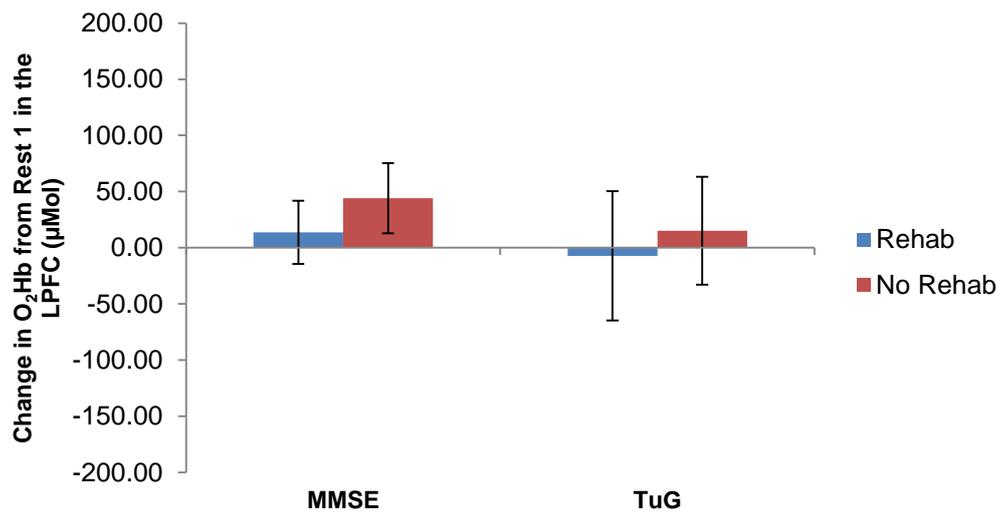


Figure 6.26. Changes in Oxyhaemoglobin (O₂Hb) from baseline in the LPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

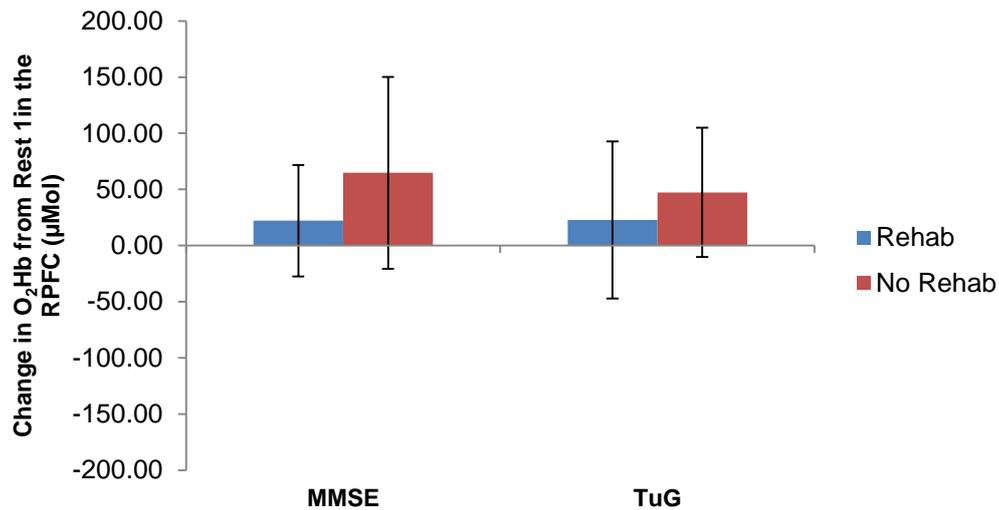


Figure 6.27. Changes in Oxyhaemoglobin (O_2Hb) from baseline in the RPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

5.2. Deoxy-haemoglobin

Changes in HHb between the two groups in the LPFC and RPFC are shown in *Figure 6.28* and *Figure 6.29*, respectively. The rehab and no rehab groups showed similar patterns during the TuG in both the LPFC and RPFC, with the no rehab group showing an increase of similar magnitude in the LPFC and RPFC. There was a 33% greater increase for the rehab group in the RPFC when compared to the LPFC with no statistically significant differences found between the rehab and no rehab group ($p > 0.05$). During the MMSE, the no rehab group had a decrease in both the LPFC and RPFC with the decrease in the LPFC being 92% higher than the RPFC and 44% greater than the rehab group. The rehab group had a marginal increase in the RPFC, although no statistical significance was found between the two groups ($p > 0.05$). There were mostly negligible to small differences of practical significance between the two groups, with only the TuG in the LPFC showing a difference of moderate significance ($ES = -0.57$) as shown in *Table 6.14*.

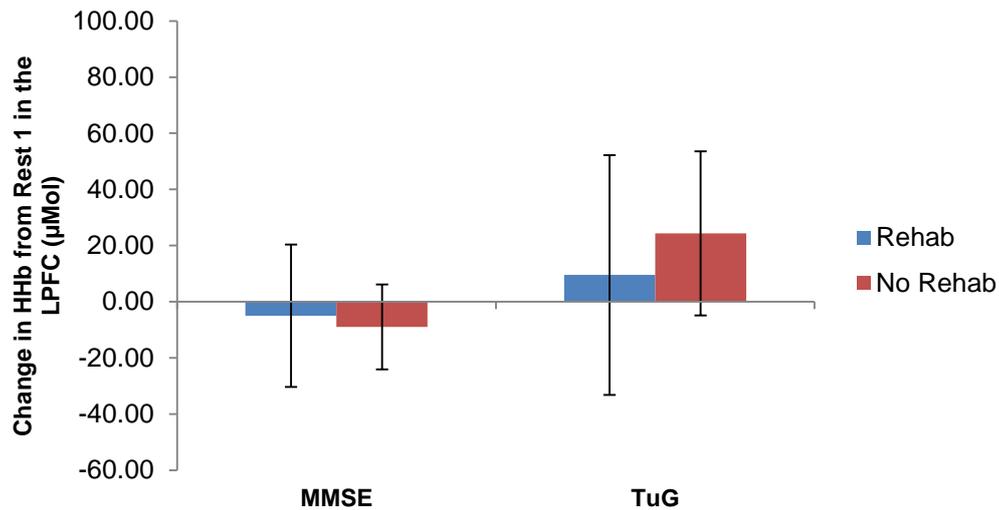


Figure 6.28. Changes in Deoxy-haemoglobin (HHb) from baseline in the LPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

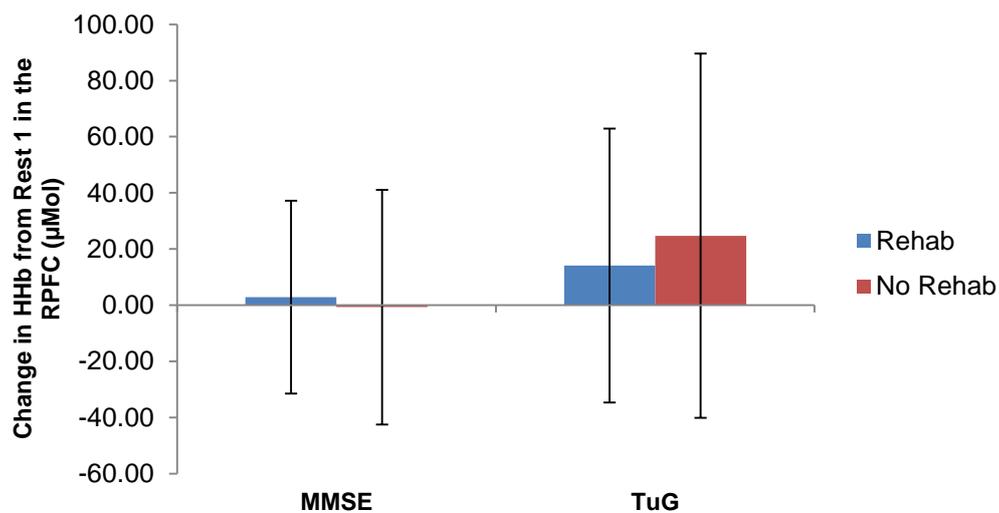


Figure 6.29. Changes in Deoxy-haemoglobin (HHb) from baseline in the RPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

5.3. Total Haemoglobin Index

Changes in THI between the two groups during the MMSE and TuG in the LPFC and RPFC are shown in *Figure 6.30* and *Figure 6.31*, respectively. Once again, a similar pattern was seen in the no rehab group with an increase from baseline seen in both the LPFC and RPFC during the MMSE and TuG, however, the magnitude of the change was far greater in the RPFC. There was a statistically significant difference between the two groups during the TuG in the RPFC ($p = 0.005$) and differences of moderate practical significance during the TuG in the LPFC ($ES = -0.69$) and RPFC ($ES = -0.67$), as well as the MMSE in the LPFC ($ES = -0.62$), shown in *Table 6.14*.

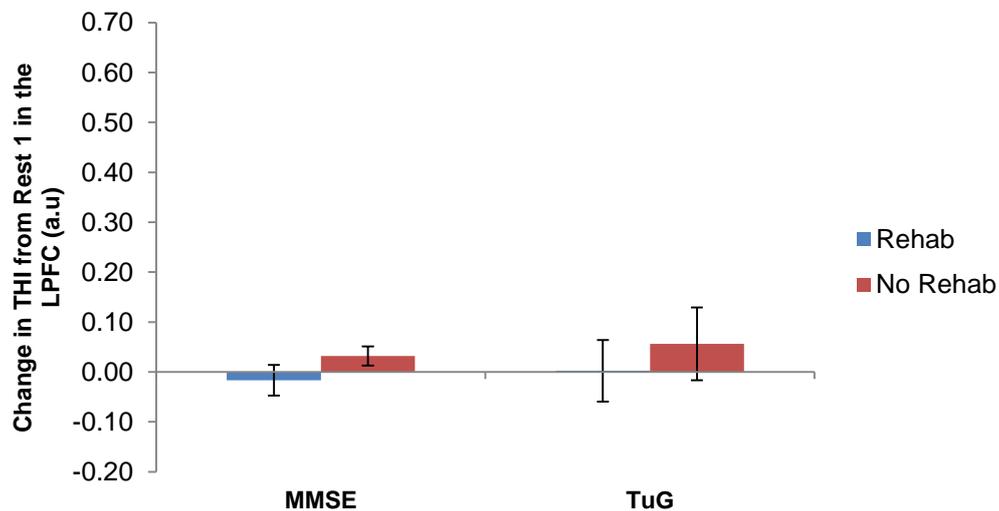


Figure 6.30. Changes in Total Haemoglobin Index (THI) from baseline in the LPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

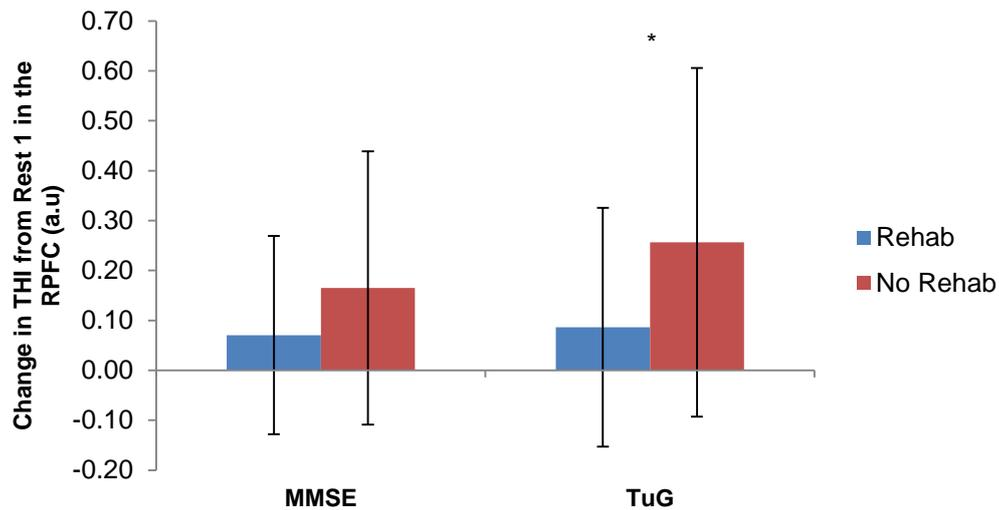


Figure 6.31. Changes in Total Haemoglobin Index (THI) from baseline in the RPFC during the Mini Mental State Exam (MMSE) and the Timed Up-and-Go (TuG) between stroke patients who have had rehabilitation and those who have not.

Table 6.14. Effect Sizes for changes in NIRS variables between stroke patients who have had rehabilitation and those who have not.

NIRS Variable	Condition	LPFC			RPFC		
		ES	95% CI	Qualitative Outcome	ES	95% CI	Qualitative Outcome
O ₂ Hb	MMSE	-0.92	-2.02 ; 0.18	L	-0.63	-2.00 ; 0.74	M
	TuG	-0.68	-2.57 ; 1.21	M	-0.36	-1.47 ; 0.75	S
HHb	MMSE	0.15	-0.78 ; 1.08	S	0.08	-0.96 ; 1.12	N
	TuG	-0.57	-2.21 ; 1.07	M	-0.23	-1.83 ; 1.37	S
THI	MMSE	-0.62	-0.99 ; -0.24	M	-0.37	-1.56 ; 0.82	S
	TuG	-0.69	-1.75 ; 0.38	M	-0.67	-2.16 ; 0.83	M

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; MMSE, Mini Mental State Exam; TuG, Timed Up-and-Go; N, negligible; S, small; M, moderate; L, large

C. COGNITIVE FUNCTIONING

The MMSE and modified Stroop Task were used to measure cognitive functioning in the experimental and control group, as well as within the experimental group for those patients who had received regular rehabilitation following their stroke and those who have not.

1. Global Changes

Differences in the Mini Mental State Exam (MMSE) scores, as well as reaction time (RT) and error frequency during the various stages of the modified Stroop Task were compared between the experimental and control group. Furthermore, Cohen's Effect Sizes (ES) were calculated and reported to indicate practically significant differences.

1.1 Mini Mental State Exam

Differences in MMSE score between the experimental and control group are displayed in *Figure 6.32*, and show that the control group scored slightly higher (3%) than the experimental group, however, this difference was not statistically significant and showed only a small practical significance ($ES = -0.26$; $p > 0.05$).

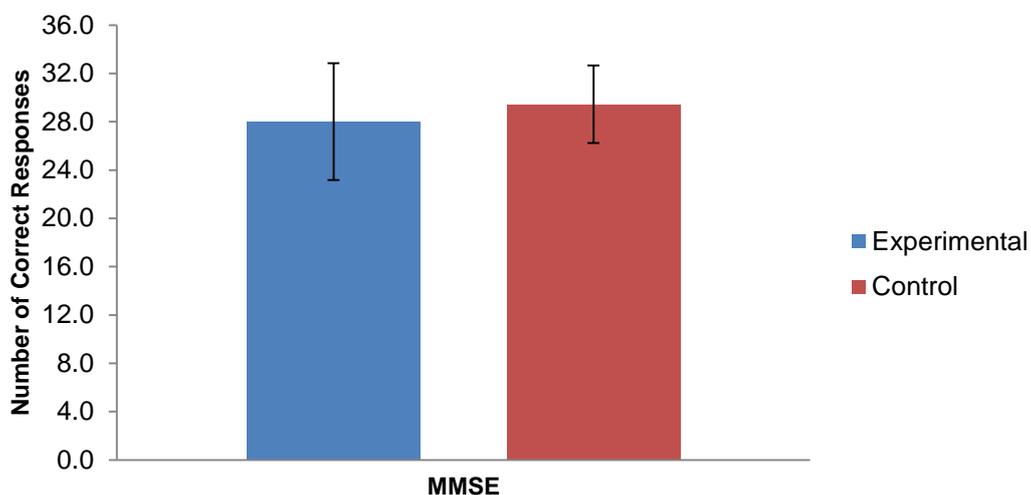


Figure 6.32. MMSE scores between the experimental and control group. MMSE, Mini Mental State Exam.

1.2. Modified Stroop Task

The various stages of the modified Stroop Task before exercise and the differences between the experimental and control group are shown in *Figure 6.33*. The experimental group had a higher reaction time (i.e. reacted slower) than the control group for all the testing conditions, except for C4, where they reacted 1% quicker (0.3 seconds) than the control group. C2 showed the quickest mean reaction time for both groups, with the C3 and C4 showing the slowest mean reaction time in both groups. There was a 28% (1.15 seconds), 23% (0.67 seconds) and 21% (1.25 seconds) difference between the experimental and control group for C1, C2 and C3, respectively, however, these differences were not statistically significant ($p > 0.05$). Moderate practically significant differences were seen in C1 and C2 ($ES = 0.58$; $ES = 0.54$) as shown in *Table 6.15*.

