The Long-Term Impact of Stroke on Cognition: Prevalence, Predictors, and Assessment

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Abstract

Stroke is indiscriminate and has the potential to erase a lifetime of experiences or abilities in an instant. Given that stroke sequelae can have long-lasting consequences, with many stroke survivors experiencing ongoing adverse effects several years later, there is mounting evidence supporting stroke not only as an acute but also as a chronic medical condition. Cognitive impairment is a frequently reported symptom post stroke, occurring in more than two thirds of stroke patients. Unlike physical impairments which can often recover following stroke, cognitive impairment becomes increasingly worse over time resulting in poor prognosis. Moreover, symptoms commonly associated with cognitive impairment are often overlooked, leading to increased rates of admission to private hospitals and higher rates of mortality. This is further complicated by the fact that assessment of post stroke cognitive function is not routinely carried out therefore prevalence of cognitive deficits may be underestimated. Existing data on long-term outcomes specific to stroke are scarce in NZ, particularly in terms of cognition. The purpose of this thesis was to determine prevalence, profiles, predictors, and trajectory of cognitive impairment in a cohort of four-year stroke survivors in NZ. Additionally, this thesis also sought to determine the accuracy of a screening tool to detect post stroke cognitive impairment.

This population-based follow-up study adopts a quantitative approach and includes a sample drawn from the fourth Auckland Regional Stroke Outcomes Study (ARCOS-IV). Two and hundred and fifty-seven people with stroke, completed cognitive assessments at baseline or within two weeks of stroke, and/or 1 month, 6, 12 and 48 months after stroke onset.

At four years post-stroke, the greatest proportion (84%) of stroke survivors exhibited below average cognitive functioning as assessed by the Montreal Cognitive Assessment Scale (MoCA) (M = 20.7, ± 4.70). Specific domains of cognition most affected by chronic stroke included attention, memory, information processing speed and executive functioning. While there was some recovery of cognitive function within the first 12 months, cognition steadily declined from this time-point to four-years. Regression analysis revealed baseline predictors including; older age (>75 years), male gender, not working, greater cognitive impairment at baseline and stroke-related vascular risk factors (i.e. hypertension, diabetes mellitus and arrhythmia) were associated with declining cognition over the four-year period. Vascular territory and stroke subtype as

classified by the Oxfordshire Stroke Community Stroke Project (OCSP) were associated with specific-domain impairments, more than hemisphere, pathological stroke type and lesion location.

ROC analysis comparing the MoCA to a more comprehensive computerized neuropsychological battery (CNS-VS), revealed the MoCA was found to have acceptable sensitivity and specificity to detect global cognitive impairment and high sensitivity to detect domain-specific impairment in executive function, visuo-spatial ability and memory.

This study identified that cognitive impairment following stroke does not resolve and continues to decline over time in the vast majority of people with stroke. The trajectory of cognitive recovery is influenced by sociodemographic and stroke-related risk factors. Additionally, assessment of post-stroke global cognitive impairment and certain domain-specific impairments could be accurately detected using the MoCA. Early identification of individual cognitive domains and risk factors that result in cognitive decline may inform the development of rehabilitation interventions targeting restoration, remediation and adaptation of cognitive function. The first step in the management of cognitive impairment is to educate health professionals working in stroke units and hospitals about the importance of recognising and diagnosing deficits prior to discharge. This can be achieved by standardisation of the MoCA in all health settings as the primary method for initial assessment of post stroke cognitive impairment. Finally, evidence gathered in this research should be used to further investigate the effects of early assessment, rehabilitation and frequent monitoring of cognitive function throughout the stroke journey.

Keywords: Stroke, Cognitive Impairment, Neuropsychology, Predictors, Prevalence, Long-term outcomes, Cognition, Assessment

Overview

Cognitive impairment is a common but often neglected consequence after stroke. Given the heterogeneity and complexity of stroke, it is not surprising that there is no specific or single identifying neuropsychological pattern. Stroke can interfere with the complex cognitive and integrative processes that are responsible for our ability to communicate, our talents and creativity, our individuality, our intellect, our ability to relate to one another, and our emotions. Reliable data on long-term cognitive outcomes is needed to inform evidence-based clinical decision-making, optimize development and implementation of cognitive rehabilitation interventions, and most importantly improve outcomes for those people, and their families who are living in our communities with persistent cognitive impairments.

The purpose of this thesis was to examine the effects of stroke on long-term cognitive impairment using a population-based approach. The overall research question was "What is the trajectory and predictors of cognitive impairment in long-term stroke survivors? This study sets out to answer these questions *"what does cognition look like 4 years after stroke?", "how many people still have persistent deficits in cognition?", "which factors combined with cognition, contribute to decline over time?", "can a brief assessment predict domain-specific impairment?* These questions are posed within the field of neuropsychology, a branch of psychology and neurology that is focused on understanding the function of the brain as they relate to specific psychological processes and behaviours. To answer these questions, a population-based perspective embedded in an epidemiological approach was used and quantitative methods were employed.

Within this thesis, three research studies are presented. Each study examines a different objective, with the findings combined into a cohesive whole in order to address the principle research question.

The objectives of this thesis were to:

1) Determine the long-term prevalence of cognitive impairment
2) Characterize long-term neuropsychological profiles
3) Explore the trajectory and predictors of changes in cognitive function over a four-year period

4) Examine the accuracy of a brief screening tool to identify global and domain-specific cognitive impairments

The overall structure of the thesis is divided into seven chapters:

- Chapter One provides an overview of stroke, pathophysiology, incidence, risk factors, classification and treatment and highlights the importance of this study in the context of the overall burden of stroke.
- Chapter Two explores the literature and the current evidence on cognition and stroke, cognitive profiles, predictors of cognitive impairment, long-term cognitive deficits and cognitive assessment of stroke
- Chapter Three describes the overall study methods, a brief description of the ARCOS-IV parent study, procedures, outcome measures and statistical analyses.
- Chapter Four presents the first study which investigates the first and second research objectives and will characterizes long-term cognitive profiles and prevalence of impairment in people with stroke
- Chapter Five presents the second research study (objective three), which examines the “trajectory and predictors of changes in cognition over time”.
- Chapter Six presents the third research study which explores the accuracy of the MoCA in detecting global and domain specific impairment (objective four).
- Chapter Seven provides an integrated discussion which combines evidence from the literature review with the research conducted within this thesis. The implications of the research findings for development of cognitive rehabilitation programmes, stroke management, and future research are proposed.

Each of the three research studies incorporated within this thesis, will be described in three separate chapters of this thesis (chapters four to six). A brief discussion of the limitations and strengths pertaining to each study will be incorporated within the chapters. The findings are then integrated in the final chapter (chapter seven) with a discussion of the findings relating to the thesis as a whole.

Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

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Co-Authored Works

Although the work in this thesis and individual studies were my own ideas and work, they were only achievable with the advice and support of my supervisors, mentor and several collaborators.

All studies within the thesis were conducted under the supervision of Doctor Rita Krishnamurthi, Doctor Kelly Jones and Dr Priya Parmar and my mentor Professor Valery Feigin.

The results from Study Two described in Chapter five, have been published in the Journal of Neuroepidemiology (see Appendix L). Overall my contribution was 90%, as I was the first author, writing the first complete draft. I was responsible for overall conceptualisation of the research idea, reviewing the literature, developing the hypotheses, study design, ethical approval, data collection, analysis, writing results and preparing the manuscript for publication. I was also responsible for addressing reviewer's comments and making revisions. Co-author, Dr Priya Parmar advised on the preliminary statistical analysis. Co-authors Dr Rita Krishnamurthi, Dr Kelly Jones, Associate Professor Alice Theadom, Associate Professor Suzanne Barker-Collo and Professor Valery Feigin provided advice and consultation on the draft.

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During my PhD, I had been faced with some really tough challenges. My father Peter, passed away very suddenly from cancer in 2014. My Dad was a very proud man, even in his final days and would have been so happy to see I have finally got to the end. In 2016, I also developed cancer and at the same time found out I was BRCA2 positive. I had to undergo major surgery, but so thankful it was caught in time and having the BRCA test saved my life.

My main inspiration comes of course from my family. For my oldest son Josh, you are my inspiration and I would never have made it if was not for your support and unconditional love over the past 27 years. You had to grow up far too quickly and put up with all of the tears and dramas which have accompanied various stages of my study. For my daughter Olivia, thanks for keeping me laughing, crying and always believing I can do this. Your positivity always shines through even when times are tough. For Harry, thanks for letting me be your Mum, you inspire me to keep going every day, and your disability has never been a hindrance for you. You never complain and you are living proof that people can live with chronic conditions and still have meaningful lives, even at times when it is so hard just to carry out basic everyday tasks. The three of you have had to face your fair share of adversity and I so admire your courage and strength in times when it's tough and so incredibly proud of you all.

Lastly, my heartfelt thanks to my partner, my best friend and my love Jon, who has had to put up with the tantrums, tears and hysteria (at times) over the past 12 years. Even in my undergraduate days, you were always so patient, proof reading all of my assignments which in the early days was pretty challenging. You nursed me when I was sick, and have continued to be by side throughout my PhD. Never forgetting to tell me how proud you are of me, especially at times when I am sure you didn't want to. We have been tested over the years and now I am looking forward to having some time to enjoy spending quality time together. Thank you, thank you, thank you.

Ethical Approval

Ethical approval was obtained from the Northern X Regional Ethics Committee of the Health and Disability Ethics Committee (HDEC) and Auckland University of Technology Ethics Committee (AUTEC) for the studies encompassed in this thesis.

HDEC approval (ref: NTX/10/09/090/AM07) was received on 24th April, 2014 (see Appendix A). AUTEC (ref: 11/297) approval was received on 13th May, 2014 (see Appendix B).

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Chapter 1 Introduction

This chapter will provide an overview of stroke, including pathophysiology, classification, risk factors, incidence, ethnic disparities and acute stroke management in the hospital setting.

1.1 Overview of Stroke

In New Zealand (NZ), stroke accounts for approximately 4% of health loss (measured by disability-adjusted life years) in people aged 65-74 and 7.3% of health loss in those aged 75 years and over (Ministry of Health, 2017). Stroke continues to be the leading cause of adult disability and second leading cause of death after cancer (Ministry of Health, 2017). As treatment and management for stroke has improved, individuals are living with the effects of a stroke for longer, with up to 57,000 stroke survivors in NZ (Ministry of Health, 2016). Given that stroke sequelae can have long-lasting consequences, with many stroke survivors experiencing ongoing adverse effects several years later, there is mounting evidence supporting stroke as a chronic medical condition (F Arba et al., 2016; Ayerbe, Ayis, Crichton, Wolfe, & Rudd, 2014; Barker-Collo et al., 2016; Crichton, Bray, McKevitt, Rudd, & Wolfe, 2016; Douiri, Rudd, & Wolfe, 2013).

Stroke is a highly preventable condition, associated with mainly modifiable risk factors (Feigin et al., 2016), the most prevalent being hypertension (Al-Hashel et al., 2016; Feigin et al., 2016; O'Donnell et al., 2016). Other risk factors include; atrial fibrillation, diabetes mellitus, obesity, hypercholesterolemia, blood glucose, smoking, poor diet and physical inactivity (Al-Hashel et al., 2016; Feigin et al., 2016). Over the past 30 years in NZ, evidence has shown an increase in the number of Māori and Pasifika people with modifiable risk factors (Feigin et al., 2015; Fink, 2016), yet stroke awareness in terms of knowledge of risk factors within these populations remains low (Bay et al., 2015).

Onset of stroke is acute, and regarded as a “brain at risk” condition, with a person needing immediate hospitalization for diagnosis and treatment. Intervention depends on a number of factors including type of stroke (*ischaemic* or haemorrhagic) and severity (Jaunch, Saver, & Adams, 2013). Intravenous thrombolytic therapy (a non-invasive procedure) can be given within four and a half hours after stroke, and can significantly improve not only survival but also cognitive and functional outcomes (Broome, Battle, Lawrence, Evans, & Dennis, 2016; Jaunch et al., 2013). However, only 6.4% of patients receive thrombolysis in NZ, (Liu, Ranta, Abernethy, & Barber, 2017), these rates are

lower when compared to Australia up to 7% (National Stroke Foundation, 2009) and the United Kingdom (UK) up to 11% (Royal College of Physicians, 2017). While, haemorrhagic strokes may require more aggressive therapy involving surgery to relieve intracranial pressure within the skull caused by bleeding, or clipping/coiling of an aneurysm (Sykora, Diedler, & Steiner, 2014; Wartenberg, 2014). However, medical interventions as mentioned above, come with higher risk of intracranial haemorrhage (intravenous thrombolytic therapy) and increased risk of perioperative stroke (clipping and coiling) resulting in early death, therefore not suitable for all patients (S. Brown, Macdonald, & Hankey, 2013; Kashkoush et al., 2017).

Prognosis after stroke depends on factors such as the severity of stroke and how fast it is diagnosed and treated. Patient disabilities can be temporary or permanent, partial or complete, and can affect function, language, physical ability, emotional state, mood and cognition (Chuluunbaatar, Chou, & Pu, 2016; Cumming, Brodtmann, Darby, & Bernhardt, 2014; Esparrago, Castilla-Guerra, Fernandez Moreno, Ruiz Doblado, & Jimenez Hernandez, 2015; Kootker et al., 2016; Leach, Gall, Dewey, Macdonell, & Thrift, 2011; Ullberg, Zia, Petersson, & Norrving, 2015).

1.2 Defining Stroke

Stroke is a clinical syndrome, classically characterized using the World Health Organization (WHO) definition which describes stroke as "*rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin"* (World Health Organisation, 1978).

1.3 Epidemiology

Globally it is estimated there will be approximately 17 million new strokes annually, of which 5.7 million will result in death (Feigin et al., 2016). The amount of people experiencing their first stroke is projected to increase by the year 2030 to 23 million worldwide (E. Benjamin et al., 2017; Feigin et al., 2016). Stroke affects around 9000 people in NZ annually, with an estimated 57,000 stroke survivors living with moderate disability and needing significant help with daily living (Ministry of Health, 2016). The economic burden is projected to cost the NZ health sector over $700 million per year (Feigin, Krishnamurthi, Barber, & Arroll, 2014). The Global Burden of Disease, Injuries and Risk Factors Study (GBD 2010), highlighted that although mortality rates have significantly decreased worldwide (37% high income countries compared to 20%

in low to middle income countries) over the past twenty years, the absolute number of people who experience a stroke annually, stroke survivors and stroke-related deaths has increased due largely to the ageing population (Feigin, Forouzanfar, et al., 2010). Global burden of stroke has increased for both men and women, with higher rates occurring among males (Barker-Collo et al., 2015). Overall stroke burden (measured by disability-adjusted life years-*DALYS*) increased from 38 million to 102 million (1990 to 2010 respectively) (Feigin, Forouzanfar, et al., 2010). Over the last 30 years, NZ stroke incidence rates has declined by 12 % (Feigin et al., 2015). This is in contrast to other developed countries where stroke incidence rates have declined by 42% over the last four decade (Feigin et al., 2016). Moreover, the prevalence of stroke survivors is projected to increase, given improvements in stroke acute care and rehabilitation (high income countries) and the ageing world population (Feigin et al., 2016; O'Donnell et al., 2016).

1.4 Pathophysiology of Stroke

A stroke is caused by disruption of blood flow to the brain (Kim, 2014). It is a very heterogeneous disease with three major pathological types (ischaemic, intracerebral haemorrhage, and subarachnoid haemorrhage) and a number of aetiological subtypes (small artery disease, large artery disease, cardio embolic strokes and strokes due to blood diseases and genetic causes) (Kim, 2014). Regardless of the underlying etiology between stroke types, the consequences remain the same. This can result in potentially irreversible damage, ultimately leading to neuronal cell death (Ankarcrona et al., 1995). The sequelae resulting from neuronal death are on a spectrum, depending on the region of the brain affected. Symptoms could be very mild at one end and catastrophic at the other end, resulting in death. Cellular death is primarily associated with the dysfunction of glutamate causing an ischaemic biochemical cascade (Ankarcrona et al., 1995; Campos et al., 2011). Dysfunction occurs through two processes; the depletion of glucose and oxygen which are necessary for normal cellular functioning and changes to cellular metabolism which causes the ischaemic cascade and a loss of the cell’s integrity (Zazulia, Markham, & Powers, 2011).

At a cellular level, stroke affects underlying mechanisms of hemostasis (a process which causes bleeding to stop) and disrupts connections between circulating blood elements, the brain parenchyma (functional tissue) and blood vessels (Lo, 2015). At a functional level, the regulation and dysregulation of blood circulation and metabolism is compromised, organs are affected when stroke induces abnormal changes in all neural,

glial and vascular cells (Kunz & Iadecola, 2009; Powers, 2016). The degree of damage to the brain is dependent on the severity, duration and location of ischaemia (Deb, Sharma, & Hassam, 2010). On average an acute stroke patient loses 1.9 million neurons per minute (Saver, 2006), therefore rapid restoration of blood flow to the ischaemic tissue is essential to limit the size of the potential infarct and subsequent sequelae (Powers, 2016).

Ischaemic strokes (ISC) occur when arteries become blocked, resulting in reduced blood flow to the brain (hypoperfusion) (Kim, 2014). A reduction in cerebral blood flow (CBF) below a critical threshold results in biochemical, functional and structural changes in the brain causing neurons to die (Bandera et al., 2006). The hypoperfused ischaemic area consists of two distinct regions: the infarct core, an area of unsalvageable brain tissue and the ischaemic penumbra, which surrounds the core and although functionally impaired still contains potentially viable tissue (Appireddy et al., 2016; Campos et al., 2011; Nedeltchev & Mattle, 2014). The length of cerebral hypoperfusion is a good predictor of long term outcomes, as ischaemia lasting more than four and a half hours can lead to permanent disability or death (Auer, 2016). Poor outcomes are related to the degree of reduction of CBF (<10-22 ml/100gm/min), level of glucose (between 6.1 and 7.0 mmol/L) and brain temperature (>37.6 degrees C) (Hafez, Coucha, Bruno, Fagan, & Ergul, 2014; Mrozek, Vardon, & Geeraerts, 2012; Powers, 2016).

In comparison, haemorrhagic strokes occur when a vein or artery ruptures into the surrounding brain tissue (subarachnoid haemorrhage-SAH) (Thines & Cordonnier, 2014) or into the brain (intracerebral haemorrhage-ICH) (Rossi & Cordonnier, 2014) (Ay, 2015). ICH represents about 10% of strokes, and is considered the least treatable, with the poorest prognosis. Most cases of ICH occur when small arteries burst, which results in leakage of arterial blood into the brain parenchyma. Injury is attributed to the physical disruption to adjacent tissue and the degree of impact caused by the ICH (Kim, 2014). Case fatality rates range from 35% at 1 week to 59% at 1 year (Ikram, Wieberdink, & Koudstaal, 2012; Manoei et al., 2016; Rincon & Mayer, 2012; Sacco, Marini, Olivieri, & Carolei, 2009). Approximately half of ICH patients will not survive the first 48 hours, those who do will have poorer outcomes, with less than a fifth of survivors being independent in daily living 6 months after stroke (Hemphill, Greenberg, & C, 2015; Manoei et al., 2016; Rathor et al., 2012; Rincon & Mayer, 2012; Sacco et al., 2009; Sykora et al., 2014). Admission to an intensive care unit (ICU) or specialized

stroke unit is associated with improved outcomes and decreased mortality rates (Diringer & Edwards, 2001; Manoei et al., 2016).

The volume of blood in the brain (shown on non-contrast CT images) is one of the strongest independent predictors of outcome after ICH, with a hematoma volume of 30ml representing cut-offs for higher rates of death and poorer functional outcomes (Broderick, Brott , Duldner, Tomsick, & Huster, 1993; Salihović, Smajlović, & Ibrahimagić, 2013). Blood volume > 60 ml combined with a Glasgow Coma Score (GCS) <8, at the time of injury can accurately predict 30-day case mortality rates (Broderick et al., 1993). Long-term prognosis after ICH is poor, with estimates of survival rates at 46% to 49 % 1-year after ICH and 29% to 33% at 5-years (Poon, Fonville, & Al-Shahi Shaman, 2014). Predictors most associated with death beyond 1-year post stroke, were older age, decreasing GCS, presence of intraventricular haemorrhage (IVH), increased intracranial pressure (ICP), recurrent ICH, and bleeds located in the deep/infratentorial region (Poon et al., 2014)

SAH is the least common type of stroke constituting 5% to 10% of all strokes. They occur at a younger age (45-55) and are associated with higher rates of disability (80%) and mortality (45%) (Cross & al, 2003; Kapapa & Konig, 2015a; Nieuwkamp, Setz, Algra, & al, 2009). After the initial bleed into the subarachnoid space, a biochemical cascade of events occur which result in increased ICP, a decrease in cerebral perfusion pressure (CPP) and CBF (Parra, 2015). This series of events can ultimately lead to one of the most frequent and serious complications after SAH, delayed vasospasm (DV), which affects about 70% of individuals. DV refers to a delayed vascular contraction/spasm, occurring three to 14 days post SAH and contributes to the greatest percentage of adverse outcomes following SAH resulting in permanent disability and death (Parra, 2015). Reduced long-term survival and higher mortality rates of patients with SAH were more likely if they had received poor preoperative clinical treatment, were older, had experienced multiple aneurysms, had conservative aneurysm management, and had poor clinical outcome at one year (Huhtakangas et al., 2015).

1.5 Classification of Ischaemic Stroke by Pathological Subtype

Classification systems for ischaemic stroke are based on topographic location, size of lesion, stroke mechanism, etiology and initial neurological symptoms following examination. Two of the most widely used classification systems are the Oxford Community Stroke Project Classification (OCSP) (Bamford, Sandercock, Dennis, Burn,

& Warlow, 1991) and the Trial of Org 10172 in Acute Stroke Treatment Subtype Classification (TOAST) (Adams et al., 1993).

OCSP classification system divides stroke into four subtypes, differentiating between cortical and lacunar syndromes, anterior and posterior territory infarcts: 1) lacunar infarction (LACI) are small infarcts confined to deep perforating arteries while 2) posterior circulation infarct (POCI) are associated with the vertebrobasilar arterial territory, primarily affecting the cerebellum and brainstem 3) a total anterior circulation infarct (TACI) usually a large infarct involving subcortical regions compared to a 4) partial anterior circulation infarct (PACI), smaller infarcts which involves predominately cortical regions and adjacent white matter (Bamford et al., 1991). In addition to location and size of lesion, specific clinical features define each subtype. For example, patients who experience one of the following symptoms: contralateral weakness of their face, arm and leg, behavioural and cognitive deficits and/or homonymous hemianopia will be classified as TACI (Bamford et al., 1991).

The nature of symptoms among subtypes differ, and related to the underlying cause, the area of the brain affected, the size of the stroke and prognosis with respect to disability, recurrent stroke and mortality (Dewey et al., 2003). TACI are associated with higher mortality and poorer cognitive and functional independence (Barker-Collo et al., 2012; Di Carlo et al., 2006; Pittock et al., 2003; Sprigg et al., 2007; Y. Yang et al., 2016), and a higher risk of stroke recurrence. LACI and POCI have better outcomes and higher short and long-term survival rates (Anderson et al., 1994; Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010).

A study which examined OCSP subtypes of 5-year stroke survivors, found that TACI and PACI have more long term cognitive impairment than the other two subtypes (Barker-Collo et al., 2012). OCSP is a useful clinical tool to predict recurrent stroke, complications, mortality, and functional recovery (A Pinto et al., 1998). Few studies have assessed the use of the OCSP classification system to predict stroke related outcomes in terms of cognition, independence, level of disability, health quality of life, mood, fatigue, and sleep (Ilzecka & Stelmasiak, 2000; Paci, Nannetti, D'Ippolito, & Lombardi, 2011; A Pinto et al., 1998; Sturm et al., 2004; Tei et al., 2000). The limitation of the OCSP is it does not determine the exact site of arterial pathology nor the cause of the stroke.

Compared to OCSP, TOAST system classifies patients with ischaemic stroke into five categories, according to the underlying pathophysiological mechanisms and etiology based on clinical, neurological examination and neuroimaging (Adams et al., 1993; Ay, 2015). These categories include; small artery occlusion, cardio-embolism, large artery atherosclerosis, other determined etiologies, and undetermined etiology. Stroke of other determined etiology is caused by mechanisms such as hypercoaguable conditions or haematological disorders. In comparison, stroke of undetermined etiology has either no probable etiology or more than one potential cause (Adams et al., 1993). Identification of the causes of stroke is important as it may influence treatment at both the acute phase and aid in developing secondary preventative strategies. The TOAST classification is still the most widely used reliable and valid classification system in clinical settings and epidemiological research (L. Goldstein et al., 2001; Rothwell et al., 2004).

1.6 Risk Factors

1.6.1 Modifiable Risk Factors

Stroke is a preventable condition, associated predominately (90%) with modifiable risk factors (Boehme, Esenwa, & Elkind, 2017). There is compelling evidence from two epidemiology studies; Global Burden of Disease (GBD) Study and the INTERSTROKE case-control Study which support a contribution of 10 modifiable risk factors associated with acute stroke, consistent across all populations (Feigin et al., 2016; O'Donnell et al., 2016). These include hypertension, ratio of apolipoprotein B (ApoB) to apolipoprotein A1 (ApoA1), diabetes mellitus, cardiac disease, smoking, poor diet, obesity, binge alcohol consumption, lack of regular exercise, psychosocial factors (including stress).

Elevated blood pressure (BP) or hypertension is the most significant modifiable risk factor for both ischaemic and haemorrhagic strokes, across gender, ethnicity and age with approximately 50% of strokes prevented by controlling BP (M. Lee et al., 2011). About 77% of patients who experience their first stroke will have an elevated systolic blood pressure of >140 mmHg or diastolic blood pressure of > 90mmHg (Soga, 2011). A systolic BP of >160mmHg or higher and/or diastolic BP of >95mmHg increases the relative risk (RR) of stroke by four times compared to people with normal blood pressure (120mmHg/80mmHg).

Age is an important predictor of stroke and hypertension, with the risk of stroke and elevated BP increasing in older aged people compared to middle aged individuals (Pandey, Aljehani, & Soga, 2016). A meta-analysis of 12 prospective cohort studies,

found an association with baseline hypertension and higher risk of stroke (M. Lee et al., 2011). Moreover, hypertension is a powerful contributor to atherothrombotic brain infarction (ABI*)* in people aged between 75-84 and a precursor for myocardial infarction and atrial fibrillation (Seshadri & Wolf, 2016). While hypertension is the main risk factor for both stroke types, the INTERSTROKE study found it is more strongly associated with ICH and SAH strokes, while smoking, high cholesterol and diabetes mellitus were more strongly linked to ischaemic strokes (O'Donnell et al., 2016). The GBD study also identified environmental risk factors such as exposure to air pollution as a significant contributor to stroke burden (Feigin et al., 2016). There are also differences in risk factors between genders, with males more likely to smoke and abuse alcohol than women (Stróżyńska, Fiszer, Ryglewicz, & Zaborski, 2016) while women have a higher prevalence of cardio-embolism, coronary artery disease and atrial fibrillation.

1.6.2 Non-Modifiable Risk Factors

Non-modifiable risk factors for all stroke types include age, sex, ethnicity and familial/genetic causes (E. Benjamin et al., 2017; Gulli, Rutten-Jacobs, Kalra, Rudd, & Wolfe, 2016; Hawkes et al., 2015; Lindgren, 2014; Mozaffarian et al., 2016; Wolf & Kannel, 2007). Stroke is regarded as a disease of ageing, with incidence doubling for every decade after the age of 55 (Boehme et al., 2017). On average females are four years older than men at stroke onset (75 to 71 respectively), and have a significantly higher life-time risk compared to males (E. Benjamin et al., 2017; Seshadri et al., 2006). In the Framingham Heart Study (FHS), the lifetime risk of stroke for those aged between 55 to 75 years, was one in five for females compared to one in six for males. This is attributed to females outliving their male counterparts (Seshadri et al., 2006). Factors such as early onset of menopause (Lisabeth et al., 2009), low-estrogen-dose oral contraceptives (Renoux, Dell'aniello, Garbe, & Suissa, 2010), migraine with aura (Sheikh, Pavlovic, Loder, & Burch, 2018) and AF contribute to their risk (Bhave, Lu, Girotra, Kamel, & Vaughan Sarrazin, 2015). In fact, younger females, who have migraine with aura and take oral contraceptives, have a nine-fold increased risk compared to females without these factors (Abanoz et al., 2017; Champaloux et al., 2017; MacClellan et al., 2007).

Familial and genetic risk factors for increased incidence of stroke have also been well documented. In the FHS, parents who had ISH by the age of 65 years, increased the risk of stroke for their offspring by three-fold (Seshadri et al., 2010). A large meta-analysis

(METASTROKE Collaboration) examining genome-wide data association with ISC stroke, reported that genetic susceptibility differs by age and by sex, with a trend toward increased heritability, in women and with younger age (Traylor et al., 2012). Heritability of ISH varies by stroke subtype, with higher rates for large-vessel disease (40 3%) and cardio embolic stroke (32 6%) compared to small-vessel disease (16 1%) (Traylor et al., 2012).

1.7 Ethnic Disparities in Stroke Incidence

The burden of stroke does not fall equally across the population, with stroke incidence and mortality rates persistently higher in black versus white ethnic groups (Gulli et al., 2016; G. Howard et al., 2011; Howard & Howard, 2016; V. Howard et al., 2011; Kleindorfer et al., 2010; Sealy-Jefferson et al., 2012; Wang, Rudd, & Wolfe, 2013). There is strong evidence to show low socioeconomic status (SES) contributes to black-white disparities, with low levels of SES associated with increasing the incidence of stroke two fold (Addo, Ayerbe, & Mohan, 2012; A. Cox, McKevitt, & Rudd, 2006; Marshall et al., 2015). Epidemiological research in NZ supports the international data showing stroke burden disproportionate in certain ethnic groups, with Māori and Pasifika people experiencing higher incidence rates of stroke than NZ European (K. Carter et al., 2006; Dyall, Feigin, & Brown, 2008; Feigin et al., 2006; Feigin et al., 2015; Fink, 2016). Over the past 30 years in NZ, the age of stroke onset has increased in most ethnic groups with Europeans experiencing stroke at 75.3 years, compared with Maori at 59.6 years and Pasifika 61.6 years (Feigin et al., 2015). Although recent research has reported a decline in stroke incidence and mortality rates over the past three decades in NZ, the 15 year age difference between Māori and Pasifika compared to NZ European has remained the same (Feigin et al., 2015). The difference in stroke onset is a stark indication that ethnic disparities in stroke are worsening

Māori and Pasifika also have significantly greater risk of poor functional outcomes than NZ European after stroke (Feigin, Barker-Collo, et al., 2010; Feigin et al., 2015; Feigin, McNaughton, & Dyall, 2007). Additionally, higher proportions of Māori and people of Pacific descent have significantly increased frequency of modifiable risk factors (Feigin et al., 2015). The continued increase in prevalence of vascular risk factors (high blood pressure, diabetes mellitus and myocardial infarction) has attenuated the risk of stroke for Māori and Pacific groups. While lower SES may be a contributing factor to these disparities, (Ministry of Health, 2014), the complete explanation of this disparity remains unclear. However, what is known is that Non-European New Zealanders

present with more severe strokes, which is likely due to reduced rates of presentation to hospitals and lack of stroke awareness and knowledge (Bay et al., 2015; Fink, 2016).

1.8 Treatment for Ischaemic Stroke

Management for acute ischaemic stroke primarily focuses on two approaches, restoration of blood flow to the ischaemic area and minimization of the deleterious effects of the ischaemic cascade on neurons (Deb et al., 2010). Reperfusion of the blocked artery induced by thrombolysis has shown to be effective when administered intravenously within 4.5 hours after onset (Nedeltchev & Mattle, 2014). The goal of thrombolysis is to remove the blockage and restore blood flow to the hypoperfused brain tissue in the penumbra zone (Appireddy et al., 2016). Restoration of blood flow permits ischaemic and dysfunctional (but still viable) neurons to regain function and clinical recovery (Broome et al., 2016; Campos et al., 2011; Heiss et al., 1998; Hillis et al., 2006; Ramos-Cabrer, Campos, Sobrino, & Castillo, 2011; Sahota & Savitz, 2011). Endovascular clot retrieval is an effective treatment and shown to improve functional outcomes in the acute phase of stroke (Barber, 2015). Despite its efficacy in improving outcomes following stroke, intravenous thrombolysis is underutilized with around 3% to 5 % of acute stroke patients receiving therapy (Adeoye, Hornung, Khatri, & Kleindorfer, 2011; Cheng & Kim, 2015). Limitations with thrombolysis are the narrow therapeutic window time frame and increased risk of intracranial bleeding (Ozpeynirci, Schmitz, & Schick, 2016; The IST-3 Collaborative Group, 2012).

1.9 Treatment for Intracerebral Stroke

ICH is the second most common subtype of stroke, and least treatable with the poorest prognosis. The volume of blood in the brain (shown on non-contrast CT images) is one of the strongest independent predictors of outcome after ICH, with a hematoma volume of 30ml representing cut-offs for higher rates of death and poorer functional outcomes (Broderick et al., 1993; Salihović et al., 2013). Blood volume > 60 ml combined with a GCS < 8 at the time of injury, can accurately predict 30-day case mortality rates (Broderick et al., 1993). Current treatment of ICH target mainly blood pressure and hematoma growth, using both medical and surgical management. Medical interventions include, intubation and ventilation (dependent on level of consciousness) in the acute phase to stabilize respiratory and cardiac functions (J. Goldstein & Gilson, 2011), blood pressure reduction, which has been shown to reduce the risk of further bleeding (Manoei et al., 2016), and hemostatic therapy (Mayer, 2003; Zhou et al., 2013). Surgical

interventions include decompressive hemicraniectomy (to reduce intracranial pressure-ICP) and hematoma evacuation (reduces ICP and metabolic effects of hematoma on surrounding tissue, especially in cases of ICH in the cerebellum) both procedures has been shown to improve 3 month survival rates in ICH patients (Esquenazi et al., 2015; Lopponen & al, 2013). Early rehabilitation, admission to an intensive care unit (ICU) or specialized stroke unit is associated with improved outcomes and decreased mortality rates (Diringer & Edwards, 2001; Manoei et al., 2016).

1.10 Treatment of Subarachnoid Stroke

Management of SAH primarily focuses on stopping re-bleeding, reducing pressure in the brain (Kapapa & Konig, 2015b) and prevention of delayed vasospasm. In acute SAH, general emergency management includes control of ICP, stabilizing systemic oxygenation and haemodynamics to improve cerebral perfusion and oxygen supply, blood pressure control, seizure control and, in selected cases, antifibrinolytic agents to prevent further bleeding of aneurysm (Kapapa & Konig, 2015a; Wartenberg, 2014). Prevention of delayed vasospasm in aneurysmal SAH includes early surgery and/or use of calcium channel blockers. Endovascular management includes surgical clipping or endovascular coiling. Early intervention is vital in order to stop the initial bleed and prevent rebleeding; one the major complications occurring within the first 24 hours and associated with a poor prognosis and high mortality rate (Matias-Guiu & Serna-Candel, 2013; Naidech et al., 2005).

1.11 Conclusion

Worldwide, stroke is a common cause of adult morbidity and mortality, yet highly preventable. The impact of stroke can be deleterious and profoundly affect a person's ability to function independently. Although rates of incidence have decreased in NZ, stroke burden continues to be disproportionate, with Māori and Pasifika people experiencing stroke at least 15 years earlier compare to NZ Europeans. An increase in major risk factors has attenuated this risk. Given the improvements in stroke management and treatment combined with an increasing ageing population, the number of people surviving a stroke will significantly increase. While research has largely focused on secondary prevention, current evidence would suggest targeting primary prevention strategies in order to reduce modifiable risk factors and overall stroke burden in NZ.

Chapter 2 Cognitive Impairment following Stroke

This chapter provides an in-depth review of the current literature on post stroke cognitive impairment, starting with a brief overview of the topic. The main cognitive deficits following stroke, associated prevalence rates, and risk factors will be discussed. In addition, the cognitive assessment tools used to assess post stroke cognitive impairment are briefly reviewed.

2.1 Defining Cognition

Cognition works as an "interface" between the brain and its environment, directing the mental processes involved in obtaining information, knowledge and understanding (Sternberg & Sternberg, 2009). These processes are essential for carrying out normal everyday activities. While not considered a unitary concept, cognition is comprised of multiple mental processes which are associated with the acquisition, awareness, retrieval, storage, organization, comprehension and communication of information. These processes are organized into specific domains of function which include; *intelligence* (ability to obtain and apply knowledge and skills), *executive function* (organizing thoughts, ability to sequence, plan, control, and inhibition), *attention* (dividing, sustaining and shifting attention), *language* (expressive and receptive), *memory* (visual, verbal, long term, working) and *visuo-spatial ability* (construction, drawing, visual scanning) (Cumming, Marshall, & Lazar, 2013). Combined, these processes form part of a person’s experiences and unique intellectual development. Executive function is a multi-faceted construct, which governs goal directed actions by interacting with other cognitive processes to manage, regulate and control behaviour (see Figure 1).

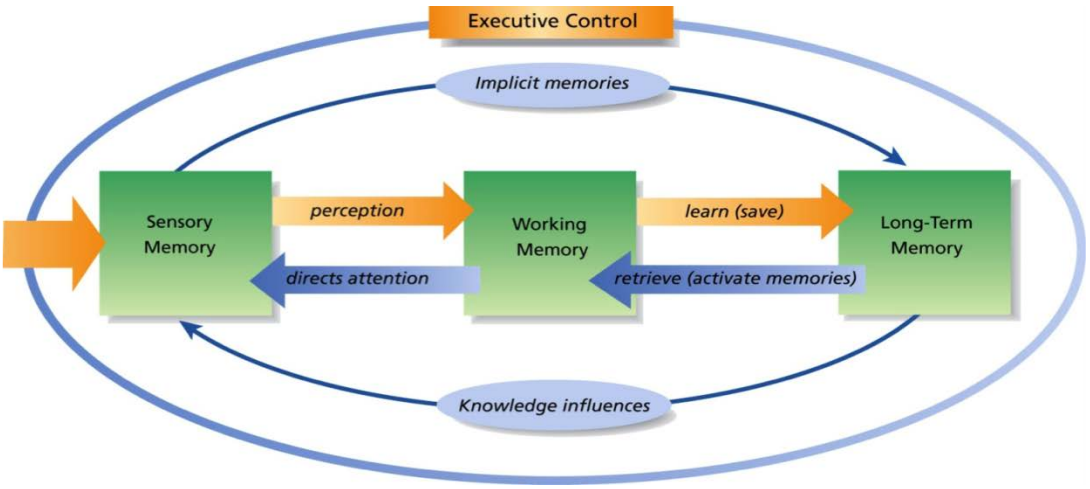

Figure 1. The Model of Cognitive Processes
Note: Reprinted from *Educational Psychology Interactive* by W, Huitt, 2003. Retrieved from http://www.edpsycinteractive.org/topics/cognition/infoproc.html. Copyright (2003) by Valdosta State University. Reprinted with permission.

2.2 Neuropsychology within the Context of Stroke

Neuropsychology is a branch of psychology, which aims to understand the influences brain dysfunction has on cognitive functions and behaviours. Within the context of stroke, neuropsychology is primarily concerned with identifying, assessing and treating the extent of cognitive and emotional sequelae, in addition to perceptual impairments associated with strokes pathophysiology (Delaney & Ravdin, 1997; Sila & Schoenberg, 2011). Identifying domain-specific impairments, can quantify cognitive deficits, assist in predicting outcomes, and guide the development of interventions for cognitive rehabilitation (Sinanovic, 2010). An integrated biopsychosocial approach is employed to understand the influences of biological/neurological factors, psychological and social factors on assessment, recovery and rehabilitation.

2.2.1 Cognitive Impairment

Cognitive impairment refers to a condition in which there is deterioration in a person's normal cognitive abilities, which changes a person's level of functioning (American Psychiatric Association, 2013). The construct of cognitive impairment that is associated with stroke has gone through many variations. Currently the most commonly used terms are Vascular Cognitive Impairment (VCI), (Gorelick et al., 2011) and Post stroke Cognitive Impairment (PSCI) (Sun, Tan, & Yu, 2014). Despite the diversity of opinion on how best to define and classify cognitive impairment following stroke, there is general consensus on the underpinning elements; a) presence of at least one primary cognitive deficit determined by cognitive assessment; b) diagnosis of stroke; and c)

relationship established between stroke and cognitive impairment (American Psychiatric Association, 2013; Nyenhuis, 2014).

2.3 Domains of Cognition affected by Stroke

Cognitive domains commonly affected by stroke include; language, memory, executive function, attention, and visual spatial function. Information processing speed is also affected, however this is not considered a stand-alone domain but rather interplays with executive function and attention (Barker-Collo, Feigin, & Krishmnamurthi, 2013; Barker-Collo et al., 2016; Martin, Caeiro, & Ferro, 2013; Planton et al., 2012).