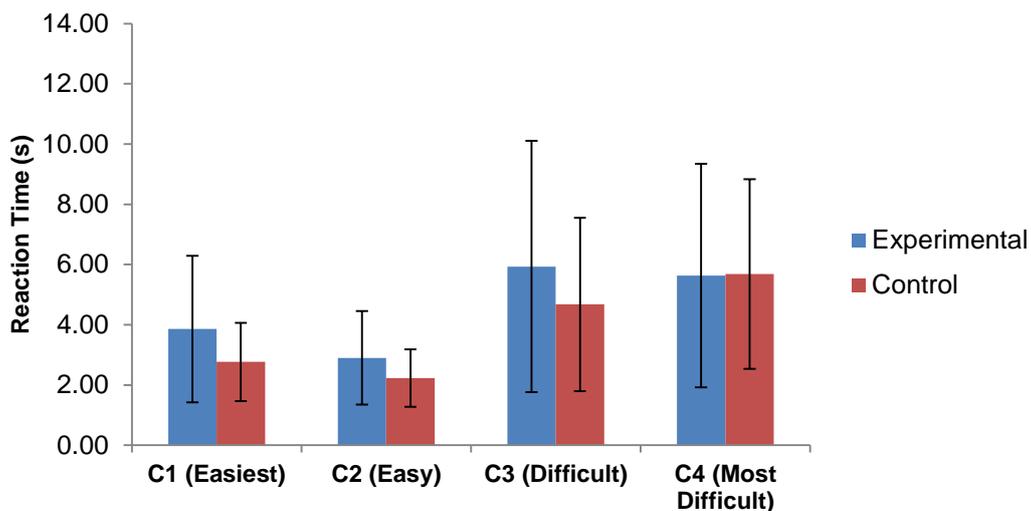


Figure 6.33. Reaction time (RT) before exercise during the various stages of the modified Stroop Task. C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult).

Differences in reaction time following exercise between the two groups can be seen in *Figure 6.34*, and generally followed a similar pattern to before exercise. The exception was C4, where the control group had quicker reaction times than the experimental group after exercise (4.42 ± 2.16 seconds versus 6.44 ± 5.90 seconds, $p > 0.05$). Furthermore, the experimental group's reaction time was 27% (0.68 seconds) and 31% (2.02 seconds) slower than the control group during C1 and C4 respectively, but these differences were not statistically significant ($p > 0.05$), although differences of moderate practical significance were found in C1 and C4 ($ES = 0.61$; $ES = 0.48$) as shown in *Table 6.15*.

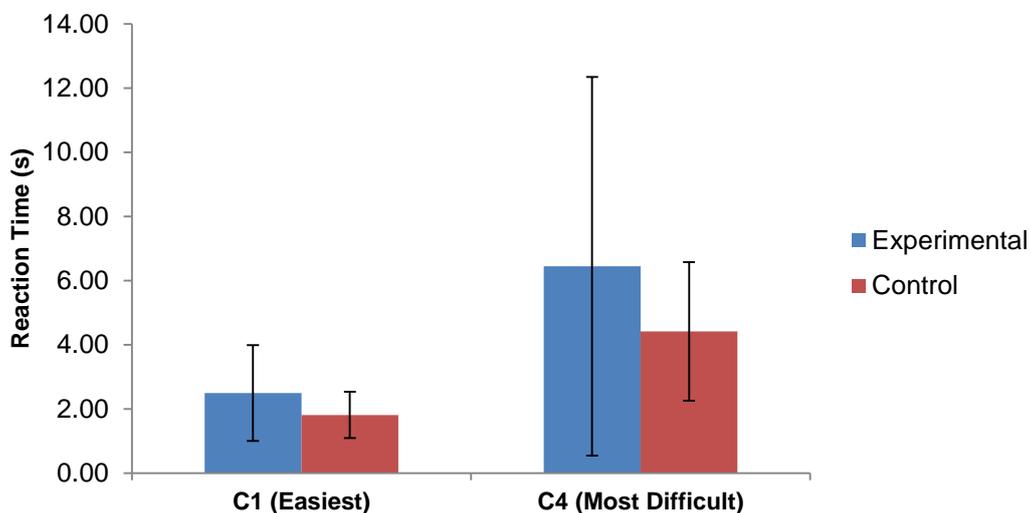


Figure 6.34. Reaction time (RT) after exercise during C1 and C4 of the modified Stroop Task. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

The effect of exercise on the reaction time during the modified Stroop Task is displayed in *Figure 6.35*. The control group presented with a faster reaction time in both C1 and C4 following exercise (1.81 ± 0.72 seconds versus 2.77 ± 1.30 seconds in C1 and 4.42 ± 2.16 seconds versus 5.69 ± 3.15 seconds in C4), with the experimental group only showing faster reaction times in C1 following exercise (2.49 ± 1.49 seconds versus 3.86 ± 2.43 seconds). There were, however, no statistically significant differences between the

reaction times of the groups following exercise ($p > 0.05$), although differences of moderate practical significance were seen in C4 ($ES = 0.57$), shown in *Table 6.15*.

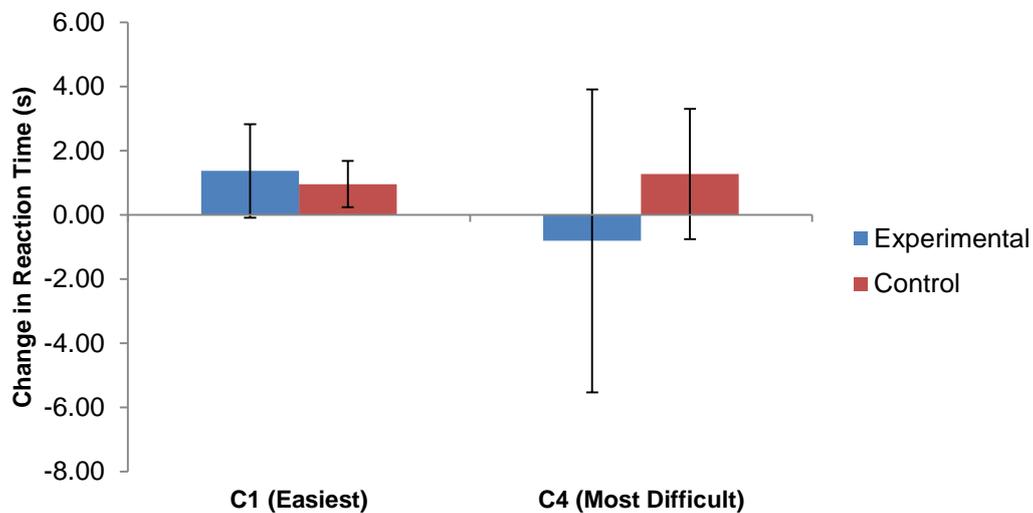


Figure 6.35. Relative changes in reaction time (RT) after exercise for C1 and C4 of the Modified Stroop Task. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

The effect of exercise on the number of errors during the various stages of the modified Stroop Task and between the experimental and control group are displayed in *Figure 6.36*. The experimental group had a higher error count during C1 and C2 compared to the control group, whereas the control group had a higher error count in C3 and C4 compared to the experimental group. Errors in both groups steadily increased as task complexity increased, with the experimental group making 2.4 mistakes on average over the whole task, while the control group made 2.5 mistakes on average. Although no statistically significant differences were found between the two groups ($p > 0.05$), differences of moderate practical significance were seen in C1 ($ES = 0.69$; $p = 0.06$) as shown in *Table 6.16*.

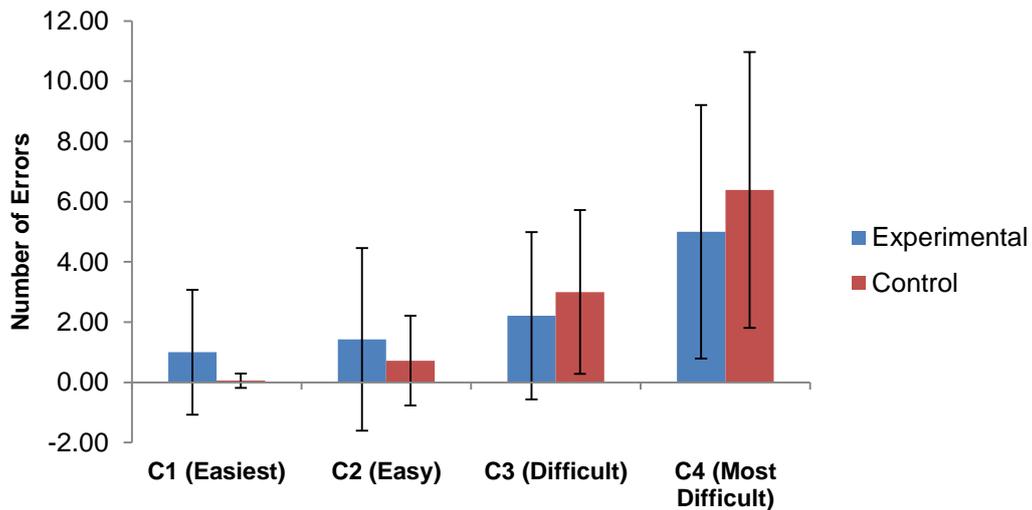


Figure 6.36. Number of errors before exercise during the various stages of the modified Stroop task. C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult).

The number of errors during C1 and C4 of the modified Stroop Task following exercise for the two groups are displayed in *Figure 6.37*. A similar pattern to the error rate before exercise was seen following exercise, with the experimental group having a higher error rate in the easiest condition (C1) and the control group having a higher error rate in the most difficult condition (C4). On average the experimental group made 3.1 errors during the whole task, while the control group made 3.5 errors on average. Although these differences were not statistically significant ($p > 0.05$), differences of moderate practical significance ($ES = 0.57$) were found and are shown in *Table 6.16*.

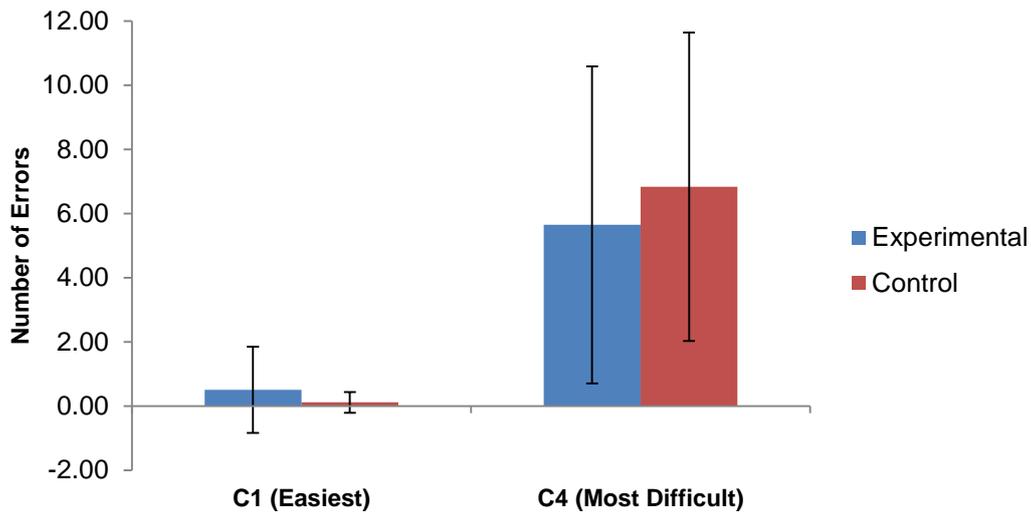


Figure 6.37. Number of errors after exercise during C1 and C4 of the modified Stroop task. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

Table 6.15. Effect Sizes for differences in reaction time (RT) between the experimental and control groups during the various stages of the modified Stroop Task.

Phase	Condition	ES	95% CI	Qualitative Outcome
Before Ex	C1	0.58	-0.13 ; 1.30	M
	C2	0.54	-0.18 ; 1.25	M
	C3	0.36	-0.34 ; 1.06	S
	C4	-0.02	-0.72 ; 0.68	N
After Ex	C1	0.61	-0.10 ; 1.32	M
	C4	0.48	-0.23 ; 1.19	M
Relative Change	C1	-0.37	-1.08 ; 0.33	S
	C4	0.57	-0.15 ; 1.28	M

C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult); N, negligible; S, small; M, moderate; L, large

Table 6.16. Effect Sizes for differences in error frequency between the two groups during the various stages of the modified Stroop Task.

Phase	Condition	ES	95% CI	Qualitative Outcome
Before Ex	C1	0.69	-0.03 ; 1.40	M
	C2	0.31	-0.39 ; 1.01	S
	C3	-0.29	-0.99 ; 0.42	S
	C4	-0.31	-1.02 ; 0.39	S
After Ex	C1	0.42	-0.28 ; 1.13	M
	C4	-0.24	-0.95 ; 0.46	S

C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult); N, negligible; S, small; M, moderate; L, large

2. Rehabilitation versus No Rehabilitation

The experimental group was once again subdivided into those who had regular rehabilitation following their stroke, and those that had not. Differences between the MMSE score, modified Stroop Task reaction time and error frequency, both before and after exercise were examined for potential differences between the two groups and Cohen's Effect Sizes (ES) were calculated and reported for differences in practical significance.

2.1. Mini Mental State Exam

The MMSE scores displayed in *Figure 6.38*, show that the no rehab group scored 10% lower than the rehab group, although this difference was not statistically significant ($p > 0.05$). However, according to Cohen's effect size, this difference is of moderate practical significance (ES = 0.61).

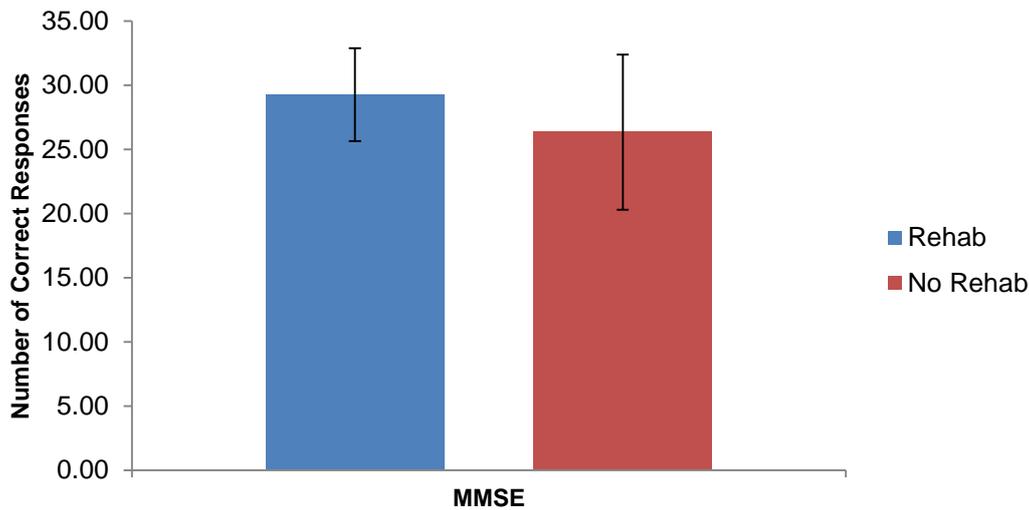


Figure 6.38. MMSE scores between stroke patients who have had rehabilitation and those who have not. MMSE, Mini Mental State Exam.

2.1 Modified Stroop Task

Differences in reaction time between the rehab and no rehab group during the various stages of the modified Stroop Task are displayed in *Figure 6.39*. Across all the conditions the no rehab group had slower reaction times, with the slowest being during C3 (7.45 ± 6.15 seconds). The same pattern was seen for the rehab group where the slowest reaction time also occurring during C3 (4.80 ± 1.34 seconds). The rehab group had a 22% (0.95 seconds), 26% (0.87 seconds), 36% (2.65 seconds) and 38% (2.70 seconds) faster reaction time when compared to the no rehab group during C1, C2, C3 and C4 respectively, although these differences were not statistically significant ($p > 0.05$). However, differences of moderate practical significance were found in C2 (ES = -0.56) and C3 (ES = -0.65), with differences of large practical significance in C4 (ES = -0.75) as shown in *Table 6.17*.

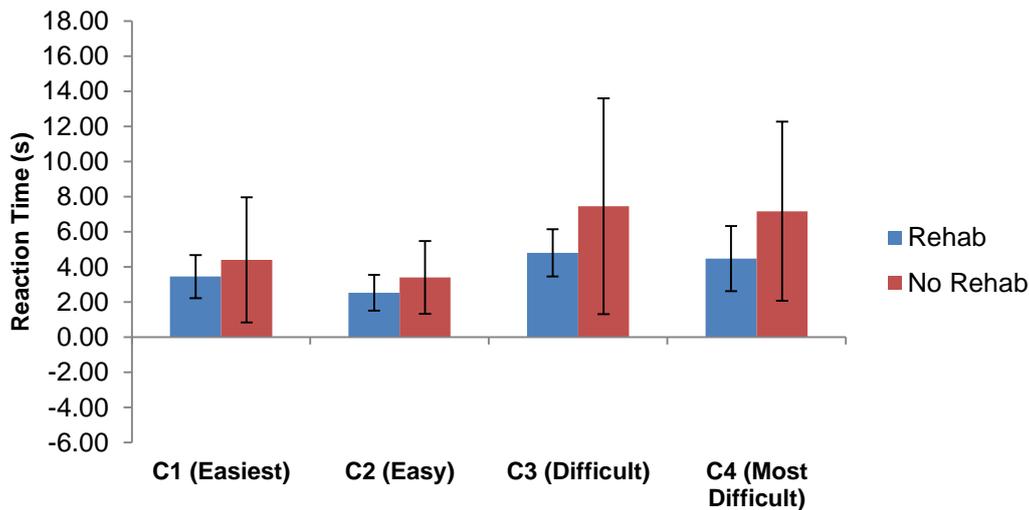


Figure 6.39. Differences in reaction time (RT) before exercise during the various stages of the modified Stroop Task between the rehab and no rehab group. C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult).

A similar pattern in reaction times following exercise was found in the rehab and no rehab group and is displayed in *Figure 6.40*. The rehab group had a 31% (0.94 seconds) and 30% (2.33 seconds) quicker reaction time than the no rehab group during C1 and C4 following exercise, although these differences were not statistically significant ($p > 0.05$). Only C1 provided evidence of differences of moderate practical significance ($ES = -0.65$) as shown in *Table 6.17*.

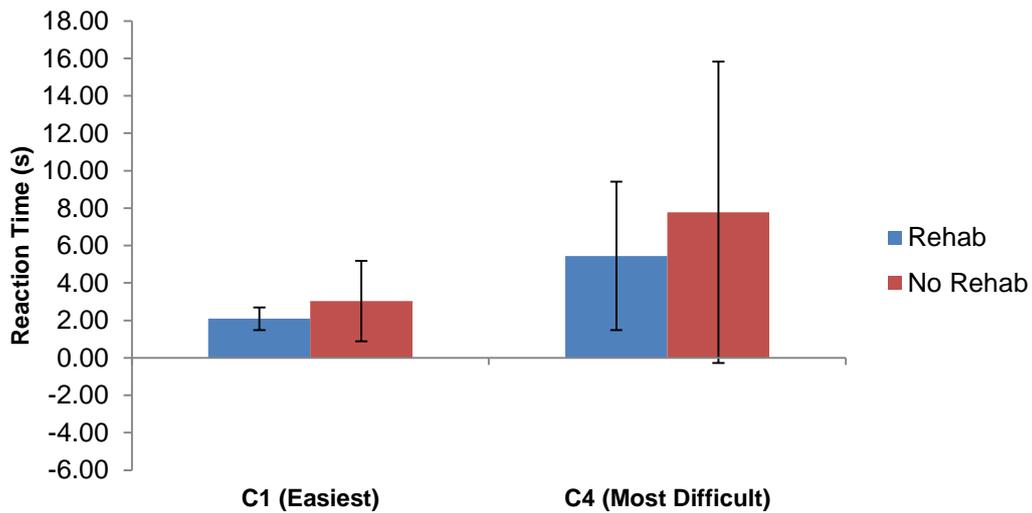


Figure 6.40. Differences in reaction time (RT) after exercise during C1 and C4 of the modified Stroop Task between the rehab and no rehab groups. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

The relative change in reaction time following exercise for both groups in C1 and C4 is displayed in *Figure 6.41* and showed no significant differences between the two groups, although moderate practically significant differences were once again seen in C1 (ES = 0.44; $p > 0.05$), displayed in *Table 6.17*. Interestingly, reaction time was quicker in both the rehab and the no rehab group during C1, while it was slower following exercise in C4. The change in reaction time during both conditions was similar, with the rehab group presenting with a slightly greater decrease (or slower) reaction time in C4.

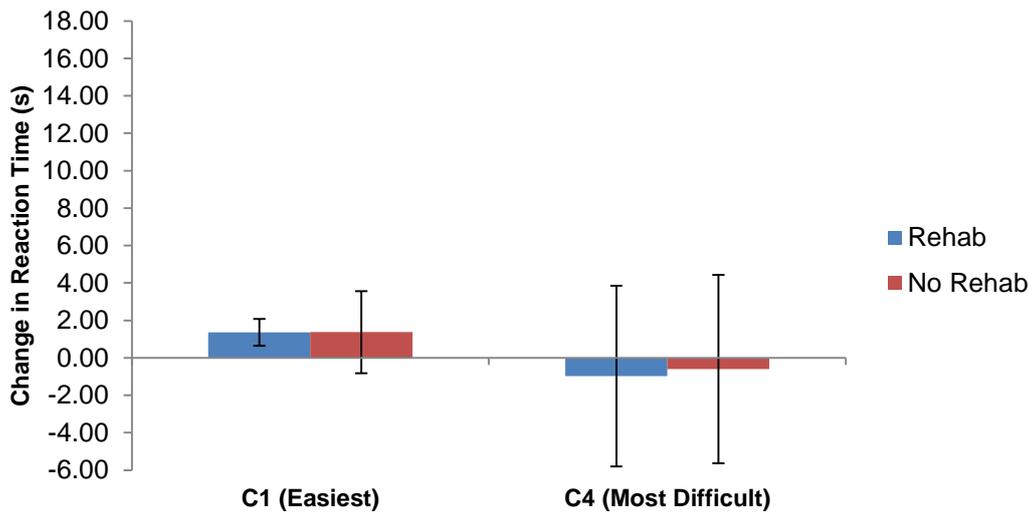


Figure 6.41. Relative changes in reaction time (RT) after exercise for C1 and C4 of the Modified Stroop Task for those who have had rehabilitation and those who have not. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

The number of errors made by both groups during the various stages of the modified Stroop Task before exercise is shown in *Figure 6.42*. The no rehab group made the highest number of errors during C1, C2 and C3, while the rehab group made the highest number of errors during C4. The no rehab group made on average 3 more mistakes over all the testing conditions, whereas the rehab group only made 2 mistakes on average. Furthermore, the highest error rate in both groups was seen in C4 (5.5 for rehab versus 4.3 for no rehab), whereas the lowest error rate was in C1 for the no rehab group (1.67) and C2 for the rehab group (0.38). No statistically significant differences were found between the groups ($p > 0.05$). Moderate and large differences of practical significance were found in C1 (ES = -0.57), C3 (ES = -0.49) and C2 (ES = -0.85) respectively as shown in *Table 6.18*.

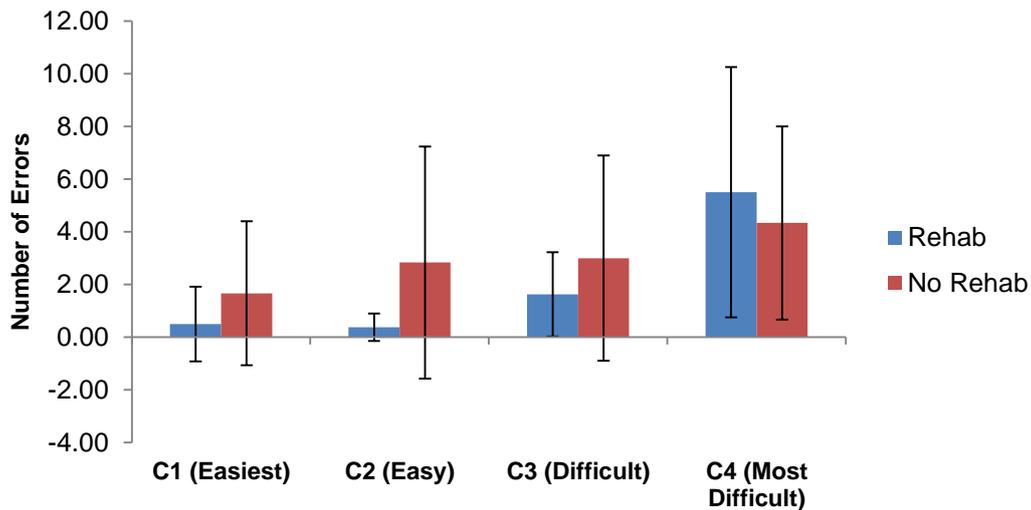


Figure 6.42. Number of errors before exercise during the various stages of the modified Stroop Task for those who have had rehabilitation and those who have not. C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult).

The number of errors made by both groups following exercise during the modified Stroop Task is displayed in *Figure 6.43*. Once again, no statistically significant differences were found between the groups ($p > 0.05$), however, error frequency did decrease following exercise in both groups during C1, resulting in a difference of moderate practical significance ($ES = -0.43$; *Table 6.18*). This was, however, not the case for C4 where error frequency increased by 4% and 21%, respectively, for the rehab and no rehab group. Similarly to before exercise, the rehab group had a lower number of errors during C1, but a higher number of errors during C4 following exercise.

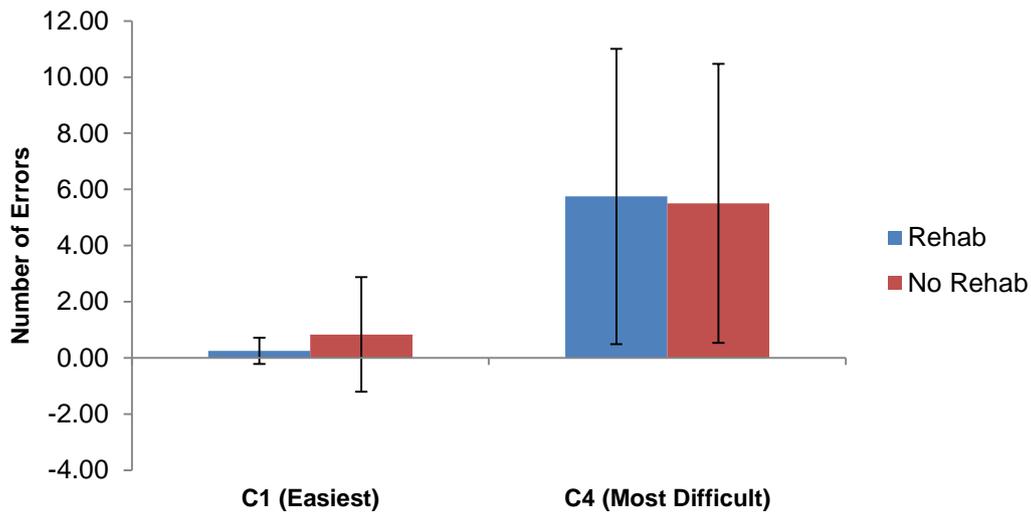


Figure 6.43. Number of errors after exercise during C1 and C4 of the modified Stroop Task for those who have had rehabilitation and those who have not. C1, Condition one of the modified Stroop Task (easiest); C4, Condition four of the modified Stroop Task (most difficult).

Table 6.17. Effect Sizes for differences in reaction time (RT) between the rehab and no rehab groups during the various stages of the modified Stroop Task.

Phase	Condition	ES	95% CI	Qualitative Outcome
Before Ex	C1	-0.38	-1.45 ; 0.69	S
	C2	-0.56	-1.64 ; 0.52	M
	C3	-0.65	-1.73 ; 0.44	M
	C4	-0.75	-1.85 ; 0.34	L
After Ex	C1	-0.65	-1.73 ; 0.44	M
	C4	-0.39	-1.46 ; 0.68	S
Relative Change	C1	-0.44	-1.09 ; 0.21	M
	C4	0.00	-0.60 ; 0.61	N

C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult); N, negligible; S, small; M, moderate; L, large

Table 6.18. Effect Sizes for differences in error frequency between the two groups during the various stages of the modified Stroop Task.

Phase	Condition	ES	95% CI	Qualitative Outcome
Before Ex	C1	-0.57	-1.65 ; 0.51	M
	C2	-0.85	-1.96 ; 0.25	L
	C3	-0.49	-1.56 ; 0.58	M
	C4	0.27	-0.79 ; 1.33	S
After Ex	C1	-0.43	-1.50 ; 0.64	M
	C4	0.05	-1.01 ; 1.11	N

C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult); N, negligible; S, small; M, moderate; L, large

D. FUNCTIONAL TESTING

The Timed Up-and-Go Test (TuG) as well as the Six Minute Walk Test (6MWT) were used as the functional tests with time to completion in seconds and distanced walked in meters being used as the outcome measure. The TuG was further used as the functional task to examine whether differences exist between stroke patients who have had regular rehabilitation and those who have not.

1. Global Changes

1.1 Timed Up-and-Go

The differences in time to completion of the TuG for the experimental and control group are displayed in *Figure 6.44*. The experimental group took 53% longer (14.36 seconds) to complete the TuG, which was statistically as well as practically significant ($p = 0.04$; ES = 0.77) as shown in *Table 6.19*.

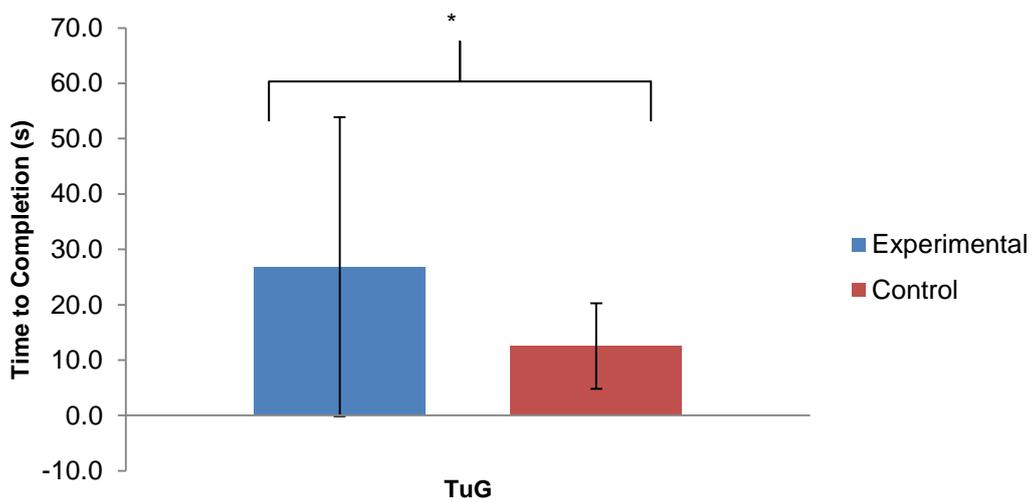


Figure 6.44. Difference in time taken to complete the Timed Up-and-Go test between the groups. TuG, Time Up-and-Go. * Statistically significant difference between experimental and control group ($p < 0.05$).

1.2. Six Minute Walk Test

Differences in distance walked, as well as work performed during the Six Minute Walk Test (6MWT) are displayed in *Figure 6.45* and *Figure 6.46*, respectively, with the ratings of perceived exertion (RPE) for the two groups displayed in *Figure 6.47*. No statistically significant difference was found between the experimental and control group during the 6MWT ($p > 0.05$), even though the control group walked 27% (89.7 meters) further than the experimental group, although a difference of moderate practical significance was seen ($ES = -0.73$). However, there was a statistically significant difference in the RPE score for the two groups ($p = 0.04$) with the experimental group experiencing a 21% higher level of subjective fatigue than the control group. The amount of work performed during the test was also higher (15%) in the control group, which is expected due to the difference in distance walked. No statistically significant difference was observed between the two groups with respect to total work performed ($p > 0.05$), however, a moderate practically significant difference was seen ($ES = -0.44$) as shown in *Table 6.19*.

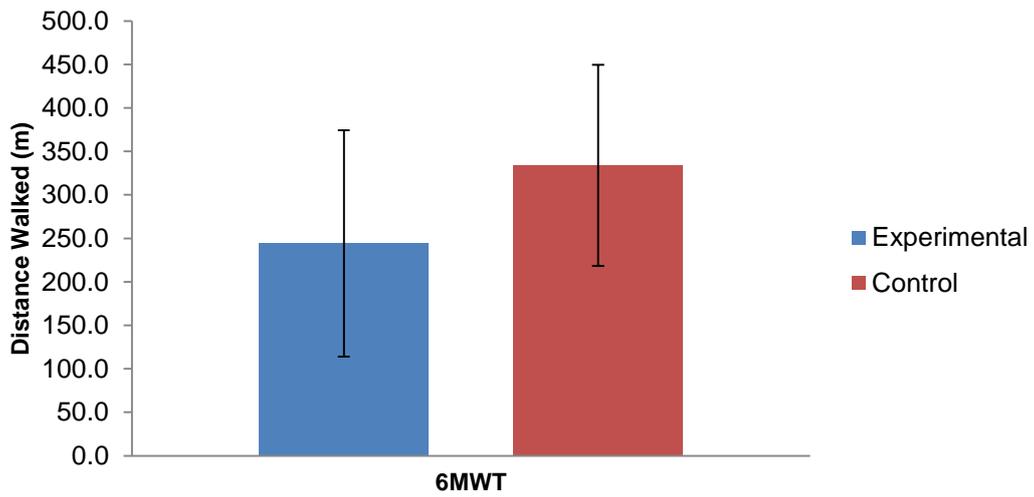


Figure 6.45. Differences in distance walked in the Six Minute Walk test (6MWT) between the experimental and control groups.