2.3.1 Language

The presence of language disorders post stroke are frequent and include; aphasia (inability to formulate or comprehend language, apraxia (loss of ability to plan and execute speech), alexia (loss of ability to read), agraphia (inability to write) and acalculia (inability to manipulate numbers) (Flowers et al., 2017; Sinanovic, Mrkonjic, Zukic, Vidovic, & Imamovic, 2011; Vidovic, Sinanovic, Sabaskic, Haticic, & Brkic, 2011).

Aphasia is a common consequence of lesions in the left hemisphere and the most common neuropsychological consequence of stroke (Sinanovic et al., 2011). Aphasia typically involves a disturbance or loss of language function in four primary areas (depending on the size and location of the lesion) which include; spoken language processing or comprehension (Pillay, Binder, Humphries, Gross, & Book, 2017), written expression and/or reading comprehension. It occurs more in older people and those who have ischaemic stroke, (Ellis & Urban, 2016) with data from international studies reporting frequency ranging from 18 % to 38 % (Dickey et al., 2010; Ellis, Hardy, Lindrooth, & Peach, 2018; Flowers, Skoretz, Silver, Rochon, Fang, Flamand-Roze, et al., 2016; Gonzalez Mc, Lavados, & Olavarria, 2017; Lalor & Cranfield, 2004; Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Law et al., 2009; Pedersen, Stig Jørgensen, Nakayama, Raaschou, & Olsen 1995). Not surprisingly, there is a strong association between aphasia and presence of anxiety and mood disorders, with findings from a recent study reporting prevalence of anxiety in aphasic stroke survivors at 44% compared with non-aphasic stroke patients (Morris, Eccles, Ryan, & Kneebone, 2017). Survivors of stroke who develop aphasia often face increased risks for longer hospital stays, inpatient complications, and mortality (Boehme, Martin-Schild, Marshall, & Lazar, 2016; Lazar & Boehme, 2017). Additionally, patients may experience more

psychological distress, social isolation (Hilari & Northcott, 2017) and diminished participation in social activities due to persistent difficulties in communication (Dalemans, De Witte, Beurskens, Van Den Heuvel, & Wade, 2010; Flowers, Skoretz, Silver, Rochon, Fang, Flamand-Roze, et al., 2016; H. Lee, Lee, Choi, & Pyun, 2015; Mazaux et al., 2013; Shehata, El Mistikawi, Risha, & Hassan, 2015). Further, many patients with post stroke aphasia may experience a greater financial burden that exceeds the cost of stroke alone because of a long-standing need for rehabilitative services for their communication difficulties (Ellis et al., 2018; Ellis, Simpson, Bonilha, Mauldin, & Simpson, 2012).

Aphasia is often reported to co-occur with dysarthria (speech disorder), for example; Bahia and colleagues (2015), reported a co-occurrence of dysarthria and aphasia in 29% of stroke patients (Bahia, Mourao, & Chun, 2016). Most patients with aphasia improve to some extent within the first few months, with the severity of the initial aphasia significantly predicting long-term deficit (Dunn et al., 2016). For example, large lesions in the left hemisphere with global amnesia have poorer outcomes compared to patients with small subcortical anomia (form of aphasia where patients are unable to recall names of objects) (Sul et al., 2016).

It is important to note that inconsistent measurement of aphasia and selection bias across studies may have led to an underestimation of prevalence rates. For example, some studies have not used standardised measures for aphasia (Azka, Maqbool, Butt, Iftikhar, & Iftikhar, 2016), and often aphasic patients are not approached to take part in research as they may not meet the eligibility criteria due to their deficits (Hotter et al., 2017).

2.3.2 Memory

Memory deficits are commonly encountered following a stroke, even after successful clinical recovery from physical impairments (Al-Qazzaz, Ali, Ahmad, Islam, & Mohamad, 2014; Jannink et al., 2009; Jokinen et al., 2015; Kalaria, Akinyemi, & Ihara, 2016; N. Karimian, K. Asgari, H. T. Neshat Doost, H. R. Oreizi, & M. R. Najafi, 2017; Lowry et al., 2014). Memory is a complex system that comprises of different functionalities, depending on whether information needs to be encoded (acquisition), stored (consolidation), or retrieved (recognition or recall) (Baddeley, 2012). Types of memory affected by stroke include; visual memory (remembering faces, shapes and everyday stimuli), verbal memory (remembering names, stories and information having

to do with words) and working memory (holding and manipulating information) (Barker-Collo et al., 2016; Negar Karimian et al., 2017; Middleton et al., 2014; Novitzke, 2008). Although memory impairment at the acute phase of stroke is frequently reported, (Cho et al., 2014) deficits can persistent long-term (Barker-Collo et al., 2016; Schaapsmeerders et al., 2013). A 2016 survey conducted in England found that 77% of stroke survivors continue to have long-term memory impairments three years after stroke (UK Stroke Association, 2016). Furthermore, approximately 50% of respondents had not received any form of cognitive rehabilitation (Stroke Association, 2016; Tang, Price, Stephan, Robinson, & Exley, 2017).

2.3.3 Executive Function

Executive function is commonly affected after stroke, reportedly affecting up to 75% of people in the acute phase of stroke (Conti, Sterr, Brucki, & Conforto, 2015; Laino, 2010; Y. Park et al., 2015). Executive functions encompass a wide range of higher cognitive skills, involving all aspects of brain functioning, communication and organization and act to control complex tasks in frontal regions of the brain (Elliott, 2003). Functions include; decision making, reasoning, creativity, performing complex tasks, impulse control, emotional regulation and problem solving and are connected and can interfere with each other (Diamond, 2013; Lohner, Brookes, Hollocks, Morris, & Markus, 2017). Deficits in these functions contribute to disability and adversely influence rehabilitation outcomes for stroke survivors (Conti et al., 2015; Elliott, 2003; Miyake, Emerson, & Friedman, 2000; Y. Park et al., 2015; Terroni et al., 2012). Stroke location (for example frontal lobe lesions) is not the only factor associated with executive function deficits; with male sex, abnormalities in white matter, pre-stroke dementia and temporal atrophy all contributing to post-stroke executive dysfunction (Hua et al., 2014; Scheffer et al., 2016).

2.3.4 Information Processing Speed

The ability to complete a cognitive task or process information within a defined period is known as information processing speed. Although not previously considered a stand-alone domain of cognition, it has now been suggested that deficits in processing speed should be included in standard post-stroke cognitive profile along with measures of executive function and attention (Cumming, Marshall, et al., 2013; Nigg et al., 2017). At the acute phase of stroke, up to 70% of survivors may experience impaired information processing speed, with symptoms likely to continue regardless of rehabilitation (Lesniak, Bak, Czepiel, Seniow, & Czlonkowska, 2008). Impaired

processing speed after stroke, slows the ability of the brain to process information, which in turn impacts performance on everyday tasks (Winkens, Van Heugten, Wade, Habets, & Fasotti, 2009). For example; the ability to make decisions is often affected, such as the ability to pay a bill, cook, grocery shop or even driving (Winkens, Van Heugten, Fasotti, Duits, & Wade, 2006). If difficulties persist long-term this can adversely affect quality of life and functional recovery in stroke survivors (Barker-Collo, Feigin, Parag, et al., 2010; Narasimhalu et al., 2011; Viken, Jood, Jern, Blomstrand, & Samuelsson, 2014).

2.3.5 Attention

One of the most prominent cognitive deficits following stroke is attention, with prevalence estimates ranging between 46% to 92% at the acute phase of stroke, and persisting in up to 50% of stroke survivors for at least five years (Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010; Duffin, Collins, et al., 2012; Geiger, Bonnyaud, Fery, Bussel, & Roche, 2017; Hyndman, Pickering, & Ashburn, 2008; Loetscher & Lincoln, 2013a). Attention comprises a dynamic set of processes that influence the interaction between the external environmental and other cognitive functions such as memory, language and perception (Cohen, Malloy, Jenkins, & Paul, 2014). The primary role of attention is to govern the processing and flow of information within each of the cognitive domains, facilitating, inhibiting or enhancing cognitive processes (Cohen et al., 2014). This enables individuals to respond to certain stimuli in the presence of competing information.

When attention is impaired, survivors of stroke will find it difficult to effectively allocate cognitive resources to a specific task (Cohen et al., 2014). Even though other domains of cognition such as language comprehension, memory and sensory perception remain intact, an individual may fail to consistently perform these tasks at optimal levels. Inconsistencies in task performance are a hallmark feature of deficits in attention (Cohen et al., 2014). Deficits in attention following a stroke typically manifest in a varying range of dysfunction; such as loss of concentration, increased distractibility, diminished information processing speed, mental fatigue and difficulties in multitasking (Loetscher & Lincoln, 2013a). This is further complicated at the acute phase of stroke by alterations in consciousness, which are common and inevitably have an impact on attention.

2.3.6 Visuospatial

Visuospatial ability plays an important role in everyday functioning, allowing individuals to process and analyse visual stimuli in the environment. Deficits in visuo-spatial skills occur when this process is impaired resulting in some form of spatial neglect **(**Kaplan & Hier, 1982). Regarded as one of the most disabling features of stroke, spatial neglect is an attentional-perceptual disorder, which can present in up to 82% of stroke survivors in the acute phase, and associated with greater risk of falls and long-term disability **(**Nijboer, Kollen, & Kwakkel, 2013; Timbeck, Spaulding, Klinger, Holmes, & Johnson, 2013; Wing, Burke, Clarke, Feng, & Skolarus, 2017). The disorder is distinguished by a diminished ability to report, respond or orientate to stimuli in contralateral (opposite side) regions of the brain (Heilman, Valenstein, & Watson, 2000). Although spatial neglect traditionally presents in right hemisphere lesions (A. Carter et al., 2017) some studies have shown the disorder can also present with left hemisphere lesions (Schendel, Dronkers, & Turken, 2016). Although visuo-spatial deficits may improve or even resolve, prolonged disruption of cognitive networks responsible for higher complex functions, may persist and result in significant long-term functional disability (Burgess, Veitch, de Lacy Costello, & Shallice, 2000; C. Wright et al., 2008).

2.4 Cognition and Stroke

Post stroke cognitive impairment is a continuum of intellectual decline ranging from mild, moderate to severe deterioration (A. Wong & Mok, 2015). As highlighted in Chapter 1, cognitive impairment in the acute phase of stroke can occur in approximately 70% of people. While some of these deficits resolve quickly (Gottesman & Hillis, 2010; Middleton et al., 2014; Nys et al., 2007), over 50% of stroke survivors experience persistent long-term cognitive deficits, even after good functional recovery (Crichton et al., 2016; Delavaran, Jonsson, et al., 2016; Jokinen-Salmela et al., 2015; Levine et al., 2015). For example, at three years after stroke, 68% of patients had regained good functional recovery but still experienced persistent cognitive deficits (Kapoor et al., 2017).

Cognitive deficits arise from a combination of neurological disturbances which occur in acute stroke and may be the consequence of a variety of factors including brain hypoperfusion (inadequate oxygen supply), lesion location and volume of intracranial pressure (ICP) on surrounding brain tissue (Grysiewicz & Gorelick, 2012).

Cognitive deficits have been associated with older age (>60 years), female sex, and lower education level (Danovska, Stamenov, Alexandrova, & Peychinska, 2012; Douven et al., 2016; Lo Coco, Lopez, & Corrao, 2016). Stroke-related factors such as type of stroke, vascular co-morbidities, lesion location (cortical region) and recurrent stroke, are also risk factors for the presence of cognitive impairment (Blake, Duffy, Myers, & Tompkins, 2002; Chen et al., 2016; Jaillard, Grand, Le Bas, & Hommel, 2010; Kalaria et al., 2016; Kim, 2014; Rist et al., 2013b; Zinn et al., 2004).

Deficits in cognition contribute to overall functional outcomes from stroke (Arsic et al., 2015; Barker-Collo, 2006; Barker-Collo, Feigin, Lawes, Senior, & Parag, 2010; Patel, Coshall, Rudd, & Wolfe, 2002) and are linked to wider outcomes (F Arba et al., 2016; Crichton et al., 2016; Feigin, Barker-Collo, McNaughton, Brown, & Kerse, 2008; Patel et al., 2002; Peixoto et al., 2017; Verhoeven et al., 2011). While, psychological factors have been shown to be more important determinants of cognitive outcomes after stroke, more than physical disability (F Arba et al., 2016; Bonita, Solomon, & Broad, 1997; Hackett, Duncan, Anderson, Broad, & Bonita, 2000; Hommel, Carey, & Jaillard, 2015; Kootker et al., 2016; Taub, Wolfe, Richardson, & Burney, 1994) and contribute to stress in caregivers (Bakas et al., 2016; Chuluunbaatar et al., 2016; De Souza Oliveira et al., 2013; Godwin, Swank, Vaeth, & Ostwald, 2013; Pesantes, Brandt, Ipince, Miranda, & Diez-Canseco, 2017). Post stroke cognitive impairment is also associated with medication non-adherence, which can further increase disability, level of dependence and greater caregiver burden (AlShaikh, Quinn, Dunn, Walters, & Dawson, 2016; Crayton et al., 2017; Rohde et al., 2017).

There is also evidence from some studies that cognitive impairment independently predicts low mood, health-related quality of life, dependence and disability (Ankolekar et al., 2014; Barker-Collo, Feigin, Parag, et al., 2010; Bays, 2001; Bieńkiewicz et al., 2015; Cumming et al., 2014; Feigin, Barker-Collo, et al., 2010; Leach et al., 2011). Nakling and Colleagues (2017), reported baseline cognitive impairment was associated with depression a year after stroke. While a more recent cross-sectional study of 147 patients, reported higher incidence of cognitive impairment (58%) was significantly associated with poorer quality of life compared to controls (Sarfo, Akassi, Adamu, Obese, & Ovbiagele, 2017). These findings strongly suggest cognitive rehabilitation may beneficial for improving a broad range of outcomes for stroke patients beyond enhancing cognitive function. Yet traditionally little attention has been given to

cognitive deficits in rehabilitation programmes (Gillespie et al., 2015; McNaughton, Thompson, Stinear, Harwood, & McPherson, 2014; Weistein et al., 2016).

2.5 Prevalence of Cognitive Deficits

A number of studies have reported prevalence rates of post stroke cognitive impairment, ranging from 7.5% to 72% (Mohd Zulkifly, Ghazali, Che Din, Singh, & Subramaniam, 2016). There is some variability across studies as to how cognition is measured, either using an "overall" measure of global cognition (using screening tool such as the MoCA or mini-mental state examination: MMSE) or domain-specific function (assessed by a more detailed neuropsychological battery) with mixed variability in results. This adds some complexity into interpreting prevalence and recovery rates when different constructs of cognition are measured.

For example; a French study, which used a global measure of cognition, found nearly half of patients (47.3%) were cognitively impaired (categorized as a MoCA score of <26), at 12 weeks following stroke (Jacquin et al., 2014). Chinese studies measuring global cognitive function global have reported high prevalence rates (70% to 80.97%) during the acute phase of stroke (within two weeks) (Blackburn, Bafadhel, Randall, & Harkness, 2013; Qu et al., 2015). In comparison, a cross-sectional study in the United Kingdom (UK) involving 209 survivors of stroke, reported prevalence of cognitive impairment at 30% in the first month after stroke (Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013). However, cognitive recovery was found at 3 months, with prevalence of information processing speed and attention significantly decreased from 72.4% to 37.9 %. Another study which used a more detailed neuropsychological assessment, showed 74% of patients demonstrating cognitive deficits, predominately in executive function and visuo-spatial perception, within three weeks of stroke (Nys et al., 2007).

In contrast, longitudinal studies seem to predominately use more global measures of cognitive function to determine prevalence, with rates ranging from 21 % to 61% (Tang et al., 2018). While the majority of these studies have shown a trajectory of further decline over time, (Lowery et al., 2002; Rajan, Aggarwal, Wilson, Everson-Rose, & Evans, 2014; Sachdev, Lipnicki, Crawford, Wen, & Brodaty, 2014; Tan et al., 2017; Turunen et al., 2018) results are variable (Suministrado et al., 2017). In a population-based sample of 145 Swedish survivors of stroke, 61% of people with stroke had cognitive impairment at 10-year follow-up (Delavaran, Jonsson, et al., 2016). While a

prospective study of 515 participants reported decline in global cognition over six-years compared to those without stroke (Levine et al., 2015). Nakling and colleagues (2017) reported 60% of people with stroke had cognitive impairment at one-year post stroke.

In comparison, some longitudinal studies have reported some cognitive recovery within six-months of stroke. The South London South Register study (SLSR) followed patients up to 15 years after stroke, prevalence of cognitive impairment remained stable at 21 % from 3 months to 14 years post stroke event (Crichton et al., 2016). Similar findings were reported by Turunen and Colleagues (2018), with 49% (n=153) of survivors who were cognitively impaired at baseline, showing a trend in cognitive recovery from 41% at six-months to 39% at two year follow-up (Turunen et al., 2018). Rasquin and colleagues (2002) compared prevalence of deficits at 1 and 6 months post stroke in the specific domains of memory, simple speed and cognitive flexibility. They found that while deficits in all three domains remained in a number of patients, a substantial group improved at 6 months. Similarly, an Auckland study reported improvement in executive function and psychomotor speed at six months after stroke, although no further improvement was made between six and 12 months (Barker-Collo et al., 2016). Finally, a prospective cohort study of 324 stroke patients reported prevalence of cognitive impairment at 51.9% 6 months after stroke. However, although prevalence was high, the overall MoCA score improved by 1 point (23.7 to 24.7) between two and six month follow-up (Nijsse et al., 2017).

Although the aforementioned studies may indicate that cognitive recovery may be possible within first six months, this information suggests that prevalence of cognitive deficits still remains high in the long-term. The interpretation of these findings are further complicated by methodological constraints; using hospital (Demeyere et al., 2016; Qu et al., 2015; Turunen et al., 2018) and community-based studies (Douiri et al., 2013; Ghosal et al., 2014), short term follow-up < one year (Barker-Collo et al., 2016; Nijsse et al., 2017) and variability in assessment measures (Crichton et al., 2016). Therefore, the actual frequency of cognitive deficits may be underestimated. On the other hand, population-based studies have provided more robust evidence, that cognition does decline > than one year after stroke (Delavaran, Jonsson, et al., 2016; Ghosal et al., 2014; Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010; Rajan et al., 2014; Sachdev et al., 2014; Stephan, Richardson, et al., 2017). Additionally, most studies have examined cognitive impairment at different time points rather than measure

the effects of time and predictors associated with the trajectory of cognitive decline or recovery.

2.6 Risk Factors and Predictors of Cognitive Deficits

Risk factors for cognitive deficits are varied and include clinical factors (hemisphere, lesion size, type and location, previous stroke), (Gorelick et al., 2011; Kalaria, 2016; Mohd Zulkifly et al., 2016), demographic factors such age, sex and education status and stroke-related risk factors, (i.e. vascular risk factors, hypertension, diabetes mellitus). Certain cognitive deficits (hemi-neglect and aphasia), following stroke are more common with older age and lower education level independent of severity and infarct size (De Ronchi et al., 2007; Jaillard et al., 2010; Kelly-Hayes et al., 2003; Nicholas, Hunsaker, & Guarino, 2017; Ones, Kalcinkaya, Toklu, & Caglar, 2009; Rajan et al., 2014; Sealy-Jefferson et al., 2012). Increased age has been found to be a good predictor of long-term stroke cognitive impairment and greater disability (Denti, Umberto, Caminiti, Giambanco, & Casella, 2013; Liman et al., 2011; Lo Coco et al., 2016; Maineri, Xavier, Berleze, & Moriguchi, 2007). In a cohort from the Framingham Study (n=200), almost 43% of elderly (aged >79 years) stroke survivors had moderate to severe neurological deficits and were significantly more disabled in all domains (Kelly-Hayes et al., 2003). A 2017 survey, of Mongolian and Chinese stroke patients (n=444), prevalence of cognitive impairment (MoCA $\leq$ 26) was associated with older age and disability (C. Zhang et al., 2017).

In terms of gender, females tend to have worse outcomes than males and experience strokes at an older age (Denti et al., 2013; Feigin, Barker-Collo, et al., 2010; Gibson & Attwood, 2016; Reid et al., 2008; Stahlhut, Grotemeyer, Husstedt, & Evers, 2014). However, females also have more premorbid cognitive impairment which may not be accounted for in age-adjusted analyses. In addition, females tend to have more severe strokes and therefore greater mortality (Phan et al., 2017).Women also experience more cardio embolic strokes and heart disease which may explain higher frequency of cognitive deficits than males (Reid et al., 2008; Stróżyńska et al., 2016). Education status is also a commonly reported predictor of cognitive deficits, with lower levels of education resulting in prevalence of deficits (Arsic, Konstantinovic, Eminovic, & Pavlovic, 2016; Boehme et al., 2017; Sarfo et al., 2017). Several studies have shown cognitive recovery in those with higher education, this suggests that higher education and cognitive reserve, may mitigate the effects of impairment (Mirza et al., 2016; C. Zhang et al., 2017). On the other hand, a meta-analysis of the effects of formal

education on post stroke cognitive impairment found no relationship, however the sample of stroke patients was much younger (mean=50) and therefore lacked generalizability (Kessels et al., 2017).