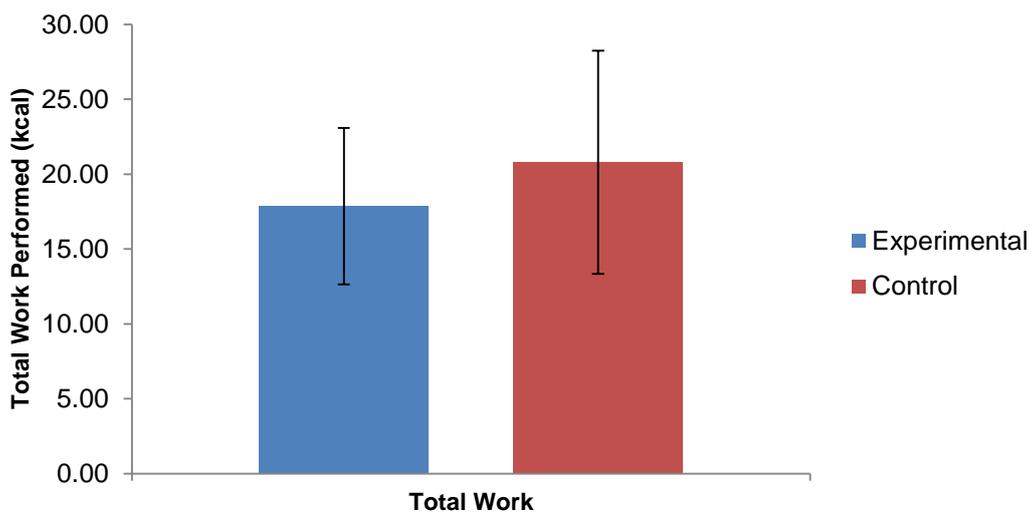


Figure 6.46. Differences in the total work performed during the Six Minute Walk test (6MWT) between the groups.

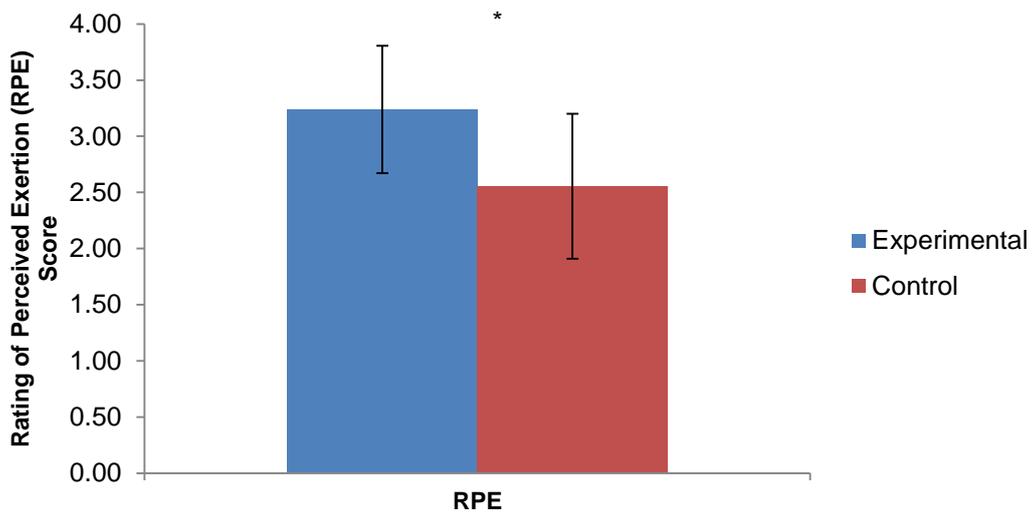


Figure 6.47. Rating of perceived exertion for the experimental and control group while performing the six minute walk test (6MWT). * Statistically significant difference between the two groups ($p < 0.05$).

2. Rehabilitation versus No Rehabilitation

Figure 6.48 shows that the no rehab group completed the TuG 12% (3.53 seconds) faster than the rehab group, although this difference was not statistically significant ($p > 0.05$) and showed differences of negligible significance ($ES = 0.13$) as shown in *Table 6.19*.

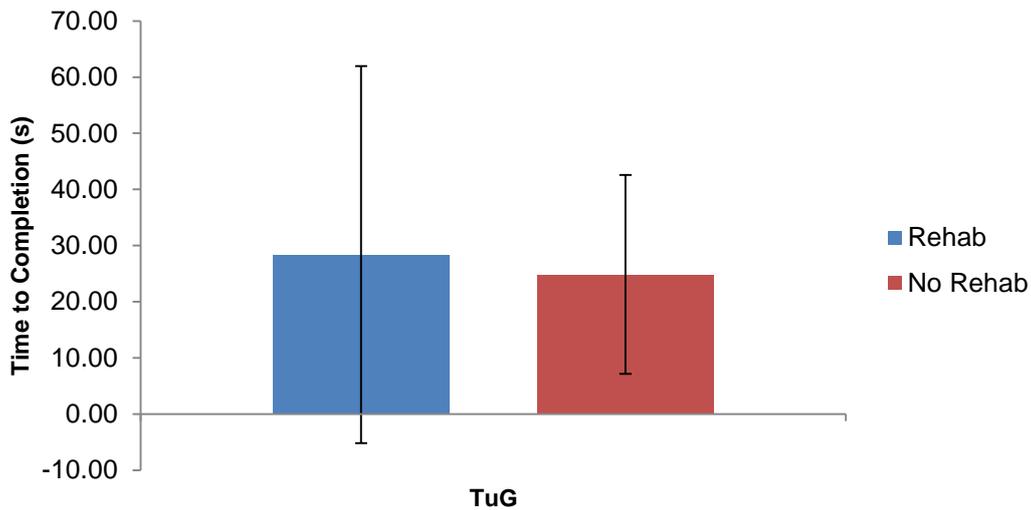


Figure 6.48. Difference in time taken to complete the Timed Up-and-Go test in stroke patients who have had rehabilitation and those who have not. TuG, Timed Up-and-Go

Table 6.19. Effect Sizes for differences between the experimental and control groups during functional testing as well between the rehab and no rehab group.

Group	Variable	ES	95% CI	Qualitative Outcome
Experimental vs Control	TuG	0.77	0.04 ; 1.49	L
	6MWT	-0.73	-1.45 ; -0.01	M
	Work	-0.44	-1.15 ; 0.26	M
Rehab vs No Rehab	TuG	0.13	-0.93 ; 1.19	N

TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test; N, negligible; M, moderate; L, large

E. CORRELATIONS

Correlations between time post-stroke and NIRS parameters, as well as the scores of the various cognitive and functional tasks were performed and are shown in *Table 6.20* to *Table 6.23*. Furthermore, correlations between the NIRS parameters and scores of the various cognitive and functional tasks are shown in *Table 6.24* to *Table 6.27*.

1. Time Post Stroke

Weak correlations were found between most of the NIRS variables during the cognitive tasks and time post stroke (*Table 6.20*), with only HHb in the LPFC during the MMSE, O₂Hb in the LPFC and RPFC during Stroop 1 and THI in the LPFC during Stroop 1 showing moderate positive correlations ($r = 0.33$; $r = 0.34$; $r = 0.33$; $r = 0.31$).

Table 6.20. Correlation of time post stroke and NIRS parameters for cognitive tasks

Side	Variable	MMSE		Stroop 1	
		r value	p value	r value	p value
Left	O ₂ Hb	0.23	0.43	0.34	0.24
	HHb	0.33	0.25	0.05	0.87
	THI	0.25	0.39	0.31	0.27
Right	O ₂ Hb	0.14	0.64	0.33	0.26
	HHb	0.14	0.62	0.02	0.95
	THI	0.08	0.79	-0.11	0.70

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; MMSE, Mini Mental State Exam

Table 6.21 depicts the correlations between the functional tasks and the NIRS values. A moderate positive correlation was found between TuG and O₂Hb in the LPFC and RPFC ($r = 0.47$; $r = 0.40$), as well as between TuG and THI in the LPFC ($r = 0.34$). Small and non-significant correlations were found between the 6MWT and the NIRS outcomes.

Table 6.21. Correlation of time post stroke and NIRS parameters for functional tasks

Side	Variable	TuG		6MWT	
		r value	p value	r value	p value
Left	O ₂ Hb	0.47	0.09	-0.05	0.86
	HHb	0.17	0.57	0.29	0.32
	THI	0.34	0.24	0.22	0.45
Right	O ₂ Hb	0.40	0.16	0.02	0.95
	HHb	0.07	0.82	0.23	0.44
	THI	0.02	0.95	0.07	0.80

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test

Weak to moderate/good correlations were found between time post stroke and scores for both the cognitive and functional tasks and are displayed in *Table 6.22* and *Table 6.23*, respectively. Moderate correlations were found with C1 and C2 Error Frequency ($r = 0.43$; $r = 0.25$), as well as 6MWT distance ($r = 0.37$). A moderate to good positive correlation was found between time post stroke and work done ($r = 0.67$).

Table 6.22. Correlation of time post stroke and cognitive task scores

Task	r Value	p Value
MMSE	0.19	0.52
C1 Reaction Time	0.24	0.41
C2 Reaction Time	0.22	0.46
C3 Reaction Time	0.24	0.41
C4 Reaction Time	0.18	0.55
C1 Errors	0.43	0.13
C2 Errors	0.25	0.38
C3 Errors	-0.06	0.83
C4 Errors	-0.20	0.49

MMSE, Mini Mental State Exam; C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult)

Table 6.23. Correlation of time post stroke and functional task scores

Task	r Value	p Value
TuG	0.02	0.95
6MWT	0.37	0.42
Work Done	0.67	0.10

TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test

2. NIRS Measurements

Correlations for the NIRS parameters with the MMSE scores showed weak positive and negative, as well as moderate negative correlations which are displayed in *Table 6.24*. O₂Hb in both the LPFC and RPFC showed moderately negative correlations with MMSE scores ($r = -0.30$, $p = 0.09$; $r = -0.27$).

Table 6.24. Correlation of the NIRS parameters with MMSE scores

Side	Variable	MMSE	
		r value	p value
Left	O ₂ Hb	-0.30	0.09
	HHb	0.08	0.67
	THI	-0.14	0.45
Right	O ₂ Hb	-0.27	0.14
	HHb	0.05	0.80
	THI	-0.22	0.23

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; MMSE, Mini Mental State Exam

Correlations with the reaction time scores for ST1 showed weak to moderate positive correlations (*Table 6.25*) for most of the variables, with C4 reaction time showing only very weak correlations. Moderate positive correlations with C1 reaction time were seen with HHb in the LPFC ($r = 0.30$; $p = 0.09$) and THI in the RPFC ($r = 0.25$). Moderate positive correlations with C2 reaction time were seen with HHb and THI in the LPFC ($r = 0.26$; $r = 0.34$), with the latter tending towards borderline statistical significance ($p = 0.06$). Finally,

moderate positive correlations with C3 reaction time were seen with HHb in the LPFC ($r = 0.25$) and THI in the RPFC ($r = 0.27$).

Table 6.25. Correlation of the NIRS parameters with ST1 Reaction Time

Side	Variable	C1 Reaction Time		C2 Reaction Time		C3 Reaction Time		C4 Reaction Time	
		r value	p value						
Left	O ₂ Hb	0.03	0.88	0.13	0.47	-0.04	0.84	0.04	0.83
	HHb	0.30	0.09	0.26	0.14	0.25	0.17	0.19	0.31
	THI	0.24	0.18	0.34	0.06	0.15	0.40	0.16	0.40
Right	O ₂ Hb	0.05	0.77	0.16	0.39	0.00	0.98	-0.07	0.69
	HHb	0.14	0.45	0.05	0.80	0.15	0.41	-0.06	0.73
	THI	0.25	0.17	0.22	0.24	0.27	0.13	0.05	0.80

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult)

Correlations with the error frequency of ST1 showed both positive and negative weak to moderate correlations, and are displayed in *Table 6.26*. Moderate positive correlations with C1 errors were seen with O₂Hb in the LPFC and RPFC ($r = 0.29$; $r = 0.36$, $p = 0.05$), as well as with THI in the LPFC ($r = 0.28$). The only moderate positive correlation with C2 errors was seen with THI in the LPFC ($r = 0.44$), where it was found to be statistically significant ($p = 0.01$). A moderate positive correlation with C4 errors was seen with O₂Hb in the LPFC ($r = 0.26$), while a moderate negative correlation was seen with HHb in the RPFC ($r = -0.33$) with the latter tending towards borderline statistical significance ($p = 0.06$).

Table 6.26. Correlation of the NIRS parameters with ST1 Error Frequency

Side	Variable	C1 Errors		C2 Errors		C3 Errors		C4 Errors	
		r value	p value						
Left	O ₂ Hb	0.29	0.11	0.22	0.22	0.05	0.79	0.26	0.16
	HHb	0.20	0.27	0.16	0.39	0.04	0.81	-0.14	0.46
	THI	0.28	0.12	0.44	0.01	0.19	0.30	-0.14	0.43
Right	O ₂ Hb	0.36	0.05	0.17	0.34	-0.10	0.58	0.01	0.96
	HHb	0.13	0.49	-0.14	0.46	-0.24	0.18	-0.33	0.06
	THI	0.13	0.48	0.13	0.48	-0.05	0.79	-0.21	0.25

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; C1, Condition one of the modified Stroop Task (easiest); C2, Condition two of the modified Stroop Task (easy); C3, Condition three of the modified Stroop Task (difficult); C4, Condition four of the modified Stroop Task (most difficult)

Correlations with the functional task scores are displayed in *Table 6.27* and showed only one moderately positive correlation between work done and HHb in the LPFC ($r = 0.26$), with the remaining correlations revealing weak positive and negative correlations across the various parameters.

Table 6.27. Correlation of the NIRS parameters with the functional task scores

Side	Variable	TuG		6MWT		Work Done	
		r value	p value	r value	p value	r value	p value
Left	O ₂ Hb	0.16	0.37	0.06	0.83	-0.07	0.80
	HHb	0.02	0.93	0.01	0.96	0.26	0.32
	THI	-0.07	0.72	-0.15	0.59	-0.18	0.50
Right	O ₂ Hb	0.01	0.97	0.15	0.58	-0.10	0.72
	HHb	-0.20	0.27	-0.17	0.52	-0.05	0.84
	THI	0.06	0.76	-0.03	0.93	-0.03	0.92

O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; THI, total haemoglobin index; TuG, Timed Up-and-Go; 6MWT, Six Minute Walk Test

CHAPTER SEVEN

DISCUSSION

A. INTRODUCTION

The purpose of this study was to examine whether differences exist in cerebral haemodynamics between stroke survivors and healthy elderly individuals when performing a simple and complex cognitive task and whether an acute bout of low intensity exercise has an immediate effect on cognitive performance. Furthermore, the effect of factors such as time post-stroke and participation in rehabilitation on cognitive function, functional ability and cerebral haemodynamics in the stroke patients were also examined.

The main finding of the study was that there are differences in cerebral haemodynamics that exist between stroke patients and healthy elderly individuals while performing tasks of varying difficulty and low intensity exercise had some effect on task performance, with a greater improvement seen in the elderly participants. In general, stroke patients have lower oxygen delivery, higher oxygen utilization and negligible differences in tissue saturation with higher levels of haemoglobin content in the contralesional hemisphere being the only anomaly to the norm. Finally, both time post-stroke and rehabilitation following a stroke seem to be important predictors of the extent and quality of both cognitive and functional recovery.

Results were presented as both p-values for statistical significance and effect sizes (ES) for practical significance. This was done due to the wide intra- and inter-person variability in the NIRS measurements that arise from differences in the structural anatomy (skull

thickness and CSF thickness) and orientation of the surface vasculature between individuals. Furthermore, lesion site and size were not able to be accurately measured and the sample size, considering the clinical nature of the study, was small. In addition, improvements in any of the outcome variables in the stroke patients are of clinical and medical significance due to the benefits they offer (higher HRQoL), even though the improvements may not be statistically significant.

Due to the limited number of NIRS studies available in the stroke population, it is believed that this study will lay a foundation on which further larger scale and clinically controlled studies can be built.

B. DESCRIPTIVE CHARACTERISTICS

No studies have thus far compared cerebral oxygenation responses in elderly and stroke populations simultaneously, although a number of studies have been conducted with the two groups in isolation in a variety of scenario's (Lucas *et al.*, 2012; Takeda *et al.*, 2007). In recent NIRS studies, the mean age of stroke participants was 58.2 ± 4.82 years, while the mean age of elderly participants was 64.2 ± 1.92 years (Lin, Chen, & Lin, 2012; Durduran *et al.*, 2009; Takeda *et al.*, 2007; Murata *et al.*, 2006; Kameyama *et al.*, 2004; Schroeter *et al.*, 2003; Matsuo *et al.*, 2000). The sample for this study was therefore slightly older (68.8 ± 18.5 years). The mean age of the stroke participants in previous studies is therefore surprisingly low considering that the peak incidence of stroke occurs between the ages of 60 and 70 years in both men and women (Palmer-McLean & Harbst, 2009; Hildick-Smith, 2000a).

Body Mass Index (BMI) is used as an overall indicator of health status and the relative risk of developing cardiovascular disease (CVD) and disorders. The American College of Sports Medicine (ACSM) classifies a person with a BMI lower than 18.5 kg.m^{-2} as underweight, with the normal range being between 18.5 kg.m^{-2} and 24.9 kg.m^{-2} . Cardiovascular risk is higher in those individuals in the overweight and obese categories which is defined as between 25.0 kg.m^{-2} and 29.9 kg.m^{-2} , and between 30.0 kg.m^{-2} and 40.0 kg.m^{-2} , respectively (American College of Sports Medicine, 2010). Stroke patients that participate in research usually have an average BMI of 25.0 kg.m^{-2} , however, the range is extremely large within the group (Murakami *et al.*, 2012; Kurth *et al.*, 2002). The participants in the current study would be classified as overweight according to the ACSM guidelines with BMI values for the experimental and control group of 27.8 kg.m^{-2} and 28.3 kg.m^{-2} , respectively. While it has been shown in both elderly men and women that a BMI greater than 25.0 kg.m^{-2} increases all-cause mortality, a BMI of between 27.5 kg.m^{-2} to 30 kg.m^{-2} showed a decrease in mortality for stroke patients. This phenomenon in stroke patients is known as the obesity paradox, with research implicating cytokines and serum lipoproteins as potential influencing factors (Kim *et al.*, 2012).

When blood pressure (BP) measurements were analysed it was found that the systolic blood pressure (SBP) measurements of the participants fell within the pre-hypertension category according to the ACSM classification for adults, with diastolic blood pressure (DBP) falling in the normal category (American College of Sports Medicine, 2010). Research has shown that elderly individuals generally have an 8% higher SBP and a 7% lower DBP than their younger counterparts with no significant differences found between men and women (Cicconetti *et al.*, 2000). When compared to stroke patients, it was found that hypertensive patients who had no prior history of stroke had a non-significantly higher SBP ($137 \pm 14 \text{ mmHg}$) and a significantly higher DBP ($82 \pm 10 \text{ mmHg}$) than those who

had a prior stroke history (SBP: 134 ± 14 mmHg; DBP: 76 ± 10 mmHg). This, however, has not been consistently seen in the literature and may be due to the importance placed on adequate blood pressure control by the stroke patient's physician (Ohta *et al.*, 2005). Furthermore, SBP values higher than 150 mmHg result in a higher mortality rate and poor functional outcome, thereby making proper management essential for overall quality of life (QoL) (Donovan, Flexman, & Gelb, 2012; Grise & Adeoye, 2012).

It is difficult to quantify the average time post-stroke in most studies as the purpose, as well as the measurement variable, determine the time period selected for studying stroke patients. For acute studies, the time varies from a few days to three months post-stroke, whereas for prolonged studies the time period can be a number of years following a stroke (Donovan *et al.*, 2012; Takeda *et al.*, 2007; Murata *et al.*, 2002; Leskelä *et al.*, 1999; Sakatani *et al.*, 1998).

C. GLOBAL AND RELATIVE CHANGES IN NIRS DURING THE TESTING PHASE

Changes in the four measureable near-infrared spectroscopy (NIRS) parameters, namely oxyhaemoglobin (O_2Hb), deoxy-haemoglobin (HHb), tissue oxygenation index (TOI) and total haemoglobin index (THI), were measured over the duration of the testing period. The placement of the optodes in the proper positions according to the international 10-20 system for EEG electrode placement prevented the frontal sinus or temporalis muscle having an effect on the NIRS measurements.

Non-significant differences in O_2Hb in both the left prefrontal cortex (LPFC) and right prefrontal cortex (RFPC) were seen between the stroke patients and the control group in both the global and relative changes. Lower O_2Hb values were seen in the LPFC in the

stroke group, which was the affected hemisphere for 11 of the 14 patients, and these values were practically significantly lower than for the control group ($ES = -1.01$). This finding is in accordance with the findings of Murata *et al.* (2006) and Murata *et al.* (2002) where lower regional cerebral blood flow (rCBF) accounted for lower O_2Hb levels. Lower levels of rCBF in the ipsilesional (same side as the lesion) hemisphere may be due to lower levels of neural activation due to the damage of neurons caused by the ischemia (Inao *et al.*, 1998). This finding was similarly found by Hatazawa *et al.* (1995) where a number of neurons were shown to be intact on an MRI, but presented with reduced perfusion with tracer imaging. While no statistically significant differences were found between the two groups, large practical differences ($ES > 0.75$) were seen during the Timed Up-and-Go test (TuG), Six Minute Walk Test (6MWT), as well as the second modified Stroop Task (ST2) in the LPFC based on the relative change from R1, supporting the notion that the ipsilesional rCBF is lower. The neuronal death caused by the infarct, as well as damage to the surrounding areas is not entirely repairable, and is highly dependent on the extent of the damage. Therefore, areas of residual deficit without vascular supply will remain following a stroke, thereby contributing to the lower levels of rCBF seen.

Changes in HHb between the experimental and control group followed a similar pattern in the LPFC and RPF, with the experimental group having smaller changes in relation to baseline, and therefore an overall higher concentration of HHb. Considering that HHb is a measure of oxygen utilization, given the same task or activity, a greater degree of oxygen will be consumed. This practically translates into a greater neural effort required to complete the task or achieve the set goal of the task. Once again, the neuronal death that occurs as a result of the stroke is implicated in this finding as less neural matter is present to control brain activation.

Decreases in HHb were observed in both groups during the Mini Mental State Exam (MMSE), as well as the two modified Stroop Tasks (ST1 and ST2), and increased during the Timed Up-and-Go (TuG) and Six Minute Walk Test (6MWT). Moderate size practical significant differences were seen between the groups with respect to R3, R4, the TuG and the 6MWT, with the experimental group having higher values in all cases. These findings support the work of Sakatani *et al.* (1998) who found that there was a decrease in HHb when performing a language task, which was attributed to the substantial increase in regional cerebral blood flow (rCBF) coupled with the smaller increase in Cerebral Metabolic Rate of Oxygen (CMRO₂) which is an indication of oxygen utilization in the brain (Xu, Ge, & Lu, 2009; Sakatani *et al.*, 1998). With respect to motor tasks, Murata *et al.* (2006) found that patients with moderate cerebral ischemia had a decrease in HHb, whereas those with severe cerebral ischemia showed an increase in HHb. This finding was supported by an earlier study by Murata *et al.* (2002) where ischemic stroke patients had increases in HHb compared to normal healthy adults of a similar age range.

With the use of blood oxygen level-dependent (BOLD) contrast functional magnetic resonance imaging (fMRI), similar findings have been made with lower BOLD signals in the ipsilesional hemisphere corresponding to an increase in HHb as determined by NIRS, and higher BOLD signals in the contralesional hemisphere corresponding to a decrease in HHb as determined by NIRS. The principle underlying BOLD fMRI lies in the paramagnetic (magnetic favouring) properties of HHb and non-paramagnetic (magnetic repelling) properties of O₂Hb. When an external magnetic force acts on the body (as is the case with MRI), the BOLD signal increases or decreases in relation to the concentration of HHb in the blood. Therefore, a drop in BOLD signal is related to an increase in HHb concentration, whereas an increase in BOLD signal is related to a decrease in HHb concentration (Murata *et al.*, 2006; Röther *et al.*, 2002). The proposed mechanism responsible for this

increase in HHb is due to oxygen metabolism and the haemodynamic response associated with it. The reduced rCBF seen in resting conditions is carried over during neural activation resulting in a decreased ability of the vascular system to remove HHb, termed haemodynamic insufficiency. During haemodynamic insufficiency there is an increase in oxygen extraction in order to maintain cerebral oxygen metabolism. This would then result in an increase in HHb in the vasculature (Murata *et al.*, 2006; Inao *et al.*, 1998;).

Large practical differences in HHb were seen in both the LPFC and RPFC during the TuG test between the stroke patients and the healthy controls (with stroke patients having higher HHb values) relative to R1, with moderate practical differences for the remaining testing phases in both the LPFC and RPFC relative to R1. The large practically significant differences in HHb are expected in the ipsilesional hemisphere due to the relatively normal rCBF in the control group, but possibly restricted rCBF in the experimental group. However, the large practically significant differences in the contralesional hemisphere (i.e. higher HHb values in the RPFC in the experimental group) are an unexpected result. A possible explanation could be a reduced rCBF in the contralesional hemisphere or, in the presence of normal rCBF, increased CMRO₂ which would increase HHb concentration (Krainik *et al.*, 2005). A further reason could be due to surface vascular discrepancies amongst the participants that would have a direct effect on HHb measurements.

The Tissue Oxygenation Index (TOI), in relation to neural activation, is rarely reported in the literature. Rather, Total Haemoglobin Index (THI), together with O₂Hb and HHb are mostly reported. TOI is calculated with the aforementioned haemodynamic variables; therefore any changes thereof would reflect changes in TOI, albeit to a lesser degree. TOI provides an indication of oxygen saturation within the tissue; therefore increases in O₂Hb

due to increases in rCBF may cause an increase in oxygen saturation within the tissue in the absence of venous occlusion. Therefore, large increases in O₂Hb with a decrease in HHb, as is seen in the typical neural activation response, would cause an increase in TOI, whereas a concomitant increase of both O₂Hb as well as HHb, as seen in ischemic stroke patients, would result in a smaller increase or a possible decrease in TOI.

Although this is a very simplistic model, findings at rest between acute stroke patients and controls found that TOI was lower in the ipsilesional hemisphere, which confirms the simplistic model (Terborg *et al.*, 2009; Terborg *et al.*, 2004), in light of the haemodynamic response described by Inao *et al.* (1998) and Murata *et al.* (2006) above. These findings correspond to what was seen with the relative change from baseline in current the study, where the experimental group had smaller relative changes and overall lower TOI values compared to the control group. Due to O₂Hb and HHb being more widely reported than TOI in the literature, no further analysis of TOI was conducted after global and relative changes had been reported.

THI values were similar in the LPFC between the two groups, with statistically and practically significant higher values in the RPFC during the MMSE, ST1 and TuG for the experimental group. A typical response to neural activation would see an increase in THI over resting values in both healthy participants, as well as stroke patients in both the ipsilesional and contralesional hemisphere, with slightly higher THI values in the contralesional hemisphere (Murata *et al.*, 2006). Furthermore, you would expect to see slightly lower THI values in the stroke patients compared to the healthy participants (Murata *et al.*, 2002) as THI is related to cerebral blood volume (CBV). In this study, the experimental group had significantly higher overall THI values in the RPFC than the control group. The higher values in the contralesional hemisphere are in accordance with

the literature and can possibly be attributed to a larger degree of activation needed to complete the task, although the reason for the higher THI levels in the experimental group is unknown. A possible reason may be due dysfunction in the autoregulation of CBV. The differences in THI in the LPFC and RPFC of the experimental group could be due to the smaller number of intact neurons in the ipsilesional hemisphere, and therefore a lower rCBF and activation volume (AV). Higher THI during R2 (after completion of the MMSE) in the stroke patients compared to the healthy controls may be due to a deactivation delay in the RPFC (Sakatani *et al.*, 2006). Thus, the large practical differences in the RPFC of the experimental and control group may be attributable to the higher degree of activation needed to complete a motor task due to the residual deficits following the stroke.

D. RESEARCH QUESTIONS

Discussion of the results will be grouped according to the research questions indicated below.

- 1. Is there a difference in cerebral haemodynamics between stroke patients and healthy age-matched individuals when performing a simple and complex cognitive task, before and after exercise?**

When performing a cognitive task of varying difficulty, one can expect differences in neural activation levels. Therefore, a simple task requires low levels of activation, and hence lower levels of rCBF and CMRO₂ are elicited, whereas a more difficult task requires a greater degree of activation and higher levels of rCBF and CMRO₂. This translates into smaller increases in O₂Hb and THI, and smaller decreases in HHb with a simple task, compared to the more difficult task (Schroeter *et al.*, 2004; Toichi *et al.*, 2004). While this

response has been widely found in the healthy population, it has not yet been examined in stroke survivors. It must be noted that ageing also has an effect on the haemodynamic response, in that the response is blunted in all the measurable parameters in elderly participants when compared to their younger counterparts (Schroeter *et al.*, 2003). However, in this study participants were matched for age and therefore this confounding variable has been controlled for.

The change in O₂Hb due to task complexity followed the pattern described above in both groups in the LPFC and RPFc, although the experimental group had lower values in the LPFC (ES = 0.37). The lower O₂Hb in the LPFC of the experimental group was more than likely as a result of the decreased rCBF to the area, as there was almost no difference in the RPFc between the two groups, irrespective of task complexity. Exercise caused an increase in O₂Hb in both the LPFC and RPFc in the control group, with the magnitude of the increase being higher during the difficult task. This was in agreement with the findings of Lucas *et al.* (2012) who found an increase in O₂Hb in elderly participants when performing a difficult task compared to a simple one. The response of the experimental group was similar in that there was an increase in O₂Hb when performing a difficult task in both the LPFC and RPFc. However, the overall O₂Hb levels were lower in the experimental group, with the LPFC also being lower than the RPFc. Once again, a possible reason could be due to reduced rCBF or a delayed haemodynamic response as a result of the preceding exercise. Unfortunately, there is no literature to corroborate these results, thereby necessitating the need for further research.

Changes in HHb values were greater (i.e. lower HHb with respect to baseline) in the control group for both tasks and in both the LPFC and RPFc, indicating that the increase in rCBF was not matched by an increase in CMRO₂. Overall, HHb values for the

experimental group were higher, although not increased above baseline. This may be explained in part by the increased neuronal activity required to perform the task, although the higher values in the RPFC (contralesional hemisphere) are unexpected. A plausible reason is possible changes in neural recruitment pattern to accommodate the damaged neurons in the ipsilesional hemisphere. Following exercise, HHb values increased during the simple task and decreased during the difficult task in the control group in both the LPFC and RPFC. Once again, these findings are consistent to what has been previously reported (Lucas *et al.*, 2012). In the experimental group, HHb remained increased in the LPFC and RPFC during both task conditions. However, it must be noted that HHb levels of the experimental group were substantially lower in the RPFC than in the LPFC. The elevated HHb levels in the LPFC across both tasks following exercise could be explained by the increased use of lactate by the brain as an energy source during and following exercise, or due to the delay in deactivation following exercise (Schurr *et al.*, 1999).

THI values were higher in the experimental group in both the LPFC and RPFC, with the latter showing statistically significant differences between the groups during the difficult task. Although an increase in THI followed the typical response according to the literature, the higher values in the experimental group were unexpected and may be related to dysfunction in autoregulation of CBV. In elderly participants, Lucas *et al.* (2012) found that there was an increase in THI when performing a difficult task, which is in conflict to the results of the control group in this study who experiences a drop in THI when performing a difficult task. Interestingly, the experimental group showed increases in THI only in the LFPC when performing a difficult task, whereas a decrease in THI was seen in the RPFC. Further research is required to investigate possible reasoning for this anomaly. THI following exercise was higher in the control group in the LPFC and RPFC which is in accordance with the literature, although the change was greater in the LPFC, possibly

indicating greater neural involvement of the LPFC during completion of the task. The experimental group had an increase in THI in the LPFC following exercise during both conditions, but a decrease in the RPFC. This may also be due to greater involvement of the LPFC.

Correlations were calculated for the various NIRS parameters and task scores. An interesting finding was the moderately negative relationship between O₂Hb and the MMSE score. Possible reasoning for this unexpected result could be that the MMSE did not challenge both groups sufficiently to elicit the high activation response seen when performing a cognitive task. A more typical result was seen during the modified Stroop Task where a moderately positive relationship was seen between HHb in the LPFC and reaction time in condition one, two and three respectively. Interestingly, this relationship did not transfer to condition four. A moderate positive correlation was also seen between THI in the LPFC and RPFC in conditions one and two, and only in the RPFC in condition three. This finding corroborates what is found in the literature that a cognitive task causes an increase in rCBF and CMRO₂. When the various NIRS parameters and Stroop Task error frequency were correlated, inconsistent results were found, with moderate positive relationships found between O₂Hb in the LPFC and RPFC in condition one and in the LPFC in condition two and four. Negative moderate correlations were then found between HHb in the RPFC in condition three and four. The differences and inconsistencies with the correlations may be due to the complex and varied nature of the haemodynamic response in the experimental group.