There is mounting evidence that there is a relationship between stroke-related risk factors and increased risk of cognitive deficits (Kalaria et al., 2016; Mohd Zulkifly et al., 2016; Tang et al., 2018). Prior research has demonstrated that patients with diabetes mellitus (Narasimhalu et al., 2011), hypertension (Mok et al., 2016; Stephan, Harrison, et al., 2017), hyperlipidemia (Tu et al., 2014) and heart arrhythmia (Mahon et al., 2017), face increased risks for cognitive deficits. A retrospective study of 707 patients with ischaemic stroke, reported a score of <24 on the MMSE was independently associated with AF (Eliyahu Hayim, Anna, Marina, & Abraham, 2011). Chaudhaori and colleagues (2014), reported that higher rates of cognitive impairment were associated with hypertension and diabetes mellitus at 6 months after stroke, however, on regression analysis these factors were not significant. Longitudinal data on the relationship of medical co-morbidities and cognitive impairment is scarce, with poor study design and assessment methods (use of MMSE) limiting generalizability. For example, a two-year follow-up found diabetes mellitus was independently associated with global cognitive impairment, however, it used a cross sectional design and was not population-based (Stephan, Harrison, et al., 2017). Additionally, the MMSE was used which is limited in its use as a cognitive screen as it does not assess executive function.

Stroke location has been shown to be an independent predictor of cognitive impairment, associated with lesions in the left and right hemispheres, subcortical regions, prefrontal, basal ganglia and thalamus (P. Benjamin et al., 2018; Grysiewicz & Gorelick, 2012; Mohd Zulkifly et al., 2016; Munsch et al., 2016). For example; subcortical lesions in the basal ganglia and internal capsule have been associated with slowed processing speed, (Martin et al., 2013) anosognosia, constructional apraxia and visuospatial neglect (Martin et al., 2013; Su, Chen, Kwan, Lin, & Guo, 2007).

Lesions in the left hemisphere are likely to result in language and speech disorders (Hodgson, Benattayallah, & Hodgson, 2014), impaired prosody perception (Leung, Purdy, Tippett, & Leão, 2017), reading and writing disorders, speech apraxia (inability to produce speech) (Timpert, Weiss, Vossel, Dovern, & Fink, 2015), and verbal memory impairment (Martin et al., 2013). However, other studies have found no association between hemisphere and cognitive impairment (Barker-Collo et al., 2012).

In contrast deficits associated with right hemisphere lesions predominately result in visuospatial deficits such as neglect (A. Carter et al., 2017), and perceptual deficits (Burgess et al., 2000; Mesulam, 2000). Lesions in the MCA regions, predominately result in language disorders (Kreisler, Godefroy, & Delmaire, 2000). Haemorrhages or infarcts in the left posterior circulation artery (PCA), which involve the left occipital and medial temporal lobe, result in learning and memory impairments (Brandt, Seinke, Thie, Pessin, & Caplan, 2000).

Stroke size may be also associated with increased likelihood of cognitive impairment, (Nys et al., 2007), however this remains debatable. Larger strokes typically involve the cortex and other regions that maintain cognitive function, therefore size and location may be a confounding factor. However, other studies have reported no association between size of stroke and increased cognitive impairment (Lazar, Speizer, Festa, Krakauer, & Marshall, 2008). Individuals with subcortical infarcts (middle cerebral artery and supratentorial regions) have higher rates of cognitive impairment (Nys et al., 2007; Sundar & Adwani, 2010). Patients with lacunar infarcts are more likely to experience long-term cognitive impairment. For example, in a 5-year follow-up of 103 stroke patients, those with lacunae strokes experienced decline in executive function, processing speed and global cognitive function (P. Benjamin et al., 2018).

People who experience recurrent strokes are at higher risk for developing cognitive impairment than single stroke (Divya et al., 2017; Kalaria et al., 2016; Kozyolkin, Kuznietsov, & Novikova, 2014; Renjen, Gauba, & Chaudhari, 2015; Rist et al., 2013b). The risk of recurrent stroke increases with time. For example a systematic review on cumulative risk of stroke recurrence reported rates at 11.1% at one year, 26.4% at five years and 39.2% at 10 years (Mohan et al., 2011). Performance in information processing speed, executive function and memory were reported to be worse in people who have multiple strokes (Saczynski et al., 2009). The presence of pre stroke cognitive impairment is also a risk factor, leading to more severe cognitive decline and higher rates of recurrent stroke (Pendlebury & Rothwell, 2009).

Cognitive impairment and mood disorders frequently co-exist following stroke (Babkair, 2017; Barker-Collo et al., 2016; Barrows & Thomas, 2017; Douven et al., 2016; Hommel et al., 2015; Nakling et al., 2017; Sarfo et al., 2017). The Cardiovascular Health Study Cognition Study, reported associations between depression and increased risk for cognitive impairment in a sample of 2220 stroke patients (Barnes, Alexopoulos,

Lopez, Williamson, & Yaffe, 2006). Hommel and colleagues (2015), found significant correlations between executive dysfunction, working memory and post stroke depression (Hommel et al., 2015). Similarly, Jaillard and colleagues found adults with left hemisphere stroke were more likely than those with strokes in the right hemisphere to be characterised by depression and cognitive impairment 15 days following stroke (Jaillard et al., 2010). A more recent study found global cognitive impairment associated with increased apathy, within the first year after stroke (Douven et al., 2017).

Longitudinal data have yielded similar results. For example, 18 months after stroke, De Ryck et al. (2014), reported 23.6% of patients who had a diagnosis of depression experienced higher levels of cognitive impairment compared to those with no depression. A cross-sectional study, found stroke patients who performed below average in visuo-spatial and memory tasks, had higher levels of depression than those without impairment (Barker-Collo, Feigin, Parag, et al., 2010). Likewise, Nakling and colleagues (2017) reported cognitive performance was associated with depression one year after stroke. In contrast, a number of studies have shown no relationship between cognitive impairment and depression (Ayerbe et al., 2014; del Ser et al., 2005; Narasimhalu, Wiryasaputra, Sitoh, & Kandiah, 2013). For example, the SLSR examined depression and cognitive impairment in a population-based cohort, 10 years after stroke and found depression was associated with increased disability but not cognitive impairment (Ayerbe et al., 2014). Finally, the long-term use of medications can also influence cognitive function, (AlShaikh et al., 2016). An Irish study, of 256 stroke patients, reported that cognitive impairment was associated with prescribed medication use six months after stroke (Mellon et al., 2015). Further, the combination of new medication administered (at onset of stroke) and medication already taken, may result in persistent slowed responses and altered consciousness (R. Wright et al., 2009). This makes it problematic in determining whether or not the dose of medication affects normal cognitive processing or is in combination with stroke.

2.7 Diagnosis of Cognitive Impairment

Despite the prevalence of post stroke cognitive impairment, and the associated negative implications for survivors of stroke, screening and assessment is not routinely conducted in both acute and subacute settings (Burton & Tyson, 2015b; McDonnell, Bryan, Smith, & Esterman, 2011; Sachdeva et al., 2017). Heterogeneity in the selection of tests instruments and administration emphasizes a lack of data harmonization in current stroke research (Sachdeva et al., 2017). Specifically, in the available literature it

is evident that cognitive screening and assessment are underutilized in clinical settings, with no optimal method to assessment post stroke cognitive impairment (Y Dong et al., 2016; Lees, Broomfield, & Quinn, 2014; McDonnell et al., 2011). To add to this, some cognitive measures only involve tasks which are reliant on language and motor function; this can create barriers for survivors of stroke and exclude them from certain types of assessment (Lees et al., 2017; Wall, Cumming, & Copland, 2017; Wall, Isaacs, Copland, & Cumming, 2015). Appropriate cognitive screening and assessment is crucial, in order to enhance post stroke management by; a) identifying prevalence of global cognitive impairment, b) characterizing specific patterns of cognitive sequelae in relation to neuroanatomical structure and function, c) monitoring cognitive recovery, d) informing the development of interventions for cognitive rehabilitation.

In an effort to facilitate a consensus approach, the National Institute of Health/National Institute of Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network (CSN) sponsored a working group to develop standard neuropsychological protocols for the screening and assessment of post stroke cognitive function (Hachinski et al., 2006). Selection criteria included tests which were psychometrically sound, reliable, valid, included satisfactory standardization samples and appropriate to administer within different cultures (Hachinski et al., 2006; Han, Anderson, Jones, Hermann, & Sattin, 2014; Lin et al., 2016). Three neuropsychological protocols were proposed, for use in different settings, namely a 60, 30 and 5-minute (screening) protocol. The 60-minute protocol is used for a detailed assessment, which contains four domains: executive function, memory, language and spatial (NINDS-CSN 60), a 30-minute protocol (NINDS-CSN 30), used for screening in clinical settings and a 5-minute protocol (NINDS-CSN 5), a brief screen which can be administered in primary care settings, and large epidemiological studies (Hachinski et al., 2006; Xu et al., 2016).

Two of the most widely used pencil-paper screening instruments are MoCA and MMSE (Arsic et al., 2015; Burton & Tyson, 2015b; Cumming, Churilov, Linden, & Bernhardt, 2013; Horstmann, Rizos, Rauch, Arden, & Veltkamp, 2014; Salvadori et al., 2013; Toglia, Fitzgerald, O'Dell, Mastrogiovanni, & Lin, 2011). Cognitive screening tools can be particularly beneficial, especially in the acute phase of stroke when people often experience fatigue, aphasia, visual disturbances and attentional limitations (de Vries, Sloot, & Achterberg, 2017). As opposed to more comprehensive neuropsychological batteries, which are often lengthy, expensive and require more than one session to

administer. Moreover, they are often not conducted in hospital or inpatient settings as they need a trained neuropsychologist to administer the tests (McDonnell et al., 2011).

The MoCA is a brief clinical screening tool, widely used in longitudinal research and easy to administer, with no formal training needed (Koski, 2013; Nasreddine et al., 2005; Toglia et al., 2017). Prior research has found that the MoCA is good predictor of functional outcomes post stroke. For example; Toglia and Colleagues (2011) reported lower sub-scores on visuo executive items on the MoCA were associated with fewer decreased functional gains in self-care and mobility. Cross-cultural applicability of the MoCA has also been well reported (Fu et al., 2017; Krist et al., 2017; O'Driscoll & Shaikh, 2017; Sahathevan et al., 2014) in a number of studies. Compared to the MMSE, the MoCA has consistently demonstrated superior sensitivity to stroke-related cognitive impairment than the MMSE (Godefroy et al., 2011; Koski, 2013; Lees et al., 2017; Pendlebury et al., 2010; Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012; Salvadori et al., 2013; Schweizer, Al-Khindi, & Macdonald, 2012; Sivakumar et al., 2014; Toglia et al., 2011; Van Heugten, Walton, & Hentschel, 2015). This is because the MMSE has shown poor sensitivity as a screening tool to detect visuo-spatial impairments (Fu et al., 2017; Mai, Sposato, Rothwell, Hachiniski, & Pendlebury, 2016). This results in stroke patients often being underdiagnosed.

A few studies have compared the NIND-CNS protocols to the MMSE and MoCA (Y Dong et al., 2016; Nyenhuis, Ganda, & Gao, 2011). The 5-minute protocol was shown to be more sensitive than the MMSE but similar to the MoCA in differentiating stroke patients from age-matched controls (Nyenhuis et al., 2011; Rossetti, Lacritz, Cullum, & Weiner, 2011). In contrast, a Singapore study of 400 stroke patients, reported the MoCA superior to the NINDS-CSN 5-minute protocol for predicting vascular cognitive impairment (Y Dong et al., 2016). At respective cut-offs, the MoCA demonstrated higher sensitivity compared to the NINDS-CSN 5-minute protocol at both acute (0.89 versus 0.80) and sub-acute phases (0.90 versus 0.83) after stroke. Another study of 95 acute stroke patients reported a sensitivity of 0.72 to 0.87, compared to the NINDS-CSN 30 minute protocol (Jaywant, Toglia, Gunning, & O'Dell, 2017).

There is limited research comparing the accuracy of a screening tool such as the MoCA to detect post stroke cognitive impairment to a more comprehensive battery (Campbell, Rice, Friedman, Speechley, & Teasell, 2016; Shopin et al., 2013; Vogel, Banks, Cummings, & Miller, 2015). An Italian study comprised 137 stroke patients, evaluated

the predictive value of the MoCA compared to a more comprehensive battery of neuropsychological tests (Salvadori et al., 2013). The MoCA demonstrated excellent sensitivity (91.4%) and specificity (83.4%) to detect mild cognitive impairment between 5 and 9 days after stroke, compared to a full neuropsychological battery administered 6 to 9 months after stroke (Salvadori et al., 2013). Vogels and colleagues (2015), conducted a factor analysis of the MoCA domains compared to a standard neuropsychological battery. They concluded the MoCA domains had high factor loadings compared to the same constructs on a more comprehensive battery (Vogel et al., 2015).

Although the MoCA was not originally designed to assess domain-specific impairment, a number of more recent studies have reported its accuracy in identifying domain-specific impairment (Chan, Altendorff, Healy, Cipolotti, & Werring, 2017; Demeyere et al., 2016; Fu et al., 2017; Hendershott, Zhu, Llanes, & Poston, 2017; Mai, Sposato, Rothwell, Hachinski, & Pendlebury, 2016; Markwick, Zamboni, & de Jager, 2012; Ritter, Hawley, Banks, & Miller, 2017). For example, Hendershott and colleagues (2017), found all MoCA subsections could accurately predict impairment in their respective domains. Specifically, the executive function domain showed the highest sensitivity and specificity (89.3% and 82.5%), followed by the visuo-spatial subsection (93.5% and 45.7%) and memory (84.6% and 56.5%), compared to similar tasks on the comprehensive neuropsychological battery (Hendershott et al., 2017). However, the limitation of the aforementioned studies was that the majority did not calculate the sub-domains according to the published criteria (Nasreddine et al., 2005). This means the scores for each of the sub-tests were not necessarily representative of the specific domains of functioning. For example; the visuo-executive task score is grouped together (clock drawing test, cube copy task and trails), however, the visuo-spatial tasks (clock drawing and cube copying task) should be calculated separately to the executive function tasks (trails, fluency and abstraction). In addition, only a few studies have examined cognitive impairment in stroke populations and there is a lack of population-based data currently available (Crichton et al., 2016).

Further research is needed to investigate the accuracy of the MoCA and sub-domains, to determine specific cognitive deficits related to stroke pathophysiology. Monitoring of the temporal changes in cognitive deficits via the use of a simple and brief cognitive screening tool over different phases of the stroke journey is vital. This allows clinicians to track and monitor cognitive recovery, and most importantly provide valuable

prognostic information to assist in planning interventions for ongoing cognitive rehabilitation.

2.8 Domain-specific Impairment

Identifying the extent to which specific domains of cognition are affected post-stroke is complicated, in terms of differentiating whether cognition has been affected from stroke-related impairments (such as visual disturbances, physical disability, weakness of dominant hand and aphasia), or psychological factors such as mood and fatigue (F Arba et al., 2016; Bizon, Foster, Alexander, & Glisky, 2012; Gallagher, Kiss, Lanctot, & Hermmann, 2016; Gardener et al., 2016; Kuznetsova et al., 2016). Consideration also has to include the influence of ageing, (Gardener et al., 2016) with changes in global cognitive function, especially in the very old (aged >85) in domains such as attention and information processing speed (Stephan et al., 2018). Attention and executive functioning can also be difficult to assess as both domains can be influenced by information processing speed. While not considered an individual domain of cognition, information processing speed significantly affects cognitive performance in particular tests, especially time-sensitive tasks (Burgess et al., 2000; Gerritsen, Berg, Deelman, Visser-Keizer, & Jong, 2003). For example, if a person has slowed information processing speed, this will affect their ability to respond to the required task within the specified time limit, resulting in a low score in attention and executive function. Therefore, low scores may not reflect impairments in attention, or executive functioning but rather slowed information processing speed.

There has been a considerable amount of literature on domain-specific impairment in short-term follow-up studies, with evidence of widespread deficits across all domains; including language (expressive and receptive) (Flowers, Skoretz, Silver, Rochon, Fang, Flammad-Roze, et al., 2016), working memory, motor function, executive function, attention, and visuo-spatial function (Broome et al., 2016; Mellon et al., 2015; Srikanth et al., 2003; Sundar & Adwani, 2010; Y. Zhang et al., 2012). Tatemichi and colleagues 1994) identified a “generalized profile” of cognitive deficits (See Table 1) involving all domains (Tatemichi et al., 1994). Another large European study, reported a similar diffuse post stroke cognitive profile across domains, with tasks of attention, visuo-spatial ability and verbal fluency and memory the most impaired (Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998).

Table 1. Results from Tatemichi et al., (1994) study, showing a generalised profile of cognitive impairments.
The table shows performance of controls and subjects with stroke on neuropsychological tests (values are unadjusted means (SD), and the frequency of stroke subjects (%) falling below the fifth percentile based on standardised residual scores.

Neuropsychological test item	**Controls (n=240)**		**Stroke (n=227)**		**Frequency (%) of stroke patients below fifth percentile**
Memory					
SRT total	42.8	(10.6)	33.1	(11.5)	19.5
SRT long term	29.5	(15.2)	18.7	(13.5)	10.2
Delayed recall	5.9	(2.9)	4.2	(2.8)	18.1
Delayed recognition	11.4	(1.3)	10.3	(2.2)	21.2
Benton recognition	7.8	(1.8)	6.0	(2.2)	24.6
Orientation	9.7	(0.6)	8.6	(1.9)	25.8
Abstract Reasoning					
Similarities	10.7	(2.9)	8.2	(2.7)	16.8
Identities	14.8	(1.6)	13.3	(2.2)	25.0
Visuospatial					
Rosen construction	3.5	(1.0)	2.5	(1.2)	16.8
Benton matching	8.8	(1.4)	7.3	(2.3)	25.0
Language					
Naming	13.7	(1.7)	12.4	(2.7)	13.8
CFL	11.7	(4.9)	7.4	(4.1)	14.4
Category fluency	17.3	(4.9)	12.3	(4.8)	32.7
Repetition	7.8	(0.5)	7.4	(1.1)	15.1
Comprehension	5.5	(0.9)	4.8	(1.4)	15.3
Attention					
No. correct/second	0.17	(0.08)	0.27	(0.09)	38.5
No. errors/no. correct	0.29	(1.09)	0.05	(0.31)	20.2

Note: SRT = selective retraining test; CFL = verbal fluency. Reprinted from *Journal of Neurology Neurosurgery & Psychiatry* (p 204), by Tatemichi, Desmond, Stern, Paik, Bagiella, 1994, New York, United States of America. Copyright (2018) by BMJ Journals. (Appendix R) (Tatemichi et al., 1994).

However, more recent studies suggest that stroke tends to have greater impact on executive functioning, attention and information processing speed, than on memory (Barker-Collo et al., 2016; Bugarski I, Semnic, Gebauer Bukurov, & Kozic, 2015; Crichton et al., 2016; Divya et al., 2017; Douiri et al., 2013; Narasimhalu et al., 2011; Y. Park et al., 2015; Rasquin, Verhey, Lousberg, Winkens, & Lodder, 2002).

Heterogeneity of the results could have been attributed to the study design of the previous studies, as some were hospital-based and community-based, and compared people with stroke to healthy controls, thus may have overestimated post stroke impairments.

A meta-analysis of 12 prospective cohort studies found higher incidence of lower scores in executive function and attention, than memory and language following stroke, however these associations were not significant (Rostamian, Mahinrad, Stijnen, Sabayan, & de Craen, 2014). In a study of Chinese acute stroke patients (n=80) greater impairment in visuo-spatial ability, attention and executive function was reported (Zuo et al., 2016). Whereas a Korean study found visuo-spatial ability was impaired in a sample of 40 patients, three weeks after stroke compared to other domains (J. Park, Lee, Lee, & Jung, 2016). Although both of the aforementioned studies were limited by small sample sizes. Similar findings were reported in a cross-sectional study of 577 stroke patients, with higher incidence of executive dysfunction and visuo-spatial ability than memory and attention three months post stroke, however the cross-sectional design of the study meant a causal relationship could be determined. In comparison, the Framingham Study found people with stroke had poorer cognitive function in immediate recall of visual and logical memories, executive functioning and visuo-spatial ability (Weinstein et al., 2014a). Hurford and colleagues (2013), reported information processing speed and attention were more impaired at one month after stroke, however they also showed the greatest trend for improving in the first 6 months. While these studies have identified a shift towards cognitive impairment related to frontal lobe dysfunction, when participants have been followed up for longer periods (>3 years), studies have reported significant decline in memory (Reitz, Luchsinger, Tang, Manly, & Mayeux, 2006). The variation in domain-specific impairment across studies and poor study methods has resulted in an inconsistent profile of post stroke domain-specific impairment. Therefore, data is needed from population-based research, with longer follow-up and larger sample sizes in order to determine a more accurate profile of domain-specific impairment. This is crucial in order to develop interventions which can target specific domains of cognition rather than a more generalised intervention.