In conclusion, there appears to be differences in cerebral haemodynamics between stroke patients and healthy elderly people when completing a simple and complex cognitive task as well as before and after exercise. However, further research in stroke populations are

needed, specifically when performing tasks of varying difficulty. The inclusion of exercise before, during and after the performance of a cognitive task may reveal changes in activation patterns and haemodynamic responses between varying population groups and warrants further research. Findings could reveal at what stage tasks of varying difficulty should be introduced into a rehabilitation program for stroke patients, as well as when the simultaneous addition of exercise may be most beneficial.

2. Does low level exercise have an influence on task performance?

Extensive research has shown that there is an interaction between exercise and cognition in a number of different populations. A number of cognitive tests are used to assess cognitive ability during exercise with the Eriksen flanker task as well as the Stroop Task, and modifications thereof, being widely used. Lucas *et al.* (2012) showed that low and high intensity exercise at 30% and 70% heart rate reserve (HRR) resulted in improvements in reaction time compared to rest, in healthy young and elderly individuals, during the simple and difficult stage of the modified Stroop Task. However, the exercise did not have an effect on the error rate. Furthermore, it was found that reaction time was quicker with high intensity exercise than during low intensity exercise. These findings were similar to those by Kamijo *et al.* (2007) who found a slight, but not significant decrease in reaction time during high intensity exercise when compared to low intensity exercise in healthy adults. However, moderate intensity exercise was found to offer the greatest reduction in reaction time. Yanagisawa *et al.* (2010) showed similar effects where young, healthy adults who exercised at 50% of their peak oxygen uptake (VO_{2peak}) showed improvements in reaction time during the Stroop Task when compared to rest. The Eriksen Flanker Task was used by Hillman, Snook, & Jerome (2003) where it was found that reaction time decreased and event-related brain potential (ERP) increased following a bout of exercise in healthy young

adults. In a recent study by Hyodo *et al.* (2012) it was showed that an acute bout of moderate intensity exercise in an elderly population was sufficient to cause an improvement in Stroop Task performance, and more specifically, reaction time. A study by Netz *et al.* (2007) showed similar results where late middle-aged adults (mean age 56 ± 3 years) improved their performance during the alternate uses cognitive test following exercise.

The aforementioned studies were conducted with healthy adults as their participants, and differences in the stroke population were made evident by Ploughman *et al.* (2008) who found that performance during the trail making test, a well-known cognitive test, did not improve in response to acute exercise.

The mechanism for improvements in reaction time following exercise are unclear, but may be related to increases in blood catecholamines secondary to increased cerebral blood flow, as well as an increased arousal state due to the exercise (Hyodo *et al.*, 2012; Yanagisawa *et al.*, 2010; Ogoh & Ainslie, 2009). McMorris *et al.* (2008) evaluated the catecholamine hypothesis and concluded that, although there is some relationship between catecholamine concentrations, exercise and cognition, the hypothesis provides reasoning of a simplistic nature. He proposes that a far more complex interaction with other hormones is more plausible. Ando *et al.* (2011) provided further evidence against this proposed mechanism of improved cognition during exercise when he found an improvement in cognitive performance during the Eriksen Flanker Test that was not as a result of increased cerebral blood flow. These conflicting results provide evidence that further research is needed in this area to determine the exact mechanism.

Aside from acute exercise, chronic exercise has been shown beneficial in improving cognitive performance in the elderly, as well as up-regulating gene expression that promotes brain plasticity and brain-derived neurotrophic factor (Colcombe & Kramer, 2003; Cotman & Berchtold, 2002). Furthermore, a study by Hillman *et al.* (2004) provided evidence that higher levels of habitual activity were related to improved cognitive performance in the elderly. Higher levels of aerobic capacity have also been shown to correlate strongly with cognitive performance in chronic stroke patients (Kluding *et al.*, 2011). Similar findings were reported by Pålman, Sävborg, & Tarkowski (2011) who found that inactivity following a stroke and impaired cognition are closely linked to one another.

In the present study, the reaction time of the control group improved in both the easy and difficult condition of the modified Stroop Task following exercise, which is in accordance with previous findings in the literature. On the other hand, the experimental group showed a quicker reaction time in the easy condition but a slower reaction time in the difficult condition. Furthermore, there was a decrease in error rate following exercise in the easiest condition and an increase in the most difficult condition. Possible explanations for the increase in reaction time and error rate in the experimental group during the difficult condition are neural fatigue, or inability to adequately inhibit the prepotent response (Lucas *et al.*, 2012). A prepotent response is generally the most logical and powerful response, an instinctive response to a certain degree. E.g. If during the Stroop Task you are asked to name the TEXT COLOUR of the word “blue”, written in red, the prepotent response would be to say blue, therefore requiring you to inhibit the prepotent response in order to correctly answer the question.

In conclusion, while no statistically significant differences were seen between the two groups, the trends in both groups for the most part are in agreement with the literature that exercise, results in improvements in performance. The issue of the magnitude of the intensity and subsequent task performance warrants further study as conflicting evidence does exist with some authors suggesting that higher intensity exercise provides more benefits (Lucas *et al.*, 2012), while other authors suggest that low to moderate intensity exercise is better (Ando *et al.*, 2011; Yanagisawa *et al.*, 2010). Considering only one study has been conducted examining changes in task performance in stroke patients following exercise (Ploughman *et al.*, 2008), it is difficult to substantiate whether the finding of the present study can be considered the expected responses. Further studies in this regard, simultaneously investigating the effect of exercise intensity, are specifically required in the stroke population. Findings in this area would be of significant clinical value as various modes of exercise are used during rehabilitation following a stroke, and positive changes in task performance seen would possibly translate to greater functionality and HRQoL over time.

3. Does time post-stroke have an influence on cerebral haemodynamics or task performance?

Neural recovery following a stroke involves three distinct stages and continues for up to four months following a stroke. The first stage immediately following the incident entails removal of diaschisis, which is slowly progressive damage to surrounding tissues, as well as activation of the genes responsible for cell repair. Very often following a stroke, damage to the perilesional (area immediately surrounding the infarct) or remote regions occurs. The second phase involves functional cell plasticity which enables changes to the existing neural pathways, with neuronanatomical plasticity comprising the third stage.

Neuroanatomical plasticity involves the formation of new neural connections through gliogenesis and neurogenesis with angiogenesis (formation of new blood vessels) providing the platform. Furthermore, it has been found that axonal sprouting horizontal of the lesion site into areas that are not normally connected occurs, which accounts for the improvement in motor function seen during the sub-acute phase of stroke. Remodelling and adaptive changes have also been reported in the contralesional hemisphere following a stroke (Duffau, 2006; Nudo, 2006; Wieloch & Nikolich, 2006).

There seems to be a general consensus in the literature that activation patterns, and the accompanying haemodynamic response, changes as a patient moves from the acute, to sub-acute and finally to the chronic stages following a stroke. This pattern of activation is often referred to as the laterality of activation (i.e. activation on either the left or right sides of the brain). The unilateral movement of either the affected or non-affected hand is used as an illustration for further explanation. During the acute stage, movement with the affected hand results in weak activation in the ipsilesional hemisphere, contralateral to the movement, and weak activation of the contralesional hemisphere, ipsilateral to the movement. For example, if the left hand is affected, and is moved, weak activation would occur in the right as well as left hemisphere. Movement with the non-affected hand results in strong activation in the contralesional hemisphere, contralateral to movement, and very weak activation in the ipsilesional hemisphere, ipsilateral to movement. (E.g. If the right hand was moved, activation of greater magnitude would be seen in the left hemisphere, compared to the right hemisphere). This pattern changes during the sub-acute phase, occurring approximately two weeks to one month following a stroke. During this phase, movement of the affected hand results in weak activation of the contralesional hemisphere, ipsilateral to movement, and slightly weak activation of the ipsilesional hemisphere, contralateral to movement. (E.g. If the left hand is moved, weak activation

would occur in the left hemisphere with slightly weaker activation in the right hemisphere). Movement of the unaffected hand would result in maximal activation in the contralesional hemisphere, contralateral to movement, and minimal activation in the ipsilesional hemisphere, ipsilateral to movement (E.g. If the right hand was moved, maximal activation would be seen in the left hemisphere, while minimal activation would be seen in the right hemisphere). Finally, during the chronic phase of recovery following a stroke, movement with the affected hand results in maximal activation in the ipsilesional hemisphere, contralateral to the movement, and minimal activation of the contralesional hemisphere, ipsilateral to the movement. (E.g. If the left hand is moved, maximal activation would occur in the right hemisphere with minimal activation in the left hemisphere). Interestingly, the lateralization of the unaffected hand decreases slightly in the chronic stage when compared to the sub-acute stage, but still has higher levels of activation in the contralesional hemisphere, contralateral to movement (Cramer & Seitz, 2009).

It is important to note that age, task complexity and task familiarity may influence laterality and should therefore be carefully controlled for. In addition to changes in lateralization following a stroke, changes in activation site as well as activation size in the time period following a stroke play an important role in dictating functional recovery and ultimately task performance. The most common change related to activation site is a ventral or posterior shift in the activation site in the ipsilesional hemisphere with movement of the affected hand (contralateral movement), although dorsal or anterior shifts have also been found. Despite the differences in shifts seen, there is a general consensus that the best functional outcomes are related to the greatest return in brain function (Cramer & Seitz, 2009; Cramer, 2004). With respect to changes in activation size, better functional outcome is associated with increased activation in a number of different areas over time in the ipsilesional hemisphere, with decreased activation in a number of areas in the

contralesional hemisphere. Important to note, however, is that the degree or volume of activation is significantly influenced by the type of task. E.g. A fist clench would result in a larger activation volume compared with finger lifts (Cramer, 2004; Cramer & Seitz, 2009). Transcranial Magnetic Stimulation (TMS) studies have found similar results, although recovery was dependent on the integrity of the cortico-spinal tract system (Bütefisch et al., 2006; Cicinelli, Traversa, & Rossini, 1997). These findings provide evidence of cerebral reorganization in the time period following a stroke (Obrig & Steinbrink, 2011; Takeda et al., 2007).

Most imaging studies report improvements in motor function in the period following a stroke, but few studies examine the recovery of cognition or executive function following a stroke. A two year follow up study by Hochstenbach et al. (2003) showed that a small number of participants showed significant improvement across all the various cognitive domains (attention, language and arithmetic, memory, orientation as well as visuospatial and visuoconstructive abilities), while the majority of the participants showed no improvements or a decline. Higher levels of cognitive improvement were noted in a study by Ballard et al. (2003) where they found that 50% of the participants improved global cognitive functioning. Vascular dementia (VD) and mild cognitive impairment (MCI) following a stroke are reasonably common. Rasquin et al. (2004) reported 11% and 72% incidence rates, respectively, at one month post-stroke, decreasing to 8% and 61% at six months post-stroke and finally to 8% and 53% one year post-stroke. They also reported that participants with no VD or MCI showed increases in global cognition over the above-mentioned time periods.

Two common tests used to assess cognitive functioning post-stroke are the trail making test (Trails A and B) and the digit span test (forward and backward). Both tests have been

shown to be extremely reliable, but are not, however, able to differentiate between frontal and non-frontal damage as has been previously reported (Tamez *et al.*, 2011).

The stroke impact scale (SIS) is a subjective questionnaire that evaluates a number of domains affected by a stroke, with four of them being physical domains. Research has shown that there is a strong correlation between the SIS score in the physical domains and 6MWT performance ($r = 0.60$), with SIS score changes over a period of time related to stroke severity (Muren *et al.*, 2008). The 6MWT has been shown to correlate very well with daily step activity following a stroke and is a good predictor of cardiorespiratory fitness in most phases of rehabilitation following a stroke (Mudge & Stott, 2009; Tang *et al.*, 2006; Eng, Dawson, & Chu, 2004).

The degree of motor recovery is highly dependent on the degree of neural plasticity that occurs, as was described above. A number of motor impairment tests, as well as functional walking tests are used to predict motor impairment in stroke patients. A study by Stinear (2010) showed that if both voluntary finger extension and shoulder abduction was possible within 72 hours following a stroke, there was a 98% probability of the patient recovering a degree of manual dexterity within six months. If none of the movements were possible within 72 hours following a stroke, there was a 25% probability of the patient recovering a degree of manual dexterity within six months, falling to 14% if neither movement was possible within five days following a stroke. The Barthel Index (BI) is a stroke specific index used to measure independence during activities of daily living. In the same study it was found that the motor impairment was the strongest predictor of recovery after one, three and six months post-stroke (Stinear, 2010). The Timed Up-and-Go (TuG) Test has been shown to be a reliable predictor of functional outcome following a stroke

and correlates well with a number of gait parameters, as well as walking endurance as measured by the 6MWT (Ng & Hui-Chan, 2005).

The present study revealed some interesting results that were for the most part in concordance with the literature. Moderate positive correlations were found between O₂Hb, HHb and THI in the ipsilesional hemisphere during cognitive tasks, while the contralesional hemisphere only showed a moderate positive correlation for O₂Hb. These findings were not completely transferred to the functional tasks, with only O₂Hb in both the ipsilesional and contralesional hemisphere showing a moderate positive correlation. This suggests that vascular and cerebral plasticity in both the ipsilesional and contralesional hemisphere most definitely occur as time post-stroke increases, although the effect of rehabilitation on these results cannot be neglected.

With regards to the relationship between time post-stroke and task performance during both the cognitive and functional tasks, no overall conclusive relationship was found. There were moderate positive correlations found with error rate in the easiest Stroop Task condition before exercise, which was unexpected, as well as in the 6MWT, which was expected. Furthermore, a moderate-good positive relationship was found in work performed during the 6MWT.

In conclusion, the present study seems to indicate that time post-stroke is related to changes or improvements in cerebral haemodynamics and activation which is in agreement with the literature, although these changes did not translate into improved task performance. The large variability within the experimental group may have contributed to this finding and therefore further research with stricter participant criteria and larger participant numbers are needed to add to the limited literature. Due to the unpredictability

of the functional and cognitive outcomes following a stroke, as well as the complexities of neural repair, further studies will need to carefully examine whether there is an optimal time period post-stroke for the introduction of various intervention strategies that target all the affected domains. Furthermore, research into whether uncoupling exists between cerebral haemodynamics and neural activation following a stroke needs to be conducted. If found to be true, research into the permanency of this uncoupling will need to be investigated.

4. Does regular rehabilitation following a stroke have an influence on haemodynamics or task performance?

Rehabilitation following a stroke is common practice during the acute, sub-acute and chronic phase and the extent thereof is dependent on the severity and complexity of disability. There is extensive literature documenting the effects of various rehabilitative techniques on motor and cognitive functioning, however, very limited literature exists that examines the haemodynamic changes that accompany the changes that occur as a result of the rehabilitation. As mentioned in response to research question three, neuroplasticity following a stroke takes place irrespective of rehabilitation, however, the magnitude of the neuroplasticity, and subsequent restoration of function, is dependent on the quality of the therapeutic intervention (Hodics *et al.*, 2006). Saitou *et al.* (2000) examined the effect of rehabilitation on cerebral blood volume and cerebral oxygenation among hemiplegic patients following a stroke. They found an increase in cerebral blood volume and cerebral oxygenation with a low level cycle ergometer and manual extension of the paretic leg by a physiotherapist, with a decrease in cerebral blood volume and oxygenation during the head-up tilt (HUT) as well as during passive repeated wrist and finger extension of the affected hand. The greatest area of research regarding cortical changes that take place as

a result of rehabilitation is of gait. The overall finding across a number of studies is that during body weight-supported treadmill walking, there is an increase in O₂Hb in the medial primary sensorimotor cortex (PSMC) of the contralesional hemisphere which is greater than the ipsilesional hemisphere. Furthermore, premotor cortex (PMC) activation was found to be enhanced in the ipsilesional hemisphere (Belda-Lois *et al.*, 2011; Arenth *et al.*, 2007). Interestingly, Miyai *et al.* (2001) found that when the paretic leg was controlled through a facilitation technique administered by a physiotherapist, greater increases in cortical activation and improved gait performance were noted when compared to mechanical assistance. Another study by Miyai *et al.* (2003) showed that the asymmetry in activation during gait decreased following a two month rehabilitation program, together with increased PMC activation in the ipsilesional hemisphere. Rehabilitation through constraint-induced movement therapy (CIMT) and bilateral arm training (BAT) found similar results but tended towards a distinctly more bilateral activation pattern (Young & Tolentino, 2011; Wu *et al.*, 2010; Hodics *et al.*, 2006; Park *et al.*, 2004).

The findings of the present study are therefore in concordance with the literature for all of the NIRS parameters. Overall, both O₂Hb and THI in the LPFC and RPFc during the MMSE and TuG were higher in those patients who had not undergone regular rehabilitation relative to those who had. This was matched by the higher levels of HHb during the functional tasks, which indicates a greater degree of neural activation was required to perform the task. The smaller change in HHb in the LPFC and RPFc during the MMSE in those who had rehabilitation was expected as the assumption is that the MMSE was less challenging for those participants who had undergone rehabilitation. Due to the lower relative difficulty, less activation was needed and a lower CMRO₂ would be seen. Taken together with the smaller increase in rCBF as indicated by O₂Hb and THI, the relative concentration of HHb is expected to be lower in this group.

Rehabilitation of gait following a stroke is most widely reported as it has a significant bearing on a number of other areas of functionality and quality of life. There are a number of gait rehabilitation techniques used, each with their own methodological advantages and disadvantages. Rehabilitation takes place through the use of neurophysiological and motor learning techniques which are mentioned briefly below. Neurophysiological techniques include Bobath, the Rood Technique and Proprioceptive Neuromuscular Facilitation (PNF), while motor learning techniques include the Perfetti method, Affolter method and Ayres method. Langhammer and Stanghelle (2003) compared the Bobath and Motor Relearning Programme techniques and found no significant differences between the two during the acute post-stroke phase. To date, there is limited evidence to suggest that one rehabilitation technique is better than any other and this is evident with the positive results seen from a number of different studies.

Adapted physical activity, a traditional rehabilitative approach, was shown to significantly improve balance, gait pattern and cardiovascular endurance in stroke patients when they exercised three times a week for a six month period (Michael *et al.*, 2009). A study by Lubetzky-Vilnai and Kartin (2010) corroborate these finding by showing that intensive balance training two to three times per week resulted in significant improvements in balance. Overground gait training as well as body weight-supported (BWS) treadmill training has shown positive results with respect to restoration of a reasonably functional walking gait following a stroke. Although there is limited evidence suggesting global benefits of overground gait training, there appears to be some improvement in walking speed and walking endurance (States, Salem, & Pappas, 2009). A recent study by Combs *et al.* (2010) showed that BWS treadmill training significantly improved gait as well as balance, balance confidence and HRQoL, both pre- and post-intervention (8 weeks), as well as six months following the completion of the study. When walking outdoors was

compared to traditional treadmill walking, the treadmill walking group performed significantly better than the outdoor walking group, further adding to the notion that treadmill walking, assisted or not, has an important role to play in restoration of functional gait (Langhammer & Stanghelle, 2010).

Constraint-induced movement therapy (CIMT) and bilateral arm training (BAT) are further rehabilitative strategies that have been found to be successful in restoring motor function of the upper extremities. In comparative studies of the two techniques, it was found that both CIMT and BAT resulted in improved functioning, with CIMT being preferential if the treatment goal is to improve functional ability and use of the affected limb, and BAT being preferential if the generation of force is the treatment goal (Wu *et al.*, 2011; Wu *et al.*, 2010). The long-term effects of CIMT were evaluated by Rowe, Blanton and Wolf (2009) where they found that following two weeks of CIMT, upper-extremity function was retained after a period of five years. The role of fatigue during and following rehabilitation cannot be ignored. Tseng and Kluding (2009) and Rowe *et al.* (2009) suggested that fatigue could have an effect on performance and long-term outcome and should therefore be monitored carefully during a rehabilitation program and in the follow-up period following rehabilitation.

Aside from the improvements in motor function, improvements in cognitive function have also been well documented and generally occur concomitantly to improved motor functioning. Kluding *et al.* (2011) showed that following a 12 week aerobic and strengthening program there was a significant improvement in a number of cognitive measures including the digit span test and Flanker test. Specific executive function interventions have been investigated with promising results being found. Working memory training, strategy training, goal-management training and external compensatory approaches are the most common types of interventions (Poulin *et al.*, 2012; Levine *et al.*,

2011). Working memory (WM) is the ability to manipulate and retain information during a short delay, while making the appropriate response when required. WM training resulted in significant improvements in both WM and attention following a five week intervention in the experimental group while no improvements were seen in the control group (Westerberg *et al.*, 2007). Strategy training involves differing modes of problem solving and is viewed as one of the most complex cognitive functions. In a study by Man *et al.* (2006) the experimental group was split into three different problem-solving scenarios, namely online training, computer-assisted training and therapist administered training. Following the two month intervention period, statistically significant differences were found between the three experimental groups and the control group, with the online group proving to be the most effective. The external compensatory approach makes use of external devices such as a pager to assist with memory and planning (Poulin *et al.*, 2012). A randomised control trial (RCT) by Wilson *et al.* (2005) found that use of a paging system significantly improved both memory and planning of a number of activities of daily living, as was evident when the paging system was removed. Finally, goal-management training (GMT) utilises the theories of goal processing and sustained attention and found significant improvements in a number of measures following the intervention, as well as at a four month follow-up (Levine *et al.*, 2011).

Evidence that regular rehabilitation following a stroke is crucial for optimal recovery is provided by Langhammer and Stanghelle (2003) where they found that there was a significant decrease in ability to perform activities of daily living (ADL's) as well as an increase in mortality rate in stroke patients who did not participate in regular rehabilitation, especially when indicated. In support of these findings Olsson and Sunnerhagen (2007) found that when patients received between six to eight weeks of day hospital rehabilitation (DHR) following hospital discharge, both functional and cognitive capacity were retained at

a two year follow up period. This further substantiates the argument for regular rehabilitation in cases where it is necessary. Further research is warranted to obtain definitive information on optimal time of initiation and duration of rehabilitation due to the variability in patient characteristics. However, the general consensus is that early rehabilitation produces a greater degree of recovery (Musicco *et al.*, 2003).

The results of the present study are in concordance with the literature for the most part, with the only anomalies being the faster time to completion of the TuG in the group that did not have regular rehabilitation, and the higher number of errors during the most difficult condition of the modified Stroop Task in the group that did have regular rehabilitation. For the most part, moderate to large practical differences were found between those who have had regular rehabilitation and those who have not.

It can be concluded, with a degree of certainty, that rehabilitation following a stroke results in improvements in cerebral haemodynamics as well as motor and cognitive task performance. Despite the findings of the present study not being statistically significant, there were definite trends of practical significance and further research into the specifics of the time of onset, duration and type of rehabilitation can only add value to an increasingly popular and necessary field of research. Knowledge gained from these future studies may enable rehabilitation professionals to construct more effective rehabilitation plans in order to achieve the goals of the patient.

E. SUMMARY

No studies have to date examined the changes in cerebral haemodynamics and task performance between stroke patients and healthy elderly individuals across both functional and cognitive domains simultaneously. Most of the NIRS studies on stroke patients are focussed on the acute changes occurring immediately post-stroke, thereby making concrete conclusions on the effect of the post-stroke period and rehabilitation extremely difficult. This study revealed evidence that there may be positive trends in both. The findings of this study suggest that there are definite differences regarding cerebral haemodynamics that exist between stroke patients and the healthy elderly population, and that there may be a relationship with task performance as indicated in *Figure 7.1.* and *Figure 7.2.*, respectively. Both figures represent hypotheses based on what is known regarding neurophysiology as well as the typical response seen in healthy individuals due to the lack of literature in the stroke population. Furthermore, rehabilitation following a stroke holds significant practical benefits with respect to improved functionality and cognition as well as highlighting the differences in cerebral haemodynamics in those who have not received regular rehabilitation. Hypotheses on the mechanisms of these findings are displayed in *Figure 7.3.* and *Figure 7.4.*, respectively.

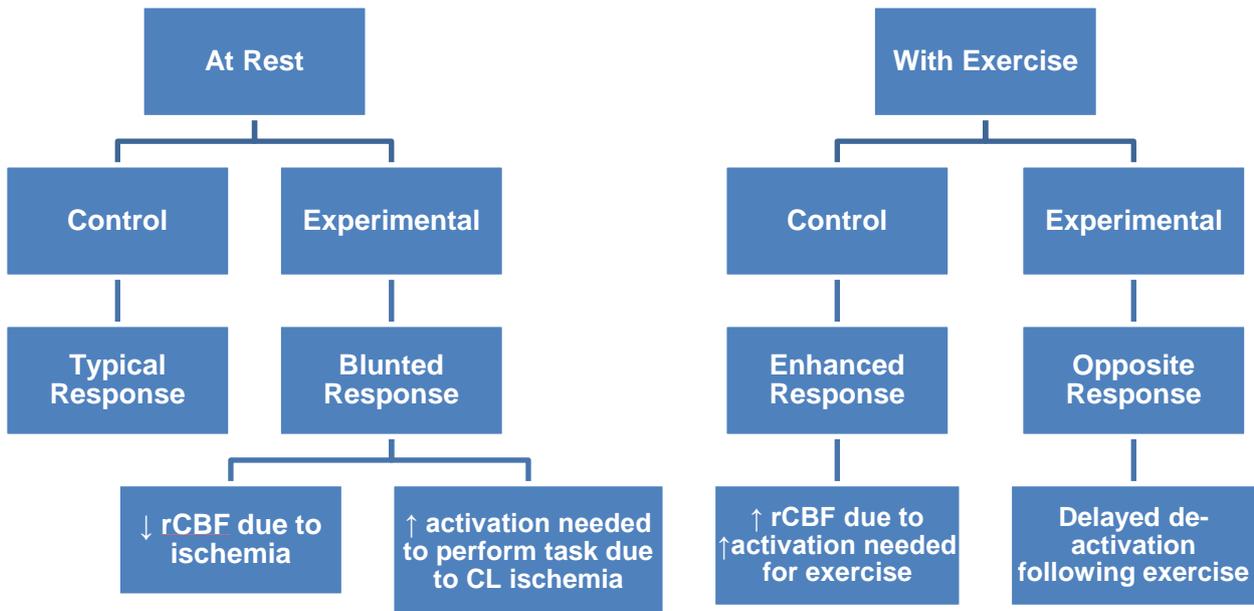


Figure 7.1. Proposed model and hypothesis for the discussion of research question 1. rCBF, regional cerebral blood flow; CL, contralesional.

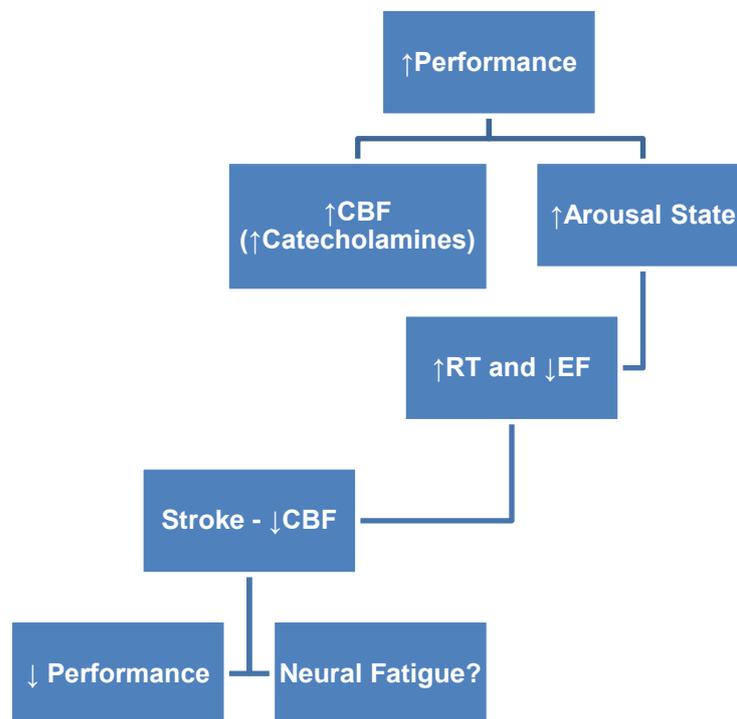


Figure 7.2. Proposed model and hypothesis for the discussion of research question 2. CBF, cerebral blood flow; RT, reaction time; EF, error frequency

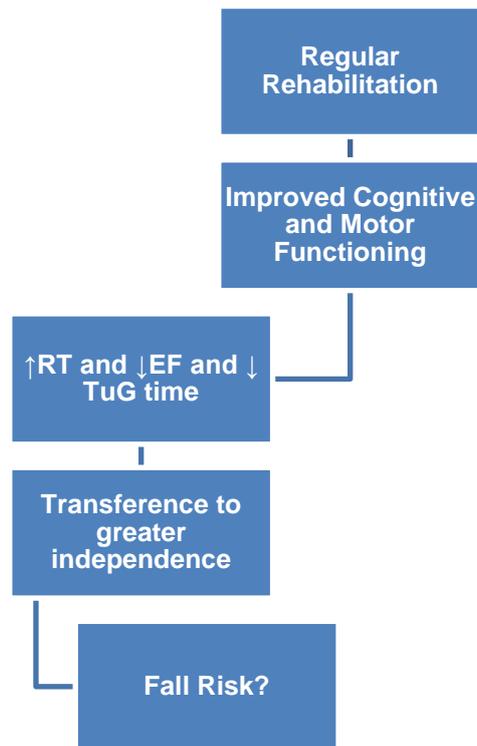


Figure 7.3. Proposed model and hypothesis for the discussion of research question 4 – task performance and regular rehabilitation. RT, reaction time; EF, error frequency; TuG, timed up-and-go

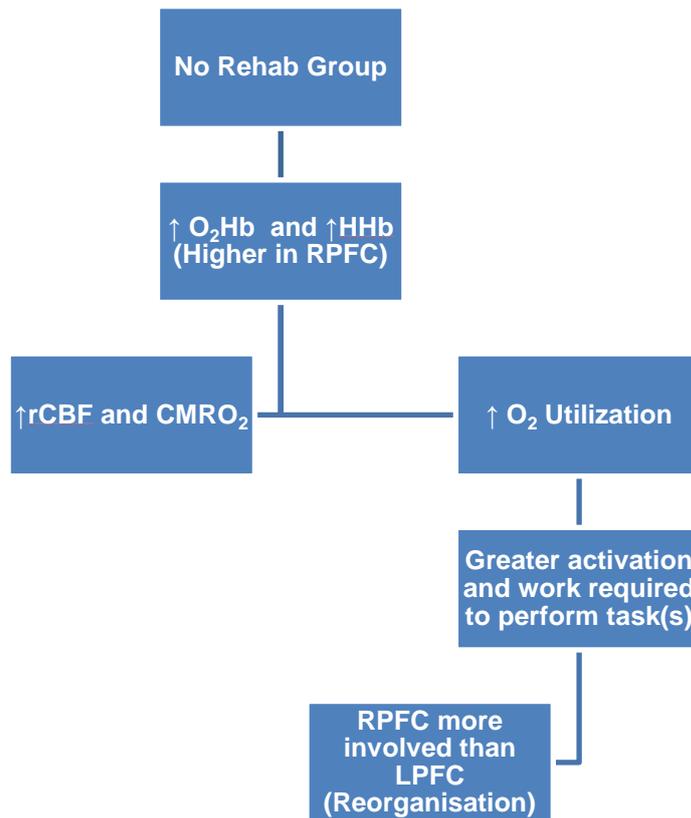


Figure 7.4. Proposed model and hypothesis for the discussion of research question 4 – haemodynamic changes and regular rehabilitation. O₂Hb, oxyhaemoglobin; HHb, deoxy-haemoglobin; RPFC, right pre-frontal cortex; LPFC, left pre-frontal cortex; rCBF, regional cerebral blood flow; CMRO₂, cerebral metabolic rate; O₂, oxygen.

F. STUDY LIMITATIONS AND FUTURE RECOMMENDATIONS

A limitation of this study was the relatively small sample size and interpersonal variation within the stroke group. Most stroke studies have large sample sizes due to the variation that is expected in this population group and this could have been a potential reason for the non-significance of the results seen.

Another limitation is the relative inexperience of the researcher with using NIRS and EEG placement. While the researcher was educated on the proper placement of electrodes according to the international 10-20 classification system, as well as on the proper

operation of the NIRO200-NX oximeter, the possibility exists that slight discrepancies in the placement of the optodes may have occurred, although every effort to ensure consistency was made.

The inter-personal vascular differences that occur within skin are a further confounding factor that could not be controlled for, and may have in some cases had an effect on the results, albeit a slight difference.

Future studies should examine the changes in haemodynamics that occur in stroke patients following rehabilitation of different types and duration, as well as establishing whether conclusive relationships do exist between haemodynamic variables and task performance outcomes, as well as investigating whether the proposed hypotheses to the research questions can be validated.

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APPENDIX A



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STELLENBOSCH UNIVERSITY

CONSENT TO PARTICIPATE IN RESEARCH

The relationship between task complexity and cerebral oxygenation in stroke patients.

You are asked to participate in a research study conducted by Bradley James Fryer (BHons Biokinetics), from the Department of Sport Science at Stellenbosch University. The results will be used as part of a master's thesis study. You were selected as a possible participant in this study because you are older than 50 years and you either had a stroke previously or did not have a stroke before.