2.9 Long-Term Cognitive Impairment

Research examining the longitudinal pattern of cognitive impairment after stroke has produced mixed results; due to small sample size, methodology (e.g. no follow-up

time), loss of patients to follow-up (early death or non-availability), design (not population-based) and selection criteria (excluding aphasic patients) (Barker-Collo, Feigin, Parag, et al., 2010; Chen et al., 2016; Hochstenbach, Anderson, van Limbeek, & Mulder, 2001; Hochstenbach, den Otter, & Mulder, 2003; Nys et al., 2005; Pendlebury et al., 2015; Planton et al., 2012; Wall et al., 2017).

While population-based studies have yielded more consistent results, the method for measuring cognition varies across studies, with cognition function either assessed as global cognition or domain-specific impairment (Barker-Collo, Feigin, Parag, et al., 2010; Barker-Collo et al., 2016; Barker-Collo et al., 2012; Crichton et al., 2016; Delavaran, Jonsson, et al., 2016; Mellon et al., 2015; Patel, Coshall, Rudd, & Wolfe, 2003; S. Paul et al., 2005; Stephan, Richardson, et al., 2017). For example: in the Lund Stroke Register Study, SLRS and Erlangen Stroke Project studies, global cognitive function was measured but not domain-specific impairment (Delavaran, Jonsson, et al., 2016; Liman et al., 2011; Wolfe et al., 2011).

The Auckland Stroke Outcome Study (ASTRO), is the one of the few population-based studies, which investigated long-term domain-specific impairment following stroke (Barker-Collo, Feigin, Parag, et al., 2010). A population-based follow-up study of (n=307), examined cognitive outcomes 5 years post stroke. Approximately 30% to 50% of the ASTRO population returned low performance scores on most cognitive tasks, providing compelling evidence of cognitive impairment in a number of domains at 5 years post-stroke (Barker-Collo, Feigin, Parag, et al., 2010). In addition, stroke subtype was found to be significantly associated with deficits in specific domains of cognition. For example, participants who experienced total anterior circulation strokes performed significantly worse on tasks of processing speed, word finding and visual abstract reasoning (Barker-Collo, Feigin, Parag, et al., 2010). Specific domains of cognition were found to be predictors of post stroke functional outcomes, with information processing speed, visual memory and visuo-perceptual/constructual deficits independently associated with disability, handicap and health-related quality of life (Barker-Collo, Feigin, Parag, et al., 2010). A more recent study, reported a similar cognitive pattern as the previous study, with 153 stroke patients experiencing deficits in psychomotor speed, executive function and visuo-spatial domains two years after their stroke (Turunen et al., 2018).

The ASTRO study also provided insight into disparities in cognitive outcome among the different ethnic groups in NZ. In terms of our unique NZ demographic, Māori and Pacific people have significantly greater risk of poorer long-term outcomes than NZ European survivors of stroke. At 5 years post-stroke, Māori and Pasifika stroke survivors faced greater risk for poor economic self-sufficiency than Europeans. Non Europeans experienced significantly more language problems, visuo-perceptual difficulties and higher rates of depression than NZ Europeans (Barker-Collo, Feigin, Parag, et al., 2010). Further, cognitive impairment indicative of dementia was two times that observed in Non NZ Europeans. However, this may be more related to low socio-economic status (SES) and education levels. Although health-related quality of life, disability, handicap and mood were assessed in the ASTRO study, the investigators did not look at other factors, such as stroke-related risk factors, and clinical factors which may have influenced cognition and long-term outcomes. A major limitation of the ASTRO study was its cross-sectional design. Cognition was only assessed from baseline and at 5 years post stroke and had limited outcome measures. Consequently, it was not possible to evaluate the extent of change in cognitive function over time. A study by the same authors, investigated cognitive outcomes and predictors in ischaemic stroke survivors (Barker-Collo et al., 2016). Deficits were evident in verbal memory, psychomotor speed, attention and executive function 12 months after stroke, however the sample comprised of only ischaemic stroke survivors and excluded the other pathological stroke types (Barker-Collo et al., 2016). Additionally, Barker-Collo and colleagues (2010), used a cross-sectional design which means that findings cannot support conclusions, nor causal relationships.

In comparison, The SLSR study, examined long-term outcomes, including cognition, 15 years after the initial stroke event (Patel et al., 2003). The three year follow-up, compared stroke survivors who were cognitively impaired at 3 months (MMSE <24, n=248) to those who were cognitively intact (>24 MMSE, n= 397) (Patel et al., 2002). The prevalence rates for cognitive impairment at 3 months, one, two and three years post-stroke were 39%, 35%, 30% and 32 % respectively, indicating that deficits in cognition remain highly prevalent 3 years after stroke (4-year data not reported). Cognitive impairment at 3 months resulted in long term poorer outcomes and was significantly associated with older age, left hemisphere stroke, ethnicity, lower socioeconomic status and urinary incontinence, higher rates of institutionalization and death or disability (Patel et al., 2002). Recovery was compromised by visuospatial neglect which is not surprising given that prolonged neglect is a strong prognostic

indicator for poorer post stroke functional independence ((Barker-Collo, Feigin, Parag, et al., 2010; Patel et al., 2002).

Several factors limit the extent to which study findings can be generalised to the wider stroke population. The SLSR study relied solely on the MMSE to assess post-stroke cognition. This measure does not encompass all domains of cognition (Pendlebury et al., 2010). In addition, a large number of participants were lost to follow-up (32 % (impaired group) versus 27 % (intact) group at 3 years) which introduced a sampling bias (Patel et al., 2002). At ten years after the initial stroke event, cognitive impairment fluctuated up to the eight year time point, then steadily increased (Wolfe et al., 2011). The recent fifteen-year follow-up, reported only 20% of people with stroke had survived, and of these people, 30%, had cognitive impairment, were depressed 39.1% and experienced anxiety 34.9% (Crichton et al., 2016). A limitation of this longitudinal research is the lack of a consistent measure of cognition during the follow-up assessment. For example; the MMSE was used to assess cognition initially, the 10-year assessment used both MMSE and the Abbreviated Mental Test (AMT), the 15-year study only used AMT (Crichton et al., 2016). The AMT lacks validity in screening populations but does accurately test for impairments in executive function (Velayudhan et al., 2014). Using a consistent measure across all time-points would allow for the long-term natural course of cognition to be more reliably determined.

2.10 Cognitive Rehabilitation

In NZ and Australia, the recently published Stroke Foundation Clinical Guidelines for Stroke Management (Stroke Foundation, 2017), have identified the assessment and "***treatment***" of cognitive impairment as one of the top research priorities. Despite this, provision and access to cognitive rehabilitation remains one of the greatest unmet needs for stroke survivors in both countries (Andrew et al., 2014; McNaughton, 2014). National clinical guidelines in NZ suggest less than 50% of inpatient stroke rehabilitation units and community based-rehab provide adequate services (McNaughton et al., 2014). Compared to other countries, NZ's access to rehabilitation is poor and while there are services available to provide rehabilitation for physical and functional deficits, cognitive rehabilitation is not considered or currently offered (McNaughton, 2014).

Improving cognitive impairment after stroke is crucial, as there is robust evidence showing that early rehabilitation can reduce the likelihood of admission to private

hospitals, healthcare costs, mortality, increase independence and overall quality of life (Cumming, Marshall, et al., 2013; Pantzartzidou et al., 2017; Weistein et al., 2016). Additionally, it can improve outcomes for older stroke patients, as engagement in early rehabilitation has been shown to significantly improve functional gains and return to the community (S. O'Brien & Ying, 2016).

Cognitive rehabilitation encompasses a range of therapeutic interventions, aimed to reduce the adverse impact that cognitive impairments have on every aspect of an individual's life following stroke (Lincoln, Macniven, & Morris, 2012). Approaches to cognitive rehabilitation traditionally focus on interventions which either restore function and/or compensate for loss of function, in order to assist adaptation and facilitate independence for stroke survivors (Cicerone et al., 2011b; Goverover, Chiaravalloti, O'Brien, & DeLuca, 2018). Compensatory strategies, attempt to adapt the external environment to the domains of cognitive function which have been affected, usually by the aid of assistive technology (mobile phones, tablets, pagers etc), or paper-based strategies (diaries, lists, notebooks) (Shigaki, Frey, & Barrett, 2014; D. Wong, Wang, Stolwyk, & Ponsford, 2017). Restorative approaches focus on reinforcing, strengthening and re-establishing previously learned behaviours (Cramer, 2018).

Currently, there is a lack of sufficient evidence to support or refute the benefits of cognitive rehabilitation for patients with stroke (Cicerone et al., 2011a; das Nair, Cogger, Worthington, & Lincoln, 2017). A number of Cochrane reviews have been conducted in the area of post-stroke cognitive rehabilitation. Specifically, these reviews have focused on therapy for memory deficits, (das Nair, Cogger, Worthington, & Lincoln, 2016) executive dysfunction, (Chung, Pollock, Campbell, Durward, & Hagen, 2013) spatial neglect (Bowen, Hazelton, Pollock, & Lincoln, 2013) and attention deficits (Loetscher & Lincoln, 2013b). Each has concluded that the effectiveness of cognitive rehabilitation has yet to be established.

Another issue is the lack of data, due to the main focus of rehabilitation and research, on the recovery of physical/motor function, with considerably less attention on cognitive recovery (Shigaki et al., 2014). For this reason, the extent to which post-stroke cognitive recovery occurs spontaneously, or can be improved with rehabilitation, remains unclear. Further, the pattern of post-stroke cognitive impairment suggests that deficits may be evident across all cognitive domains rather than being confined to one cognitive domain with lesion location predicting the severity of cognitive impairment across different

cognitive domains following stroke (Demeyere et al., 2016). Despite the prevalence of cognitive impairment post-stroke, (Mahon et al., 2017) and the associated implications for stroke survivors and their families, the efficacy of existing interventions for the rehabilitation of cognitive needs further investigation.

2.11 Conclusion

The evidence presented in this Chapter highlights that cognitive impairment is highly prevalent following stroke and can significantly affect quality of life, not only during the early phases of stroke, but can persist for years after the event. Multiple factors can contribute to and/or influence the trajectory of cognitive recovery. While some studies show that cognitive function may improve within the first six months after stroke, there is no evidence to suggest complete recovery. Additionally, there is no consistent cognitive trajectory of long-term cognitive impairments due to heterogeneity among studies, with poor assessment measures, study design and selection bias. Finally, there is a paucity of longitudinal population-based data in terms of the accuracy of cognitive screening measures to detect both global and domain-specific impairment.

The review of the existing literature demonstrates four main gaps; 1) a lack of evidence of the long-term profile of post stroke cognitive impairment using consistent criteria, 2) limited population-based evidence on the prevalence and trajectory of cognition over time, 3) a lack of clarity concerning the stroke-related clinical and socio-demographic factors which influence cognitive recovery, and 4) a lack of data investigating the accuracy of cognitive screening tools such as the MoCA against a gold-standard assessment to accurately determine cognitive impairments specific to stroke.

Therefore, the main objectives of this thesis are:

- To determine the level of cognitive impairment in long-term stroke survivors
- To characterize profiles and predictors of global and domain-specific impairment
- To examine the predictors and trajectory of cognitive function over time in a four-year cohort of stroke survivors
- To examine the accuracy of a brief screening tool to identify global and domain-specific cognitive impairments compared to a neuropsychological battery

Chapter 3 Methods

3.1 Overall design

This PhD study is a follow-up study of four-year stroke outcomes on participants who consented into the fourth Auckland Regional Stroke Community Outcomes (ARCOS-IV, 2011-2012), population-based study.

3.2 Overview of the Large Parent Study (ARCOS-IV)

The ARCOS-IV study, was a five-year (2010-2015), stroke incidence and outcomes study funded by the Health Research Council (HRC10/458) (Krishnamurthi et al., 2014). ARCOS-IV was a prospective, population-based register of all new stroke cases (first-ever and recurrent) (n=2096) in the Auckland between March 2011 to Feb 2012 (Krishnamurthi et al., 2014). Case ascertainment used the "hot pursuit" approach, using various sources of information for both hospitalized and non-hospitalized cases. Researchers who were based at four Auckland public hospitals, made daily searches from hospital emergency departments. Regular checks were made of outpatient clinics, private hospitals and rest homes to capture non-hospitalised cases (Krishnamurthi et al., 2014). Stroke was defined with WHO standard diagnostic criteria (Aho et al., 1980), and divided into pathological types ISC, ICH, SAH and undetermined according to standard clinical and CT/MRI/necropsy findings (97% cases were identified using this criteria). Cases with no imaging or confirmation of subtype were classified as undetermined type (Krishnamurthi et al., 2014). All ISC cases were categorised using OCSP classification, (Bamford et al., 1991) by neurologists using laboratory and clinical findings, medical history, and into five casual subtypes based on the TOAST criteria (Adams & Biller, 2015). Risk factors were obtained upon admission to hospital via medical records and included high blood pressure (history of hypertension or systolic BP ≥140mmHg at presentation), hypercholesterolemia (history of lipid lowering or total cholesterol ≥4.1 mmol/L) diabetes mellitus (history or HbA1c ≥48mmol/L), and arrhythmia.

Consented participants (n=821) completed face-to-face assessments within two weeks of their stroke event, and/or at one, six and 12 months (Krishnamurthi et al., 2014). Additional, baseline data were collected from medical records and via Concerto, a secure web-based system accessed from workstations at the hospitals. The information gathered at baseline included; demographic and socio-demographic information,

previous medical and neurological history, recent laboratory test results, family history, vascular risk factors. Assessments included well-validated health-related and functional outcomes and cognitive measures used within stroke populations such as; Modified Rankin Scale (mRS), (Rankin, 1957), Barthel Index (BI), (Sulter, Steen, & De Keyser, 1999), European Quality of Life Questionnaire- 5 Dimensions (EQ-5D), (Szende, Janssen, Cabases, & Goni, 2013), Fatigue Visual Analogue Scale (FVAS), (Tate, 2010) and the Hospital Anxiety and Depression Scale (HADS), (Zigmond & Snaith, 1983). Cognitive assessments included the MoCA (Nasreddine et al., 2005) and Computerized Neuropsychological Vital signs test (CNS-VS), (C. T. Gualtieri & L. G. Johnson, 2006). Outcomes measures for the ARCOS-IV study are described in detail elsewhere (Krishnamurthi et al., 2014).

3.3 Point of difference in the current research

This Neurological Foundation funded study (reference number 1423-GS), was distinct from ARCOS-IV as it examined the longitudinal impact (>12 months) of stroke, specifically focusing on cognitive outcomes (Table 2) in relation to clinical stroke characteristics, demographic and socio-demographic factors, stroke-related risk factors and psychological predictors. The parent study only followed up participants to one-year post stroke. The CNS-VS computerized test was replaced with a pen and paper neuropsychological assessment battery (screening module) as the population of interest was older and the feasibility of administering a lengthy computerized test was not appropriate within this cohort.

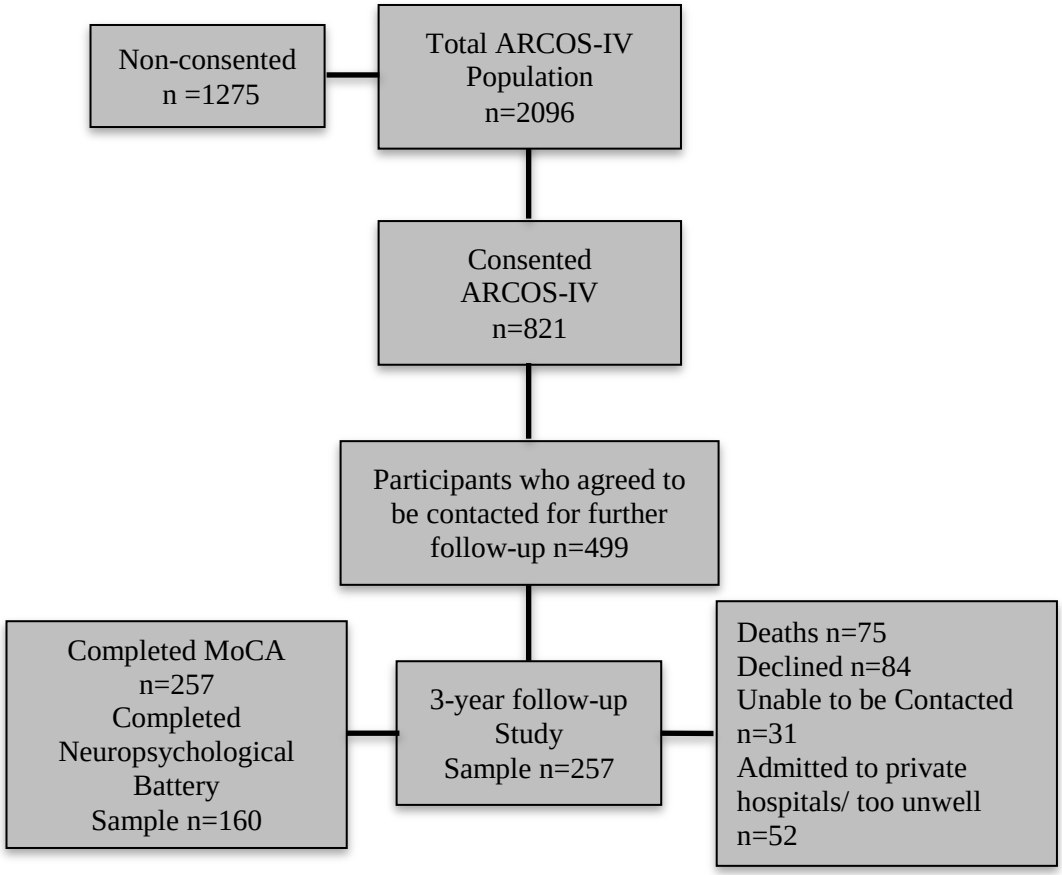

Figure 2. Flow Chart for Recruitment

3.4 Inclusion Criteria

These analyses included all ARCOS-IV cases who (1) had an incident stroke between March1, 2011 and February 29, 2012; (2) resident of Auckland; and (3) ≥ 16 years and older.

3.5 Study participants

A total of 499 participants from ARCOS-IV were approached for consent (Figure 2). Attempts were made to contact all potential participants. Information retrieved from Ministry of Health records, identified that Seventy-five participants had died since their last follow-up (12 months). Over the recruitment period of approximately one year, repeated attempts were made to contact 31 participants, however these attempts were unsuccessful and therefore these people were recorded as lost to follow-up. Of the remaining 393 participants, 84 declined to take part in the follow-up study, mostly because they were too busy, and the remaining 52 were too unwell or had been admitted to private hospitals. This left two hundred and fifty-seven participants (51.5%) out of

the four hundred and ninety-nine consenting to take part in the follow-up study. Of these 214 (83%) were first ever strokes and 43 (17%) recurrent strokes.

3.6 Procedure

Participants who completed their 12-month follow-up assessments were asked if they would be available for further follow-up. Contact information was extracted from the ARCOS-IV database (password protected spreadsheet), and the researcher contacted people via telephone and/or email to invite them to take part in the study. After verbal consent was obtained, a suitable time was arranged with the participant to conduct a face-to-face assessment, either at home or a location suitable to the participant. An information and consent form (Appendix C) was sent to the participant explaining what would be involved in taking part in the study. All outcome measures listed in Table 2 at the four-year follow-up were administered by the researcher during the face-to-face visit. Written consent was obtained at the face-to-face assessment. All participants retained a signed copy of the consent form, all consent forms were scanned and uploaded into the database, paper forms were kept in a securely locked filing cabinet, located at the offices of the National Institute for Stroke and Applied Neurosciences (NISAN), AUT University, North Campus, Auckland. Each assessment took approximately 90-120 minutes and included a number of cognitive assessments and outcome measures. Following completion of the assessment a $20 food/petrol voucher was given as appreciation (koha) for the time each participant had given by taking part in the study.

3.7 Participant Withdrawal

As part of the consent process, all participants were informed that their participation in the study was voluntary and that if they so choose they may withdraw from the study at any time. It was also explained that while they did not need to provide a reason, should they withdraw from the study, it would be useful if they did so.

3.8 Data Collection

The participant questionnaire (Appendix D) was the primary data collection instrument for the study. At the end of each assessment, all of the measures were individually scored. In addition, the additional cognitive tests had response booklets and scoring forms. The scores for the tests were entered into a special software programme (screening module neuropsychological assessment battery: S-NAB) to calculate

individual cognitive domain scores and generate an overall total score of neuropsychological functioning.

3.9 Data Management

The confidentiality of all participants was protected. Participants were identified using a unique participant ID number at the top of each form, using the first letter of their Christian name and first 3 letters of their surname. For example; Susan Brown would be recorded as SBRO. In addition, date of birth was also recorded at the top of each form in order to ensure participants with the same initials were not confused. Physical records of the data; including the questionnaire and cognitive tests were kept secure in key-locked cabinets located in key-code accessible rooms at the NISAN. No participant identifiers were present on any files. All data was entered online into a password protected Microsoft Access 2010 data base (J. Cox & Lanber, 2010). All data will be stored for 6 years and then shredded. Access to study data was limited to key study personnel.

3.10 Discontinuation Rules for Cognitive Assessment

Participants were not required to complete specific cognitive tasks if they are a) unable to perform a task due to impairment of a specific domain of function in the construct assessed by the task (For example, if a participant had expressive aphasia, a verbal test was not administered due to an inability to produce language b) where participants who demonstrated a lack of understanding in the requirements expected of that particular task.

Table 2. Description of Predictor Variables and Cognitive Measures used in ARCOS-IV parent study and for the 4-year follow-up study

Number	Description of Assessments	ARCOS-IV Baseline, 1, 6, 12 months	4-Year Follow-up	
	Assessment Details			***Predictor Variables***
1.0	Demographic Information	➳	➳	
2.0	Stroke-related Risk Factors	➳	➳	
3.0	Clinical-stroke characteristics	➳	➳	
4.0	Barthel Index	➳	➳	***Outcome Measures***
5.0	Modified Rankin Scale	➳	➳	
6.0	Fatigue Severity Scale	➳	➳	
7.0	Visual Fatigue Analogue Scale	➳	➳	
8.0	Hospital Anxiety and Depression Scale	➳	➳	
9.0	Montreal Cognitive Assessment	➳	➳	
10.0	Neuropsychological Assessment Battery-Screening Module		➳	
11.0	Modified Wisconsin Card Sorting Task		➳	
12.0	Symbol Digit Modalities Test		➳	
13.0	Comprehensive Trail Making Test		➳	

3.11 Potential Predictor Variables

Predictor baseline variables (for long-term cognitive deficits) included the following demographic variables including age, gender, ethnicity, highest education level, current marital status, current employment; clinical factors including pathological stroke type (ISC, ICH, SAH), lesion region (cortical, subcortical), vascular territory (MCA, PCA, ACA, PICA), hemisphere of lesion (left, right, both) and OCSP subtype (TACI; PACI; LACI; POCI) and stroke-related risk factors (hypertension, coronary artery disease, hyperlipidemia, diabetes mellitus and arrhythmia) in addition to, severity of stroke, functional independence, mood, and fatigue.

3.11.1 Stroke Severity

Modified Rankin Scale

The Modified Rankin Scale (mRS) (Appendix F) is the most commonly used measure for assessing the degree of disability and functional independence in stroke patients (Rankin, 1957). The 6-point ordinal scale is rated from 0 being “no residual symptoms at all” to 5 (bedridden) and 6 being deceased (Rankin, 1957). One of its strengths is that it is easy to administer and only takes five minutes to complete. The mRS has demonstrated sensitivity to detect clinical change following ischaemic and haemorrhagic stroke (Banks & Marotta, 2007; Cioncoloni et al., 2012; K. Lees et al., 2012; Nunn, Bath, & Gray, 2016; Olavarría et al., 2017). The construct validity of the mRS has been supported by numerous studies, which have shown that stroke sub-type (Petty et al., 2000), lesion volume (Schiemanck et al., 2005) and degree of stroke injury (Derex et al., 2004) are associated with short and long-term disability. The mRS can be used to in combination with the MoCA to predict functional outcomes following stroke (Y Dong et al., 2013; Ferreira, Moro, & Franco, 2015).

3.11.2 Functional Independence

Barthel Index

The Barthel index (BI) (Appendix E) is a widely used instrument in longitudinal follow-up for measuring functional recovery and level of independence after stroke (Ankolekar et al., 2014; Cioncoloni et al., 2012; López-Espuela, 2016). The measure is comprised of 10 self-report questions that assess a person’s ability to independently function in everyday activities such as; independence in feeding, personal care (bathing, grooming, dressing, toileting) and mobility (Sulter et al., 1999). The measure is useful in that it can detect and monitor improvement in activities of daily living. Scores for each of the items range from 0 to 3, based on an individual’s level of independence (Sulter et al., 1999). The higher the score the more "independent" the person is (Sulter et al., 1999). The BI has been widely used within stroke research (Chippala & Sharma, 2016; Kwakkel, Veerbeek, Harmeling-van der Wel, van Wegen, & Kollen, 2011; Lau et al., 2017; Renjen et al., 2015) and a good prognostic tool for predicting long-term outcomes after stroke (De Wit et al., 2014; Huybrechts & Caro, 2007; Lerdal & Gay, 2017). Scores have demonstrated excellent inter-rater reliability (kappa w, 0.93; 95% confidence interval, 0.90-0.96) (Duffy, Gajree, Langhorne, Stott, & Quinn, 2013) and validity within stroke populations (Hsueh, Hsieh, Lin, & Jeng, 2002; Quinn, Langhorne, & Stott, 2011; Wallace, Duncan, & Lai, 2002). The BI can also be used to monitor

functional performance/independence based on cognitive impairments post stroke (Akbari, Ashayeri, Fahimi, Kamali, & Lyden, 2011; T. Brown, Mapleston, Nairn, & Molloy, 2013).

3.11.3 Fatigue

Fatigue Severity Scale (Fatigue)

Fatigue was assessed using the Fatigue Severity Scale (FSS) (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989) (Appendix G). The FSS is a 9-item self-report scale that is designed to subjectively assess the impact of fatigue in daily life, including domains of motivation, social participation, sleep and activity. Items on the questionnaire are rated on a seven point scale, ranging from 1 (no problem) to 7 (significant problem) (Krupp et al., 1989). The average score of the 9 items represents the FSS total score, higher scores indicate greater fatigue levels, with scores of ≥ 4 or higher indicating significant fatigue (Krupp et al., 1989). FFS has been widely used in stroke research to assess post-stroke fatigue (Learmonth et al., 2013; Lerdal & Gay, 2017; Lerdal & Kottorp, 2011; Nadarajah & Goh, 2015; Naess, Lunde, Brogger, & Waje-Andreassen, 2012).

A 2016 study, reported the FSS as having excellent internal consistency for patients with stroke (Cronbach's alpha >.90), excellent test-retest reliability (determined by intraclass correlation coefficient (ICC) = 0.93) and good concurrent validity with the visual analogue fatigue scale (determined by spearman correlation coefficient r >.60) (Nadarajah, Mazlan, Abdul-Latif, & Goh, 2016). Additionally, the FFS has excellent test-retest reliability for patients with stroke (ICC=0.93) (Nadarajah et al., 2016). Several studies have used the FSS in combination with the MoCA to predict correlates of post-stroke fatigue (PSF) (Lillicrap et al., 2016; Nadarajah, Mazlan, Abdul-Latif, & Goh, 2015).

Visual Analogue Fatigue Scale

The Visual Analogue Fatigue Scale (VAFS) (Appendix G) is a measure which evaluates an individual's subjective experience of fatigue (Tseng, Gajewski, & Kluding, 2010). A person marks their perceived level of fatigue on a vertical 10 cm numbered line with possible scores from 0 (indicating no fatigue) to 100, with higher scores indicating greater levels of fatigue (K. Lee, Hicks, & Nino-Murcia, 1991; Shahid, Wilkinson, Marcu, & Shapiro, 2012; Tate, 2010). Due to the vertical layout of the measure, it eliminates difficulties for stroke survivors who may experience visual neglect and/or other visuo-spatial deficits (Tseng et al., 2010). The VAFS has demonstrated good

reliability and validity as a measure of post-stroke fatigue (Y. Benjamin, Byron, & Patricia, 2010; Kruithof, Van Cleef, Rasquin, & Bovend'Eerdt, 2016; Lerdal et al., 2009; Nadarajah & Goh, 2015; Tsoi, Chan, Hirai, Wong, & Kwok, 2015).

3.12 Mood

3.12.1 Hospital Anxiety and Depression Scale

Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) (Appendix H). The HADS is a well-validated self-administered psychometric tool, used to assess mood in stroke patients (Ayerbe et al., 2014; Barker-Collo et al., 2017; Lees, Broomfield, et al., 2014; Pedroso, Vieira, Brunoni, Lauterbach, & Teixeira, 2016). There are separate anxiety and depression subscales as well as a total HADS score. Scores range from 0 to 21, with scores from 0 to 7 representing a normal range, 8 to 10 a mild range, 11 to 14 a moderate range, and 15 to 21 a severe level of anxiety or depression (Zigmond & Snaith, 1983). A lower cut-off score of > 7 has been recommended by several studies for use in stroke populations (Bjelland, Dahl, Haug, & Neckelmann, 2002). For example, using this cut-off, Wichowicz and colleagues reported the depression subscale demonstrating a high sensitivity of 90.0% and specificity of 92.2% compared with the anxiety subscale having a sensitivity of 86.5% and specificity of 94.9% (Bjelland et al., 2002; Wichowicz & Wieczorek, 2011). The HADS has demonstrated a good level of internal consistency for the subscales of anxiety and depression (Cronbach alpha of .83 and .82), respectively (Zigmond & Snaith, 1983). However, several studies have reported the anxiety subscale for the HADS is less sensitive to detect anxiety in older stroke patients compared to other anxiety inventories (Bryant, Jackson, & Ames, 2009; Kneebone, Fife-Schaw, Lincoln, & Harder, 2016).Several studies have used the HADS as an outcome measure for assessing predictors of long-term cognitive impairment ≤ (Barker-Collo, Feigin, Parag, et al., 2010; Barker-Collo et al., 2016).

3.13 Cognitive Assessment

As the Montreal Cognitive Assessment (MoCA) Version 7, was used to assess global cognition at baseline and/or 1, 6 and 12 months follow-up in ARCOS-IV, the same measure was used in this study in order to monitor cognitive function over time. The neuropsychological assessment battery- screening module (S-NAB) was chosen in addition to the MoCA in order to determine domain-specific impairment. This battery was used as it was more appropriate for this sample of people due to its ability to ease

of administration, assesses all domains of cognition and far less time-consuming than a full neuropsychological battery.

3.13.1 Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) (Appendix I) is a highly sensitive (0.88-92.3), (Y Dong et al., 2016; Trzepacz, Hochstetler, Wang, Walker, & Saykin, 2015; Tsai et al., 2016) screening tool designed to detect global cognitive impairment (Nasreddine et al., 2005). Eight domains of cognition are assessed including; attention, concentration, memory, language, orientation, visuo-constructional skills, conceptual thinking and calculation. Responses are awarded points according to specified criteria, with a maximum score of 30. Higher scores indicate higher cognitive functioning, with participants scoring ≤26 or higher being considered to have no cognitive impairment (Nasreddine et al., 2005).

The cut off score of ≤ 26 for the MoCA has been largely debated in stroke research, with no consensus as to the most optimum threshold (Chiti & Pantoni, 2014; R Stolwyk, 2016; R Stolwyk, O'Neill, McKay, & Wong, 2014), with acceptable levels of sensitivity and specificity being reported at different cut-off points (Cumming, Churilov, et al., 2013; Godefroy et al., 2011; Salvadori et al., 2013). Several studies have reported the recommended cut-off is inadequate for stroke patients and is optimized at a lower threshold ranging from 19 to 24 (Godefroy et al., 2011; Salvadori et al., 2013; R Stolwyk et al., 2014). A 2014 systematic review reported the MoCA had high sensitivity 0.95, but low specificity 0.45 with a cut-off of ≤ 26, compared to a sensitivity of 0.84 and specificity of 0.78 for a cut off of ≤ 22 (Lees, Selvarajah, et al., 2014). However, using a more conservative threshold of ≤ 24 has been shown to reduce the sensitivity of the MoCA, to detect post stroke cognitive impairment (Cumming, Marshall, et al., 2013). While the recommended cut off (≤ 26) has consistently demonstrated adequate sensitivity to detect cognitive impairment in stroke populations at both acute, subacute and chronic phases (Borland et al., 2017; Burton & Tyson, 2015a; Larouche et al., 2016; Mijajlović et al., 2017). The sub-sections for the MoCA can be calculated according to the published criteria and include cut-off scores for each domain (see Table 3). For the purposes of this thesis those people who had a cut-off score on the total MoCA of ≤ 26 were described as cognitively impaired (poor) versus those with a cut-off score of ≥ 26 who were described as not impaired (good).

Table 3. MoCA sub-domains, points and cut-off Scores

Cognitive Domain	Task	Points	Cut-Off
Visuospatial abilities	Clock drawing task	3	≤ 3
	Three dimensional cube copy	1	
Executive Functions	Trails Test	1	≤ 3
	Fluency Task	1	
	Two-item verbal abstraction task	2	
Language	Three-item confrontation naming task	3	≤ 4
	Repetition of two complex sentences	2	
Attention	Target detection using finger tapping	1	≤ 5
	Digits forwards and backwards	1 point each (2)	
	Serial abstraction task	3	
Short-term memory	Recall task	5	≤ 4
Orientation	Time and Place	6	
Total MoCA		30	≤26

Some studies have suggested that an extra 1-point should be added to those people with equal or less than 12 years of education (Borland et al., 2017; Y. Wu, Wang, Ren, & Xu, 2013). However, the literature is conflicting. For example; Nasredinne (who developed the MoCA) only tested the use of the extra 1-point for those patients in North American populations (Nasreddine et al., 2005). In contrast, other studies have demonstrated the addition of 1 point is not adequate for stroke survivors from different cultural backgrounds (for example from Asia and Europe) (Y Dong et al., 2010; Y Dong et al., 2016; Godefroy et al., 2011) therefore may not be generalizable to the wider population. For the purpose of this PhD an extra 1-point was not added to those stroke survivors with less than or equal to 12 years education (Blackburn et al., 2013; Burton & Tyson, 2015b; Chiti & Pantoni, 2014; Horstmann et al., 2014; R Stolwyk, O'Neill, McKay, & Wong, 2014; Tan et al., 2017; Tu et al., 2013).

3.13.2 Battery Screening Module

The Neuropsychological Assessment Battery (NAB) is considered a “new generation” battery used to measure a comprehensive range of cognitive functions in adults aged 18-

97 with neurological disorders (Hacker et al., 2017; Stern & White, 2003). The NAB has a separate screening module (S-NAB), which mirrors the full battery (Appendix J). The S-NAB consists of five domain specific components; visual spatial functioning, language, attention, memory (visual and verbal) and executive functions, and is co-normed with the NAB which provides normative data for age-group, gender, and education level (Stern & White, 2003). A total screening index score is generated with a cut-off score of <85 indicating cognitive impairment. Tasks for the attention component include: digit span (forward and backward), orientation, letter cancellation and divided attention condition. A cut-off of < 74 indicates impairment. Executive function tasks include; a speeded word generation and maze test, with a cut-off of <73 indicative of impairment. Language is assessed using tasks which assess confrontation naming and auditory comprehension (cut-off <75), while memory tasks include: immediate and delayed story recall, and immediate and delayed shape recognition (cut-off <75). Finally, visuo-spatial ability tasks include; visual form discrimination and a two-dimensional design construction task (cut-off <74) (Cannizzaro, Elliott, Stohl, Hasin, & Aharonovich, 2014; Hacker et al., 2017).

The screening module has demonstrated high sensitivity (0.81) and is a more practical alternative when the full comprehensive battery is not feasible (Iverson, Williamson, Ropacki, & Reilly, 2007). Moreover, the screening module takes approximately 45 to 60 minutes to administer and around 5 minutes to score, in comparison to the NAB which takes 3 to 4 hours. The S-NAB has been tested within stroke populations and found to be a reliable and valid assessment tool for post-stroke cognition (Pulsipher, Stricker, Sadek, & Haaland, 2013). The S-NAB has demonstrated good validation through both exploratory and confirmatory factor analyses (Pulsipher et al., 2013; Stricker, Tybur, Sadek, & Haaland, 2010; Temple et al., 2009; Yochim, Kane, & Mueller, 2009; Zgaljardic & Temple, 2010).

3.13.3 Comprehensive Trail Making Test

The Comprehensive Trail Making Test (CTMT) is a widely used time-tested instrument to access executive functioning ability and cognitive processing speed in people with neurological disorders (Reynolds, 2002). Its popularity is related to ease and speed of administration (5 to 12 minutes). The CTMT is an adaptation of the Trail Making Test (TMT), (Partington & Leiter, 1949) but differs from its predecessor by comprising of 5 trials as opposed to 2. It was developed to assess frontal lobe functioning with the addition of a new set shifting task and assessment of inhibition skills (Reynolds, 2002).

The five tasks include visual search and sequencing tasks, which assess complex visual scanning, attention and motor speed and are highly sensitive to the effects of brain injury. The tasks require connecting a series of stimuli (numbers and letters) in a specific order as quickly as possible. Scores are derived for each trail based on the number of second taken to complete the task. A composite score is obtained by the sum of the T scores for each trail (Reynolds, 2002). A score of <43 is indicative of executive impairment, with scores ranging from <30 (severely impaired) to >70 (very superior) (Partington & Leiter, 1949).

Normative scores are available for the CTMT for individuals aged between 8 through 74 years, provided as percentile ranks and T-scores, with a standard deviation of 10 and mean of 50 (Reynolds, 2002). The CTMT has good validity (Sanchez-Cubillo et al., 2009; S. Smith et al., 2008) and high sensitivity to predict executive dysfunction in people with brain injury (Allen, Thaler, Ringdahl, Barney, & Mayfield, 2012; Armstrong, Allen, Donohue, & Mayfield, 2008). Attention, concentration, resistance to distraction, and cognitive flexibility heavily influence performance on these tasks (Partington & Leiter, 1949). However, it is important to note the CTMT'S suitability as a measure within the stroke population may be limited due to its reliance on motor skills (Conti et al., 2015; Kopp et al., 2015; Muir et al., 2015).

3.13.4 Symbol Digit Modalities Test

The Symbol Digit Modalities Test (SDMT) is a brief and easy to administer timed measure, used to evaluate an individual's ability to switch attention and information processing speed (A. Smith, 1968). The SDMT has demonstrated high sensitivity in detecting the presence of brain dysfunction and changes in cognitive performance over time. Within the stroke population it has demonstrated good test–retest reliability (Koh, Lu, Hsueh, Hsieh, & Hsieh, 2011; A. Smith, 1968). The SDMT has its own normative data including age, gender and level of education. There are currently two versions of the SDMT; written or oral which takes into account psychomotor and speech impairment (Koh et al., 2011). However, a recent study which assessed information processing speed in stroke patients, tested a tablet-based version of the SDMT which demonstrated good concurrent validity with the written form (Tung et al., 2016).

The SDMT is administered by asking participants to use a coded key to pair nine abstract symbols with numerical digits. A practice test is given before the test starts. The total score is calculated by the correct number of pairs over a 90 second period,

with scores ranging between 0 and 110. A cut-off score of <40 indicates impairment. Normative data is available from ages 15 through 100 (Kiely, Butterworth, Watson, & Wooden, 2014). The written format of the SDMT is relatively free of cultural bias and can be administered to people who do not speak English because it only involves universal geometric figures and numbers (A. Smith, 1968).

3.13.5 Modified Wisconsin Card Sorting Test

The Modified Wisconsin Card Sorting Test (M-WCST) is a modified version (48 cards compared to 128) of the original Wisconsin Card Sorting Test, which measures attention, problem solving and cognitive set shifting ability in response to changing environmental contingencies in people aged between 18 to 92 years (Caffarra, Vezzadini, Dieci, Zonato, & Venneri, 2004; Cianchetti, Corona, Foscoliano, Scalas, & Sannio-Fancello, 2005).The M-WCST comprises of 48 cards sorting responses by 3 attributes; colour, shape or number. Administration is simpler compared with the WCST which has 128 cards, and well tolerated by older adults, specifically those with cognitive impairment. It has greater sensitivity than the WCST to detect executive dysfunction (Caffarra et al., 2004; Su, Lin, Kwan, & Guo, 2008). The M-WCST has demonstrated good sensitivity to deficits in perseverative reasoning and problem solving in individuals with mild cognitive impairment (Nagahama et al., 2003). It has greater administration flexibility in that it can be given irrespective of speech or motor impairments, deficits which are both commonly associated with stroke. Normative data is provided for the M-WCST which include age, gender and education (Caffarra et al., 2004; Su et al., 2008).