1. PURPOSE OF THE STUDY

The purpose of this study is to examine the effect of simple and complex cognitive tasks on cerebral oxygenation of stroke patients and healthy age-matched individuals.

2. PROCEDURES

If you volunteer to participate in this study, we would ask you to do the following things:

A home visit to gather information related to health status and medical history as well as initial screening to assess eligibility to participate in the study. During the first visit to the Sport Physiology Laboratory you will complete a medical history form, complete a short test (the Mini-Mental State test), as well as two physical tests where you need to get up from a chair and walk for 20m. If, according to these tests, you qualify for the study, we would appreciate it if you could visit the laboratory for a second time. This session will last about 90 minutes. The tests during this session will examine your physical and cognitive functioning. Data will be captured using Near Infrared Spectroscopy (NIRS) which will require two electrodes to be placed on your forehead for the duration of the testing period. You will not feel anything when we attach the electrodes to your forehead or during testing.

3. POTENTIAL RISKS AND DISCOMFORTS

Although you will only perform light exercise, it is possible that you may experience some discomfort and dizziness following the exercise and symptoms will be managed in this regard. With the probes attached to the forehead there may be slight discomfort due to the unfamiliarity of the probes, but once removed, it leaves no permanent mark or discomfort.

4. POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

Participation in the study will give you a better understanding of your brain functioning when performing a cognitive task and may reveal areas of decision-making and reaction time that require improvement. Regular training to improve reaction-time has the potential to decrease your risk to lose your balance or fall. From a research perspective the project will allow us to evaluate the efficiency of your rehabilitation in terms of your functional and cognitive performance This will help us to improve rehabilitation programs for stroke patients.

5. PAYMENT FOR PARTICIPATION

You will not receive any payment for participating in this study.

6. CONFIDENTIALITY

Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. Confidentiality will be maintained by means of special coding system with C001 and E001 representing subject one from the control and experimental group respectively. Data will be stored on a password protected computer and external flash drive. Only the researcher and the research supervisor will have access to the data.

Results of the study will be published in a reputable journal with no personal information being published. Any data published will be general and non-specific to the subjects.

7. PARTICIPATION AND WITHDRAWAL

You can choose whether to be in this study or not. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind. You may also refuse to answer any questions you don't want to answer and still remain in the study. The investigator may withdraw you from this research if circumstances arise which warrant doing so. These circumstances include but are not limited to: significant decline in your health or inability to complete all the tests.

8. IDENTIFICATION OF INVESTIGATORS

If you have any questions or concerns about the research, please feel free to contact Bradley Fryer (Researcher) on 0825512318 (day), 021 8879263 (day), or via e-mail bradleyfryer@gmail.com. Prof. Elmarie Terblanche (Supervisor) may also be contacted on 021 8082742 (day) or via e-mail on et2@sun.ac.za. In the case of emergency you can contact Bradley Fryer on 0825512318 or 021 674-4461.

9. RIGHTS OF RESEARCH SUBJECTS

You may withdraw your consent at any time and discontinue participation without penalty. You are not waiving any legal claims, rights or remedies because of your participation in this research study. If you have questions regarding your rights as a research subject, contact Ms Maléne Fouché [mfouche@sun.ac.za; 021 808 4622] at the Division for Research Development.

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

The information above was described to *me* by Bradley James Fryer in *Afrikaans/English* and *I am* in command of this language or it was satisfactorily translated to *me*. *I* was given the opportunity to ask questions and these questions were answered to *my* satisfaction.

I hereby consent voluntarily to participate in this study I have been given a copy of this form.

Name of Subject/Participant

Name of Legal Representative (if applicable)

Signature of Subject/Participant or Legal Representative

Date

SIGNATURE OF INVESTIGATOR

I declare that I explained the information given in this document to _____ and/or [his/her] representative _____. [He/she] was encouraged and given ample time to ask me any questions. This conversation was conducted in [*Afrikaans/*English*].

Signature of Investigator

Date

APPENDIX B



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INITIAL SCREENING FORM

Name: _____

Contact Number: _____

Surname: _____

ID#: _____

Address: _____

DOB: _____

Doctor: _____

Next of Kin: _____

Kin Cont #: _____

History:

Family History:

Coronary Artery Disease
Myocardial Infarction
Stroke
Diabetes
Pulmonary Disease
Other Cardiovascular Disease
Other Metabolic Disease

Personal History:

Coronary Artery Disease
Myocardial Infarction
Stroke
Diabetes
Pulmonary Disease
Other Cardiovascular Disease
Other Metabolic Disease
Alzheimer's / Dementia

Current Activity Levels

Type: _____

Duration: _____

Frequency: _____

Intensity: _____

Medications (including dosage and frequency):

Any Musculoskeletal or Joint Problems:

Yes: _____

No: _____

Specify:

Initial Testing:

MMSE Score: _____

Walk 20m Unaided? _____

Handedness: _____

Colour Blind? _____

Signature of Researcher: _____

Date: _____

APPENDIX C



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STELLENBOSCH UNIVERSITY TESTING DATA CAPTURING FORM

Subject Name & Surname: _____

Subject Code: _____ Control/Experimental Group: _____

Date of Testing: _____ Time of Testing: _____

Cardiovascular Measurements	Value
Systolic Blood Pressure (mmHg)	
Diastolic Blood Pressure (mmHg)	
Heart Rate (bpm)	

Basic Anthropometric Measurements	Value
Height (m)	
Weight (kg)	

Functional Tests	Time (s)
Timed Up-and-Go	

Six Minute Walk Test (6MWT)				
Heart Rate (bpm)	Start	2min	4min	End
Rating of Perceived Exertion (RPE)	Start	2min	4min	End
Distance Walked (m)				

NIRS Measurements	Marker Number	Time (min:sec)
Start Resting Baseline	1	00:00
End Resting Baseline	2	05:00
Start Mini Mental State Exam	3	
End Mini Mental State Exam	4	
Start Rest Period 1	5	
End Rest Period 1	6	
Start Stroop Task	7	
End Stroop Task	8	
Start Rest Period 2	9	
End Rest Period 2	10	
Start Timed Up-and-Go	11	
End Timed Up-and-Go	12	
Start Rest Period 3	13	
End Rest Period 3	14	
Start Exercise (6MWT/TT)	15	
End Exercise (6MWT/TT)	16	
Start Stroop Task 2	17	
End Stroop Task 2	18	
Start Rest Period 4	19	
End Rest Period	20	

Signature of Researcher: _____

Date: _____

APPENDIX D

ETHICAL CLEARANCE

Researcher: Mr Bradley Fryer

Research Project: The relationship between task complexity and cerebral haemodynamics in stroke patients and healthy elderly men and women

Nature of the Research Project: M degree, Department of Sport Science, Stellenbosch University

Supervisor(s): Prof Elmarie Terblanche

Reference number: HS784/2012

Date: 26 April 2012

The research proposal and associated documentation was circulated and considered by the members of the Ethics Committee (as prescribed by Council on 20 March 2009 and laid down in the SU policy framework) on 26 April 2012; the purpose being to ascertain whether there are any ethical risks associated with the proposed research project of which the researcher has to be aware of or, alternatively, whether the ethical risks are of such a nature that the research cannot continue.

DISCUSSION

The Ethics Committee received the following documentation:

- An ethical clearance application form, duly signed and filled out;
- An informed consent form; and
- A copy of the research protocol
- Initial screening form
- Mini Mental State Exam
- Letter of support

The researcher will determine whether differences exist between stroke patients and healthy elderly individuals while performing a simple and complex cognitive task, and whether low level exercise has an effect thereon. Furthermore, the influence of time post-stroke as well as rehabilitation status in the stroke patients will be investigated. The testing will take place in the Motor Learning Laboratory at the Department of Sport Science, Stellenbosch University.

RECOMMENDATION

It is recommended, in view of the information at the disposal of the committee that the proposed research project continues provided that:

- a. The researcher will remain within the procedures and protocols indicated in the proposal, particularly in terms of any undertakings made in terms of the confidentiality of the information gathered.
- b. The research will again be submitted for ethical clearance if there is any substantial departure from the existing proposal.
- c. The researcher will remain within the parameters of any applicable national legislation, institutional guidelines and scientific standards relevant to the specific field of research.

- d. The researcher will consider and implement the foregoing suggestions to lower the ethical risk associated with the research.

Van Zyl, Gerhard; Bitzer, Elias; Fouche, Magdalena; Theron, Carl; Prozesky, Heidi; De Villiers, Mare; Somhlaba, Ncebazakhe; Mostert, Paul; Engelbrecht, Sidney; De Villiers-Botha, Tanya; Horn, Lynette; Van Wyk, Berte [For the Ethics Committee: 26 April 2012]

APPENDIX E

Mini-Mental Status Examination

The Mini-Mental Status Examination offers a quick and simple way to quantify cognitive function and screen for cognitive loss. It tests the individual's orientation, attention, calculation, recall, language and motor skills.

Each section of the test involves a related series of questions or commands. The individual receives one point for each correct answer.

To give the examination, seat the individual in a quiet, well-lit room. Ask him/her to listen carefully and to answer each question as accurately as he/she can.

Don't time the test but score it right away. To score, add the number of correct responses. The individual can receive a maximum score of 30 points.

A score below 20 usually indicates cognitive impairment.

The Mini-Mental Status Examination

Name: _____

DOB: _____

Years of School: _____

Date of Exam: _____

Orientation to Time

Correct

Incorrect

What is today's date?

What is the month?

What is the year?

What is the day of the week today?

What season is it?

Total: _____

Orientation to Place

Whose home is this?

What room is this?

What suburb are we in?

What city are we in?

What province are we in?

Total: _____

Immediate Recall

Ask if you may test his/her memory. Then say “ball”, “flag”, “tree” clearly and slowly, about 1 second for each. After you have said all 3 words, ask him/her to repeat them – the first repetition determines the score (0-3):

Ball	<input type="checkbox"/>	<input type="checkbox"/>
Flag	<input type="checkbox"/>	<input type="checkbox"/>
Tree	<input type="checkbox"/>	<input type="checkbox"/>

Total: _____

Attention

A) Ask the individual to begin with 100 and count backwards by 7. Stop after 5 subtractions. Score the correct subtractions.

93	<input type="checkbox"/>	<input type="checkbox"/>
86	<input type="checkbox"/>	<input type="checkbox"/>
79	<input type="checkbox"/>	<input type="checkbox"/>
72	<input type="checkbox"/>	<input type="checkbox"/>
65	<input type="checkbox"/>	<input type="checkbox"/>

Total: _____

B) Ask the individual to spell the word “WORLD” backwards. The score is the number of letters in correct position.

D	<input type="checkbox"/>	<input type="checkbox"/>
L	<input type="checkbox"/>	<input type="checkbox"/>
R	<input type="checkbox"/>	<input type="checkbox"/>
O	<input type="checkbox"/>	<input type="checkbox"/>
W	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>

Total: _____

Delayed Verbal Recall

Ask the individual to recall the 3 words you previously asked him/her to remember.

Ball	<input type="checkbox"/>	<input type="checkbox"/>
Flag	<input type="checkbox"/>	<input type="checkbox"/>
Tree	<input type="checkbox"/>	<input type="checkbox"/>

Total: _____

Naming

Show the individual a wristwatch and ask him/her what it is. Repeat for pencil.

Watch

Pencil

Total: _____

Repetition

Ask the individual to repeat the following:

“No if, ands, or buts”

Total: _____

3-Stage Command

Give the individual a plain piece of paper and say, “Take the paper in your hand, fold it in half, and put it on the floor.”

Takes

Folds

Puts

Total: _____

Reading

Hold up the card reading: “Close your eyes” so the individual can see it clearly.

Ask him/her to read it and do what it says. Score correctly only if the individual actually closes his/her eyes.

Total: _____

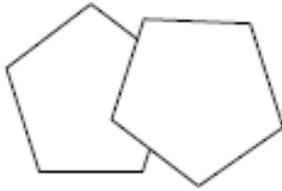
Writing

Give the individual a piece of paper and ask him/her to write a sentence. It is to be written spontaneously. It must contain a subject and verb and be sensible.

Total: _____

Copying

Give the individual a piece of paper and ask him/her to copy a design of two intersecting shapes. One point is awarded for correctly copying the shapes. All angles on both figures must be present, and the figures must have one overlapping angle.



Total: _____

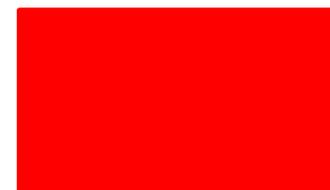
Grand Total: _____

APPENDIX F

**Select the word that
corresponds to the
middle WORD**

blue
yellow **blue**

**Select the word that
describes the
COLOUR of the block**



red **green**

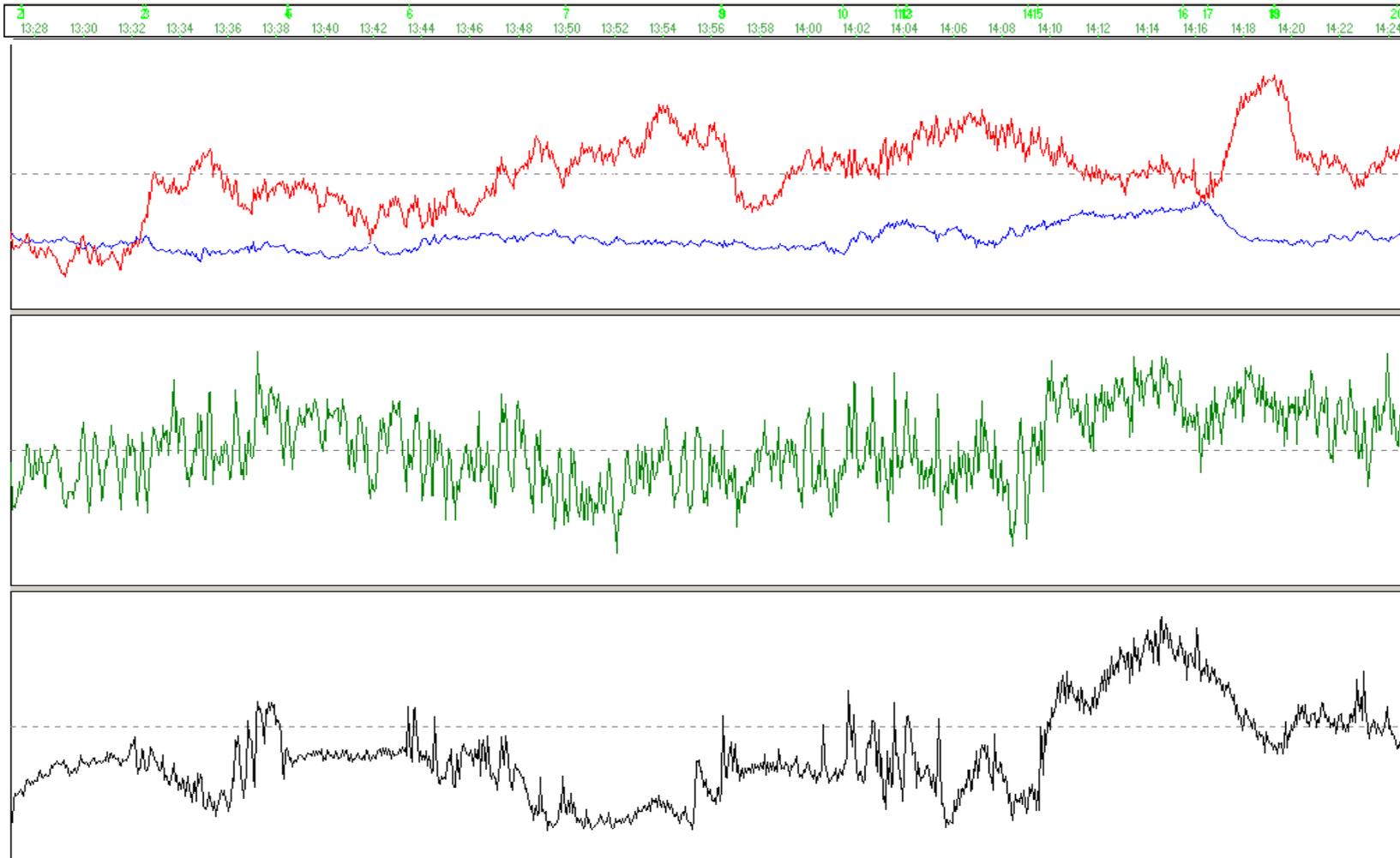
Select the word that
describes the text
COLOUR of the middle

blue
yellow red

Select the word that
describes the text
COLOUR of the middle

green
blue red

APPENDIX G



NIRS graph indicating the changes in O₂Hb (red), HHb (blue), TOI (green) and THI (black) over the testing period with relevant markers and time periods indicated.