3.14 Statistical Analysis

General approaches

The analysis for each study is described in full in Chapter Four (Study 1), Chapter Five (Study 2) and Chapter Six (Study 3). An overview of the method of statistical analysis used in this thesis will be briefly described here.

Profile analyses used descriptive statistics to summarise the demographic, socio-demographic, stroke-related characteristics, and stroke related risk factors of the sample. Reported as number and percentages for categorical variables, and means and standard deviations for continuous variables. To assess the representativeness the four-year follow-up sample (n=257) to the total ARCOS-IV incidence sample (n=2096) chi-square tests were used to compare categorical predictors. Two-sample independent t-

tests were used to compare normally distributed continuous outcomes and the Mann-Whitney test for continuous outcomes with non-normal distributions (refer Table 4). Means and standard deviations of the cognitive assessments (MoCA and S-NAB) and their-within specific test domains were summarised by demographic, stroke characteristics and stroke subtype as classified by (OCSP) and reported.

Table 4. Characteristics of the follow-up sample (N=257) compared with the ARCOS-IV total incidence sample (N=2096).

Descriptive	**Follow-up**		**ARCOS-IV**	**Test of Difference**
	n	**%**	**%**	**Value**
Age Group				X^2=0.91 p=0.34
18 to 64	91	35%	32%	
65 and over	166	65%	68%	
Gender				X^2=2.54, p=0.11
Female	121	47%	52%	
Male	136	53%	48%	
Ethnicity				X^2=13.8, p<0.001*
European	207	81%	69%	
Non-European	50	19%	31%	
Marital status				X^2=4.41, p=0.036
Married	157	61%	55%	
Never married/ Separated, divorced, or widowed	100	39%	45%	
Employment				X^2=0.27, p=0.61
Employed	50	19%	18%	
Retired/ Unemployed	207	81%	82%	
Recurrent Stroke				X^2=2.22, p=0.14
No	213	83%	79%	
Yes	44	17%	21%	
Stroke Type				X^2=15.3, p<0.001*
ISC	224	87%	80%	
ICH	15	6%	13%	
SAH	18	7%	4%	
Undetermined			3%	

Descriptive	Follow-up		ARCOS-IV	Test of Difference
	n	%	%	Value
Stroke Sub-type				X^2=0.55, p=0.55
LACI	74	29%	28%	
PACI	78	30%	33%	
POCI	69	27%	23%	
TACI	18	7%	16%	
Unknown	18	7%		
Hemisphere of Lesion				X^2=6.03, p=0.049
Left	116	45%	46%	
Right	118	46%	49%	
Both/Brainstem/Uncertain	23	9%	5%	
Vascular Risk Factors				
High cholesterol	138	55%	43.4%	X^2=6.88, p=0.009*
Hypertension	167	65%	66%	X^2=0.79, p=0.37
Diabetes	49	19%	22%	X^2=1.50, p=0.22
Coronary heart disease	54	21%	24%	X^2=1.52, p=0.22
Arrhythmia	65	26%	29%	X^2=2.06, p=0.15

***** A chi-square test was performed and a value of p<0.01 represents statistical significance

In terms of representativeness to the ARCOS-IV total stroke sample cohort, there were no significant difference between most characteristics, with the exception of stroke type, ethnicity and high cholesterol.

MoCA – categorisation for analyses

For Study 2, examining the trajectory of cognitive recovery, initial analysis using a histogram, was conducted to look at the distribution of the MoCA as a continuous variable (Appendix M). The histogram and normal Q-Q plot showed that the MoCA was not normally distributed. This was further evidenced by the Shapiro-Wilk test for normality (W = 0.95784, *p*-value = 8.843e-07), which was less than 0.05 indicating deviations from normality. This information suggested that the MoCA should not be analysed as a continuous variable. Therefore, the only other viable solution was to analyse the data as a binary variable where MOCA <26 = poor [classed as 1] and MOCA>=26 = good outcomes [classed as 0] so that the logistic regression models could identify baseline covariates which predict poor recovery [MoCA] at 4-years post stroke event. The results from the linear regression model (robust to deviations from normality) are additionally provided in Appendix N and O, which support the findings

from the more appropriate logistic regression analyses.

Bi-variate correlations (Spearman's) coefficients were used to explore baseline characteristics of continuous and discrete demographic, socio-demographic stroke-related characteristics, stroke-related risk factors, mood, fatigue and baseline MoCA and four-year cognitive impairment variables. The significant level was set to $p<0.05$ to signify statistical significance. From this covariates which were considered significantly correlated with cognitive impairment at four-years and which were not multicollinear, were selected for multiple general regression and mixed-effects analyses to determine their unique contribution. Covariates which were considered as significant predictors, were retained in the multivariate regression models if $p<0.10$. Mixed-effects analyses modelled repeated measures over time, accounting for the effect of time and the inherent correlation within-participant measures collected at different time points. Forwards conditional selection process was used to select variables based on improving the overall efficiency of the model using information criteria and retained in the final model if it resulted in a minimum 10% change in regression coefficient of the risk factor of interest when included in the model. Inferences were based on a 5% significance level and two-sided alternatives. A receiver operating characteristic (ROC) curve analysis was conducted to establish optimal cut-off points and discriminatory properties of the MoCA and CNS-VS. The area under the curve (AUC) was calculated using a generalised logistic model. All data analysis for this thesis was conducted using Statistical Package R version 3.4.3 (Verzani, 2014).

Sample Size Estimate

With a total of N=257 MoCA measures recorded at 4-years post-stroke (M = 20.69, SD=4.72), we were powered (at 80%) to detect a difference of 1.8 in the continuous MoCA score between the two groups (baseline and 4 years) if we assumed they had equal distributions. There were 25 confounders that were assessed for their relationship with MoCA (Table 14). If we adjust for the effect of multiple testing, our Bonferroni-corrected alpha = 0.05/25 = 0.002, for which age (particularly age>=75 years, marital status, employment status, education and the baseline measures of the mRS, Fatigue Visual Analogue Scale, Barthel, HADS Anxiety, HADS Depressions and MoCA remained statistically significant ($p<0.0001$, Table 14).

Multivariate models adjusted for a combined effect of seven of these confounders (Table 15). Because the confounders are adjusted for within a single model we are not required to adjust for the effect of multiple-testing. Of note however, gender, employment status, education level and baseline MoCA were all $p<0.0002$ in this multivariate model (Table 15).

Chapter 4 Prevalence, Predictors and Profiles of Cognitive Impairment

It is well known stroke has a deleterious effect on cognition (Mahon et al., 2017), affecting up to 80% of stroke survivors in the early stages following stroke (Demeyere et al., 2016; Qu et al., 2015). The complex sequelae associated with post stroke cognitive deficits lead to impaired function, are difficult to manage, and have been shown to be associated with high levels of unmet needs in stroke patients (Kamalakannan et al., 2016). Patients with a diagnosis of moderate post-stroke cognitive impairment are six times more likely to progress to dementia compared with those without cognitive impairment (Mijajlović et al., 2017). With up to 25% of survivors with cognitive impairment, diagnosed with dementia within 3 years following stroke (Pendlebury & Rothwell, 2009). The pattern of stroke impairments is variable between individuals and different cognitive impairments can cause different functional challenges in daily life (Stephan, Harrison, et al., 2017). Given that the ageing population and improvements in stroke management, there will be more people living with the effects of stroke. Although return to normal cognitive function can occur within six months, many people will be left with persistent difficulties in thinking and planning even ten to 15 years after the stroke event (Crichton et al., 2016; Delavaran, Jonsson, et al., 2016).

Cognitive deficits have been shown to adversely influence outcomes after stroke, even in those who have successful physical recovery (Jokinen-Salmela et al., 2015), and are associated with reduced quality of life (Cumming et al., 2014; Kjörk, Gustafsson, Blomstrand, Carlsson, & Lundgren-Nilsson, 2016). For instance; deficits in attention and visuospatial ability at three months following stroke, were found to be strongly associated with poor quality of life at 12 months (Cumming et al., 2014). Given the heterogeneity of stroke, the underlying mechanisms which contribute to cognitive deficits are not well known, with no single cognitive pattern that is both sensitive and specific to stroke (Gorelick, Counts, & Nyenhuis, 2016). Cognitive impairment tends to present with greater deficits in the domains of executive function, attention (Barker-Collo, Feigin, Lawes, Senior, et al., 2010), (Al-Qazzaz et al., 2014) information processing speed, (Gerritsen et al., 2003; MacPherson et al., 2017), and visuospatial ability (Nakling et al., 2017; Timpert et al., 2015).

Studies examining cognitive profiles and their association with clinical stroke factors, have found those patients with middle cerebral artery territory strokes (MCA) are more likely to experience deficits in visual spatial, executive function and language than in other vascular territories (W. Zhang, Yun, & Yu, 2014). Whereas, patients who experience total anterior infarcts, performed significantly worse on visual spatial skills and information processing speed (Barker-Collo et al., 2012). Strokes in the posterior cerebral artery are frequently associated with executive dysfunction and attention (K. Park, Yoon, & Rhee, 2011). Memory impairment has been shown to be more prevalent in subcortical strokes compared to cortical strokes (Blasi et al., 2014; Grysiewicz & Gorelick, 2012; Turunen et al., 2013). Generally adults with lesions in the left hemisphere will show language impairment and visuospatial (K. Park et al., 2011) deficits in the right hemisphere (Dacosta-Aguayo et al., 2014). However, some studies have found no association between hemisphere and domain specific impairment (Barker-Collo et al., 2012).

Current clinical stroke guidelines, have emphasized the need for a domain-specific assessment of cognition in order to tailor rehabilitation interventions to accommodate/and or compensate for the specific area of dysfunction (Stroke Foundation, 2017). Yet research on domain specific impairment following stroke is scarce, with most studies using global cognitive screening tools to assess post stroke cognitive impairment (Demeyere et al., 2016, Edwards et al., 2013). While global cognitive screening tools are useful to determine prevalence and trajectories of cognitive impairment, domain-specific assessments predict cognitive and functional outcome better than any other variable (Duffin, Roche, et al., 2012; Nys et al., 2005). Therefore, cognitive screening tools such as the MoCA can be useful as well, and have also been shown to be as effective when compared to a more comprehensive neuropsychological battery to assess domain specific impairment (Vogel et al., 2015).

There is limited data, which has examined the long-term impact of domain-specific cognitive impairment in stroke patients (Barker-Collo et al., 2016; Leśniak, Bak, Czepiel, Seniów, & Członkowska, 2008; van Zandvoort, Kessels, Nys, de Haan, & Kappelle, 2005). A population-based study conducted in New Zealand (NZ) reported deficits in executive functioning; attention and information processing speed five years after stroke (Barker-Collo, Feigin, Parag, et al., 2010). Another study found deficits in attention the most frequent symptoms one year after stroke (Leśniak et al., 2008), while a more recent study, found attention and visuospatial ability were strongly associated

with poor long-term quality of life, two years post stroke event (Stephan, Harrison, et al., 2017).

There is no consensus as to the true profile of long-term domain-specific cognitive deficits. Given their importance for predicting recovery, and the costs associated with poor outcomes such as quality of life, early identification of cognitive deficits is crucial in order to guide cognitive rehabilitation soon after stroke. Therefore, the aim of this study was to identify the long-term cognitive profiles of stroke survivors and factors which are associated with outcomes in specific cognitive domains.

This study aimed to examine cognitive performance, prevalence and profiles in four-year stroke survivors. Based on the current evidence it was it was hypothesized that;

1) A significant proportion of stroke survivors would be cognitively impaired (as demonstrated by a total MoCA score of <26) four-year post stroke.
2) Deficits in attention, executive functioning and information processing speed would be more prevalent than other domains of cognition in long-term stroke survivors
3) Stroke characteristics will influence domain-specific impairment

4.1 Methods

4.1.1 Procedure

Using a semi-structured interview format, participants (n=257) were asked to answer general questions about their health, lifestyle factors and any other changes in living, marital and employment since their last assessment. A number of cognitive assessments were administered; the MoCA to determine global cognitive impairment in terms of prevalence, the S-NAB to assess domain specific cognitive impairment and three extra cognitive tests which specifically assess executive functioning; information processing speed, and attention (WCST, SDMT, CTMT). If participants scored a low MoCA and/or at the time of assessment did not understand the requirements of the tasks then they were not asked to continue with the S-NAB (see Figure 3). Likewise, tests were discontinued if specific tests were not appropriate to administer. A $20 food and/or petrol voucher was given as a token of appreciation for taking part in the study. All baseline demographic and clinical stroke characteristics were extracted from the ARCOS-IV database (see Table 1).

4.2 Flowchart for Recruitment and Cognitive Assessments

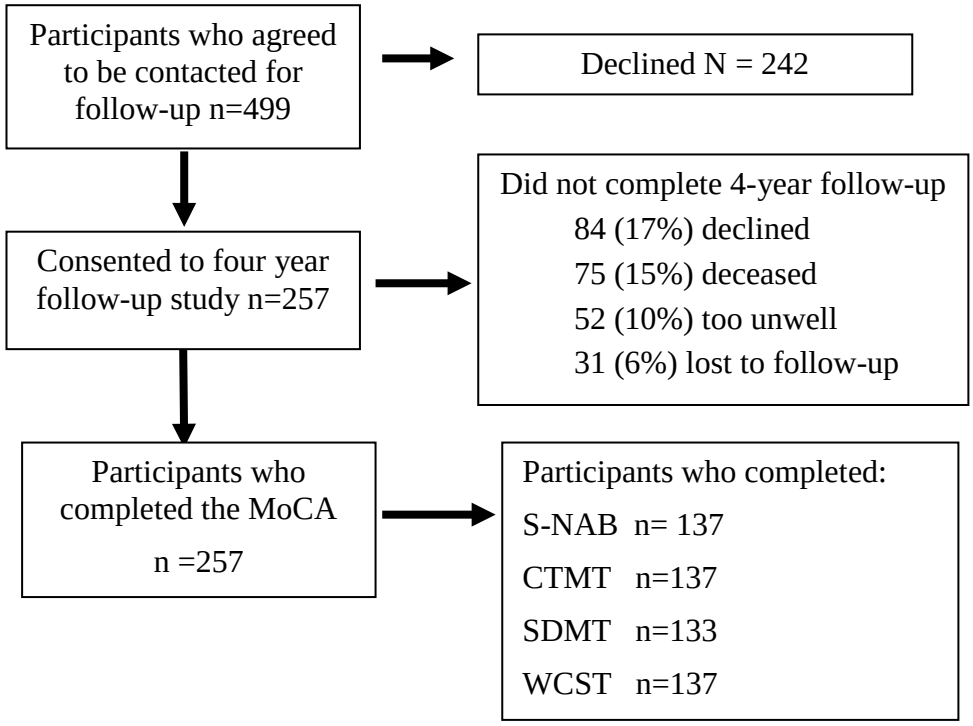

Figure 3. Study recruitment summary

4.2.1 Key Variables: Demographic and Stroke Characteristics

Covariate factors measured at baseline, and included individual demographic factors (age, sex, ethnicity, education level, marital and employment status); and stroke characteristics (subtype as determined by OCSP classification, pathological type, stroke location, hemisphere, vascular territory).

4.2.2 Outcome Measures

The MoCA was used to determine overall cognitive prevalence at four-years. The S-NAB was used to assess cognitive impairment in the specific individual domains (memory, executive functioning, visuo-spatial ability, language and attention). The WCST and CTMT were used to specifically assess executive function and attention, whereas the SDMT was used to specifically assess information processing speed. The measures have been described in-depth in Chapter Three, so a brief overview will be provided.

Montreal Cognitive Assessment

The MoCA is a pencil and paper test, has good psychometric properties and is a valid screening tool to detect cognitive impairment post-stroke (Burton & Tyson, 2015b). Compared to other cognitive screening measures (e.g. Mini Mental State examination-

MMSE), the MoCA demonstrates higher sensitivity to detect executive dysfunction in stroke patients (Fu et al., 2017). While considered a screening tool, the MoCA has been used to monitor cognitive outcomes in longitudinal studies where full neuropsychological assessment is often not practical.

Neuropsychological Assessment Battery Screening Module (S-NAB)

The screening module (S-NAB) is a pencil and paper test, similar to the full NAB, comprised of five domain-specific modules; spatial and executive function, attention, memory and language. The screening module takes approximately 45 to 60 minutes to administer and around five minutes to score, in comparison to the NAB which takes three to four hours. The score range is from 45 to 155 (Pulsipher et al., 2013). Clinical cut off scores for the specific domains include; attention (<74), memory (<75), language (<75), spatial (<74), and executive functions (<73) and <85 for the total S-NAB score. The S-NAB has been tested within stroke populations and found to be a reliable and valid assessment tool for post stroke cognition (Pulsipher et al., 2013).

Modified Wisconsin Card Sorting Test (M-WCST)

Executive function was assessed using a shortened version of the Wisconsin Card Sorting Test to measure attention, problem solving and cognitive set shifting ability in people aged 18 to 92 years (Caffarra et al., 2004). The M-WCST comprises of 48-response and four key cards. A person is required to match each one of the cards to a key card according to a set of rules, with the examinee determining the order of the sorting rule. For example: the examinee can sort the cards by shape, colour, or number. Scores range from 19 to 140, with scores below a cut-off of <98 indicative of impairment in this domain (Caffarra et al., 2004; Su et al., 2008).

Symbol Digit Modalities Test (SDMT)

The SDMT is a pencil and paper test, used to measure information processing speed and assesses the ability to switch attention (Koh et al., 2011; A. Smith, 1968). The SDMT has shown good sensitivity in detecting the presence of cognitive impairment and changes in cognitive performance over time (A. Smith, 1968). Within the stroke population it has demonstrated good test–retest reliability (Alderman, 2016; Koh et al., 2011; A. Smith, 1968). The SDMT has its own normative data including age, gender and level of education. 1 point is awarded for each correctly matched number, with a maximum score of 110. A cut-off score of <40 indicates impairment. Raw scores are converted to a z-scores which are based on education level. Low scores are 1 SD below

the mean (range from 7.98-13.54, depending on age), moderate scores 1.5 SD below the mean, and extremely low scores 2 SD below the mean. (A. Smith, 1968).

Comprehensive Trail Making Test (CTMT)

The CTMT is one of the most commonly used pencil and paper tests to access executive function (Partington & Leiter, 1949). It is comprised of five visual search and sequencing tasks (trails), which assess complex visual scanning, attention and psycho-motor speed and is highly sensitive to the effects of injury to the brain (Partington & Leiter, 1949). Participants are asked to complete the five trails, which require the participant to connect a series of numbers or letters or both with lines. A cut-off of <43 is indicative of executive function impairment. Its popularity is related to ease and speed of administration (within 5 to 12 minutes). Attention, concentration, resistance to distraction, and cognitive flexibility heavily influence performance on these tasks (Partington & Leiter, 1949).

4.3 Statistical Analyses

Hypothesis 1: To identify the level of cognitive impairment at four-year post stroke. The hypothesis is that cognitive impairment would be present in a significant number of stroke survivors, four years after stroke onset.

Hypothesis 2: To identify domain-specific impairments of cognition at four years post-stroke. The hypothesis is that attention, executive function and information processing speed would be more impaired than the other domains of cognition.

To achieve these hypotheses the following statistical method was used:

Using the statistical methods described in chapter three (3.14), profile analysis using descriptive statistics was conducted to identify the most common cognitive deficits (%) amongst stroke patients at the four-year time point for the S-NAB, WCST, SDMT and CTMT and identify potential predictors of domain-specific impairment.

Regression models were used to determine demographic differences between those who completed the S-NAB and those who did not. Multiple linear regression analyses identified predictors (demographic, socio-demographic stroke-related characteristics, stroke-related risk factors) of four-year cognitive impairment (S-NAB). Spearman's correlations were used to identify multicollinearity between baseline characteristics, where the least clinically viable variable was excluded from the models.

Hypothesis 3: To examine which stroke characteristics would influence domain-specific impairment. The hypothesis is that stroke-related characteristics would be associated with greater impairment in specific domains of function.

Profile analysis using descriptive statistics was used to determine the influence of stroke-related characteristics on specific cognitive domains including pathological stroke type stroke OCSP classification subtype, vascular territory, location (subcortical and cortical) and hemisphere (left, right or both). Raw scores for the S-NAB, CTMT, WCST, and SDMT were converted into z scores using age-matched normative data. Z scores below <-1 were considered below average.

4.4 Results

Table 5 summarises the profile analyses for the sample. Descriptive information is presented for demographic and stroke characteristics in impaired (poor) versus not impaired (good) participants. In brief, the average time since stroke was 3.7 years ± 5.6 (ranging from 3.5 to 4.5 years). Mean age of the sample was M = 71.1 ± 13.5 years (ranging from 28 to 96 years). At the time of stroke, Europeans were older by an average of 15 years compared to Pasifika and 17 years compared to Māori. The majority of the sample were NZ European, (n=206, 80.4%) and had ISC strokes (n=224, 82.7%). 214 (83.3%) experienced their first ever stroke, compared to 43 (16.7%) who had recurrent stroke. Lesions occurred predominately in subcortical areas (54.1%) compared to cortical areas (25.7%). Baseline vascular risk factors included, hypertension n=166 (65%), hypercholesterolemia, n=137 (54%), diabetes mellitus, n=49 (19%), coronary artery disease 54 (21%), and arrhythmia n=65 (26%). 137 participants (53%) completed the S-NAB and all 257 participants completed the MoCA.

Table 5. Demographic, Stroke Clinical Features and Stroke risk-factors of all impaired versus non-impaired participants

	Impaired (<26)	%	Not Impaired (>26)	%	P
Age groups					
<50	28	10.89%	5	1.95%	0.743
51-64	46	17.90%	11	4.28%	
65-74	67	26.07%	14	5.45%	
75+	75	29.18%	11	4.28%	
Gender					
Female	102	39.69%	18	7.00%	0.696
Male	114	44.36%	23	8.95%	
Ethnicity					
European	170	66.15%	37	14.40%	0.363
Māori	11	4.28%	1	0.39%	
Pasifika	6	2.33%	1	0.39%	
Asians	29	11.28%	2	0.78%	
Marital status					
Married, civil union or de-facto	132	51.36%	28	10.89%	0.598
Never married/Not specified/ Separated, divorced, or widowed	84	32.68%	13	5.06%	
Employment					
Employed	41	15.95%	9	3.50%	0.66
Not specified/ Retired/ Unemployed	175	68.09%	32	12.45%	
Education Level					
Did not complete school	60	23.35%	8	3.11%	
Completed school	41	15.95%	12	4.67%	
Post-school qualification	48	18.68%	10	3.89%	
diploma cert	43	16.73%	5	1.95%	
trade	23	8.95%	7	2.72%	
Previous stroke					
Yes	33	12.84%	10	3.89%	
No	183	71.21%	31	12.06%	0.152
Recurrent Stroke					
Yes	7	2.72%	4	1.56%	
No	209	81.32%	37	14.40%	0.059

	Impaired (<26)	%	Not Impaired (>26)	%	P
Stroke Type					
ISC	189	73.54%	35	13.62%	0.446
ICH	11	4.28%	4	1.56%	
SAH	16	6.23%	2	0.78%	
Stroke Sub-type					
LACI	61	23.74%	12	4.67%	0.943
PACI	66	25.68%	13	5.06%	
POCI	57	22.18%	12	4.67%	
TACI	16	6.23%	2	0.78%	
Unknown	16	6.23%	2	0.78%	
Hemisphere of Lesion					
Left	98	38.13%	17	6.61%	
Right	99	38.52%	20	7.78%	
Both	11	4.28%	3	1.17%	
Brainstem	8	3.11%	1	0.39%	
Uncertain					
Stroke Vascular territory					
MCA	117	45.53%	21	8.17%	0.575
PCA	42	16.34%	9	3.50%	
PICA	32	12.45%	4	1.56%	
ACA	10	3.89%	1	0.39%	
Unknown	15	5.84%	6	2.33%	
Location of Lesion					
Cortical	61	23.74%	9	3.50%	0.709
Subcortical	126	49.03%	26	10.12%	
Unknown	29	11.28%	6	2.33%	

***** *A chi-square test was performed and a value of $p<0.01$ represents statistical significance.*
Note: ISC=ischaemic stroke, ICH=intracerebral haemorrhage, SAH=subarachnoid haemorrhage, LACI=lacunar infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct, TACI= total anterior circulation infarct, MCA= middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebellar artery, ACA=anterior cerebral artery, mRS=Modified Rankin Scale, HADS=Hospital Anxiety and Depression Scale, MoCA=Montreal Cognitive Assessment Scale.

4.4.1 Prevalence of Cognitive Impairment and Demographic Characteristics as Determined by the MoCA

At 4 years after stroke, a significant proportion of stroke survivors had cognitive impairment 216 (84%) (<26, MoCA, *M* = 19.5 ± 4.7), and 41 stroke survivors who performed in the normal range (>26 MoCA *M* = 26.7) (Table 6). When examining demographic characteristics (Table 6), those aged over 75 years had nearly four-point differences in MoCA scores (*M* = 18.9 ± 4.7) compared to those aged <50 (*M* = 23.2 ± 4.8). Pasifika people had the lowest mean MoCA scores (*M* = 17.5 ± 5.6), followed by Māori (*M* = 18.9 ± 5.6), compared to Europeans (*M* = 20.71 ± 4.6), and Asians (*M* = 21.87 ± 4.9). Mean MOCA scores did not statistically significant differ between Pasifika, Māori and Asian participants compared to Europeans (Appendix S) *p*-value = 0.199. Similarly, there were no differences between females (*M* = 20.5 ± 5.0) compared to males (*M* = 20.8 ± 4.3) *p*-value= 0.697. Stroke survivors who were retired, did not complete school and separated/divorced or widowed had significantly lower mean scores (*M* = 19.7 ± 4.8, *M* = 18.9 ± 4.0, *M* = 19. 7± 4.7 respectively), *p*-value = <0.01 compared to those who were working, completed school and married (*M* = 23.4 ± 3.5, *M* = 20.2 ± 5.2, *M* = 21.2 ± 4.6).

Table 6. Mean MoCA score and Demographic Characteristics

Variable	Mean	N	SD
Age Group			
<50	23.2	34	4.8
51-64	21.9	57	3.9
65-74	20.6	79	4.7
75+	18.9	86	4.7
Gender			
Female	20.5	119	5.0
Male	20.7	137	4.3
Ethnicity			
European	20.7	205	4.6
Māori	18.9	13	4.6
Pasifika	17.5	7	5.6
Asian	21.8	32	4.9
Marital Status			
Married/defacto	21.2	155	4.6
Never married	24.0	2	2.8
Separated/divorced/widowed	19.7	96	4.7
Employment			
Retired	19.7	171	4.8
Unemployed	21.7	22	4.4
Employed	23.4	49	3.5
Not Specified	20.9	14	3.4
Education level			
Did not Complete School	18.9	68	4.0
Completed School	20.2	51	5.2
University Degree	22.2	50	4.9
Diploma/Cert	21.2	48	4.8
Trade	21.2	27	3.2
Post Grad	21.8	8	4.1
Not Specified	22.0	4	4.2

* Scores represent mean total scores (*M*) and standard deviations (SD) for the demographic characteristics of the sample (%) on the Montreal Cognitive Assessment (MoCA). Note: ISC=ischaemic stroke, ICH=intracerebral haemorrhage, SAH=subarachnoid haemorrhage, LACI=lacunar infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct, TACI= total anterior circulation infarct, MCA= middle cerebral artery, PCA=posterior cerebral artery, PICA=posterior inferior cerebellar artery, ACA=anterior cerebral artery

4.4.2 Cognitive Impairment and Stroke-related Characteristics

As highlighted on page 60 (4.2), only 137 participants from a total sample of 257 were administered the S-NAB. This was due to low MoCA scores, and participants who were not able to undertake the full assessment. When examining stroke-related characteristics (Table 6), and mean MoCA scores, we found people with TACI (M =19.6 ± 5.2), exhibited lower scores compared to the other stroke subtypes; PACI, LACI and POCI (M = 19.8 ± 4.9, M = 20.9 ± 4.6, M = 21.2 ± 4.0 respectively). Strokes in the temporal lobe, had a nearly 4-point difference (M =17.8 ± 3.6) in MoCA score compared to those who had a stroke in the frontal lobe (M = 21.3 ±4.6). Thalamic strokes also had lower MoCA scores (M =19.4 ± 5.5) compared to other locations in the brain. Looking at stroke types, those who experienced strokes in subarachnoid regions, had higher MoCA scores (23.0 ± 3.8) at four years compared to ischaemic and intracerebral stroke (M = 20.5 ± 4.5 and M = 20.4 ± 7.3). Strokes in cortical regions had lower mean MoCA scores (M = 20.0 ± 5.0) compared to those occurring in sub-cortical regions (M = 21.7 ± 4.3). There were minimal differences in mean scores, when examining hemisphere and vascular territory.

Table 7. Mean MoCA score and Stroke–related Characteristics

Variable	Mean	N	SD
Stroke location			
Frontal	21.3	38	4.6
Parietal	19.1	15	6.7
Occipital	21.6	12	3.9
Temporal	17.8	4	3.6
Basal Ganglia	20.4	29	4.4
Internal Capsule	20.0	36	5.1
Thalamus	19.4	17	5.5
Cerebellum	20.9	35	4.0
Brain Stem	21.6	16	3.9
Unknown	21.1	54	4.5
Stroke Type			
ISH	20.5	223	4.5
SAH	23.0	18	3.8
ICH	20.4	15	7.3
Hemisphere			
Left	20.3	113	4.6
Right	20.6	119	4.7
Both	23.0	9	3.6
Uncertain	27.0	1	
Vascular Territory			
MCA	20.5	137	4.7
PCA	20.5	50	5.1
PICA	20.6	36	3.9
ACA	20.6	9	5.9
SCA	23.5	3	4.9
Unknown	21.8	21	4.0
Stroke Region			
Cortical	20.0	70	5.0
Subcortical	21.7	151	4.3
Unknown	19.8	35	5.1
Stroke Sub-Type			
TACI	19.6	18	4.9
PACI	19.8	78	5.2
LACI	20.8	73	4.6
POCI	21.2	68	4.0
Unknown	23.0	18	3.8

* Scores represent mean total scores (*M*) and standard deviations (SD) for the stroke-related characteristics of the sample (%) on the Montreal Cognitive Assessment (MoCA).

4.4.3 Characteristics of participants who completed the NAB

When examining the demographic characteristics of participants who completed the S-NAB (Table 8) univariate analysis, the following were found to be statistically significant predictors: Age at event was significantly associated with incomplete S-NAB (effect=-0.0480, i.e. the older participants were at time of stroke, the less likely they were to complete the full battery), *p*-value = 5.52×10^{-6}. Participants were less likely to complete the S-NAB if they were unemployed or retired compared to those who were employed (effect = -1.8229, *p*-value = 8.84×10^{-6}) but more likely to complete the S-NAB if they completed a post-school qualification (compared to those who did not complete school) effect = 1.2528, *p*-value = 0.0001. Using a forwards selection procedure to fit a multivariate logistic regression model, age, employment status, time since stroke, education level and recurrent stroke were associated with whether or not they completed the NAB (Table 8).

Table 8. Univariate logistic regression showing demographic and stroke-related characteristics who completed the S-NAB

Variable	Categories	Estimate	Std. Error	z-value	*p*-value
Intercept		3.4174	0.7413	4.6100	**4.03E-06**
Age at event		-0.0480	0.0106	-4.5440	**5.52E-06**
Intercept		0.8329	0.3788	2.1989	**0.0279**
Age group (ref = < 50 year olds)	51-64	-0.1138	0.4709	-0.2416	0.8091
	65-74	-0.5008	0.4422	-1.1325	0.2574
	75+	-1.5261	0.4418	-3.4540	**0.0006**
Intercept		-0.0827	0.1820	-0.4544	0.6495
Gender	Male	0.4091	0.2516	1.6258	0.1040
Intercept		0.1258	0.1393	0.9030	0.3665
Ethnicity (ref = European)	Non-European	0.0346	0.3161	0.1094	0.9129
Intercept		0.4002	0.1628	2.4576	**0.0140**
Marital status (ref = Married, civil union or defacto)	Separated/divorced/widowed	-0.6820	0.2594	-2.6287	**0.0086**
Intercept	Intercept	1.6582	0.3858	4.2986	**1.72E-05**
Employment status (ref = Employed)	Employment status (Unemployed/Retired)	-1.8229	0.4102	-4.4438	**8.84E-06**
Intercept		4.9227	1.8513	2.6590	**0.0078**
Time since stroke		-1.4552	0.5621	-2.5888	**0.0096**

Intercept		-0.6931	0.2554	-2.7142	**0.0066**
Education level (ref = Did not complete school)	Completed school	0.8109	0.3794	2.1376	**0.0326**
	Post-school qualification	1.2528	0.3130	4.0027	**0.0001**
Intercept		-0.6931	0.2554	-2.7142	**0.0066**
Education level (ref = Did not complete school)	Completed school/ Post-school qualification	1.1260	0.2968	3.7933	**0.0001**
Intercept		0.0846	0.1372	0.6165	0.5376
Recurrent stroke	Yes	0.2832	0.3359	0.8430	0.3992
Intercept	Intercept	0.0536	0.1337	0.4008	0.6885
Stroke type (ref = ISC	ICH	0.0799	0.5345	0.1496	0.8811
	SAH	1.1992	0.5825	2.0587	**0.0395**
Intercept		0.0536	0.1337	0.4008	0.6885
Stroke type (ref = ISC)	HS	0.6396	0.3927	1.6285	0.1034
Intercept		-0.1625	0.2333	-0.6967	0.4860
Stroke subtype (ref = LACI)	PACI	0.3167	0.3256	0.9726	0.3307
	POCI	0.4841	0.3375	1.4345	0.1514
	TACI	0.4990	0.4107	1.2149	0.2244
Intercept		0.0345	0.1857	0.1857	0.8527
Hemisphere of lesion (ref = Left)	Right	0.0333	0.2616	0.1274	0.8986
	Both/Brainstem	1.0070	0.5099	1.9749	**0.0483**

Intercept		0.1473	0.1720	0.8567	0.3916
Stroke vascular territory (ref = MCA)	PCA	-0.3077	0.3318	-0.9273	0.3538
	PICA	0.0245	0.3804	0.0645	0.9486
	ACA	0.3047	0.3827	0.7961	0.4260
Intercept		-0.0432	0.1697	-0.2544	0.7992
Location of lesion (ref = Subcortical)	Cortical	0.3486	0.3014	1.1566	0.2474
	Unknown	0.4326	0.3296	1.3124	0.1894

***A univariate test was performed**. A value of $p<0.01$ represents statistical significance

Table 9. Multivariate logistic regression showing demographic characteristics of participants who completed the S-NAB

Variable	**Category**	**Estimate**	**Std. Error**	**z-value**	***p*-value**
Intercept		10.4882	2.6148	4.0110	**0.0001**
Age at event		-0.0418	0.0129	-3.2403	**0.0012**
Employment status (ref = employed)	Unemployed/ Retired/ Unspecified	-1.3982	0.4864	-2.8748	**0.0040**
Time since stroke		-2.2301	0.6799	-3.2801	**0.0010**
Education level (ref = Did not complete school)	Completed school	0.8329	0.4149	2.0076	**0.0447**
	Post-school qualification	1.3509	0.3569	3.7855	**0.0002**
Recurrent stroke	Yes	0.8189	0.4023	2.0355	**0.0418**

***A multivariate test was performed**. A value of $p<0.01$ represents statistical significance

4.4.4 S-NAB and Domain Specific Cognitive Profiles

The total mean index score on the S-NAB was *M* = 97.8 ± 15.4. Similar to the findings reported for the MoCA, Māori and Pasifika had (*M* = 79.5 ± 4.8 and 69.6 ± 19.0 respectively) considerably lower scores (p=0.000) than Europeans (*M* = 87.7 ± 12.2) (Appendix X), and well below the threshold of 85. When examining the five individual domains of the S-NAB the prevalence of the extent of cognitive deficit (no impairment, impairment, moderate to severe impairment) reported as percentages, was high with the majority of stroke survivors having impairment and/or moderate to severe impairment in most domains (Table 10). Memory was the most commonly impaired domain (n=130), followed by attention (n=129), executive functioning (n=122), and language (n=115), with visual spatial being the least impaired domain (n=110). Scores on the individual tests 52% (n=70), of participants had impaired information processing speed with a SD of 1 below the mean. The raw mean score was =36 ± 11.6. The majority of stroke survivors (65.2%) performed below average in the CTMT (*M* = 42 ± 11.5). Additionally, males performed below average (≤ 42) on the CTMT tests of executive functioning (*M* = 40.5 ± 12.9) compared to females (*M* = 50.7 ± 50.0). Males were also more likely to perform poorly in information processing speed (mean SDMT score *M* = 28.9 ± 17.1), than females (*M* = 31.1 ± 17.9). The majority of participants performed within the expected range in the M-WCST.

Table 10. S-NAB and individual tests for specific cognitive domains using cut-offs

S-NAB Domains	N	%
Attention		
Not impaired	8	5.6
Impaired	101	73.0
Moderately/severely impaired	28	19.4
Language		
Not impaired	22	15.2
Impaired	113	82.3
Moderately/severely impaired	2	1.5
Memory		
Not impaired	7	4.9
Impaired	123	89.2
Moderately/severely impaired	7	4.9
Visual Spatial		
Not impaired	27	18.8
Impaired	107	78.0
Moderately/severely impaired	3	2.2
Executive Functions		
Not impaired	15	10.5
Impaired	116	85.3
Moderately to severely impaired	6	4.2
Symbol Digit Modalities Test (processing speed/attention)		
Not impaired	62	48.0
Impaired	70	52.0
Comprehensive Trail Making Test (executive function/attention)		
Not impaired	46	34.8
Impaired	86	65.2
Wisconsin Modified Card Sorting Test (executive function)		
Not impaired	118	86.2
Impaired	19	13.8

4.4.5 Multivariate Analysis of Predictors of Domain-Specific Impairment

Specific regression models for the S-NAB domains (see Appendices T, U, V, W, X) found females were more likely to have a spatial impairment compared to males (p = 0.018). Those who had a PACI (p = 0.04) or POCI (p = 0.02) were more likely to have a

spatial impairment compared to a LACI. Younger patients were more likely to have a language impairment compared to older patients (p = 3.57x10-6). Those who had a LACI were more likely to have a language impairment compared to those who had a PACI (p = 0.0562) or POCI (p = 0.0333) Participants who were unemployed or retired at the time of stroke were more likely to have executive function impairment (p = 0.0061) compared to those who were employed.

4.5 Profile Analysis of S-NAB

Profile analyses were conducted to examine whether stroke characteristics (vascular territory, stroke subtype, region and hemisphere) were associated with specific domains of cognition (Table 11). Statistical differences were identified between vascular territory and stroke subtype (OCSP) and the individual domains of the S-NAB, and additional tests. No differences were found when examining hemisphere, stroke type and location (cortical and subcortical) in relation to domain-specific impairment.

Table 11. Profile analysis of stroke subtype (OCSP), hemisphere, vascular territory and stroke region

Variable	Estimate	Std. Error	Z-value	*p*-value
OCSP Classification				
Intercept	7.5830	3.2251	2.3512	**0.0187**
SDMT	-0.0027	0.0241	-0.1102	0.9123
WCST	-0.0571	0.0390	-1.4643	0.1431
CTMT	0.0047	0.0064	0.7307	0.4650
Attention	-0.0299	0.0182	-1.6426	0.1005
Language	0.0177	0.0174	1.0185	0.3084
Memory	-0.0072	0.0175	-0.4123	0.6801
Spatial	-0.0289	0.0117	-2.4708	**0.0135**
Executive	0.0056	0.0221	0.2531	0.8002
Stroke Hemisphere				
Intercept	-0.1452	2.3882	-0.0608	0.9515
SDMT	-0.0137	0.0214	-0.6408	0.5216
WCST	-0.0180	0.0270	-0.6678	0.5042
CTMT	-0.0021	0.0054	-0.3843	0.7008
Attention	0.0144	0.0149	0.9658	0.3341
Language	0.0037	0.0142	0.2606	0.7944
Memory	0.0006	0.0148	0.0387	0.9692
Spatial	-0.0112	0.0099	-1.1356	0.2561
Executive	0.0199	0.0190	1.0463	0.2954

Variable	Estimate	Std. Error	Z-value	*p*-value
Stroke Vascular Territory				
Intercept	-1.4275	2.5141	-0.5678	0.5702
SDMT	0.0222	0.0220	1.0089	0.3130
WCST	-0.0754	0.0320	-2.3543	**0.0186**
CTMT	0.0032	0.0056	0.5792	0.5625
Attention	0.0141	0.0154	0.9113	0.3621
Language	0.0401	0.0165	2.4353	**0.0149**
Memory	-0.0169	0.0153	-1.1058	0.2688
Spatial	0.0040	0.0104	0.3863	0.6992
Executive	-0.0048	0.0193	-0.2493	0.8032
Stroke Region				
Intercept	-0.0162	2.4102	-0.0067	0.9946
SDMT	-0.0036	0.0211	-0.1731	0.8626
WCST	0.0286	0.0273	1.0445	0.2962
CTMT	-0.0004	0.0054	-0.0804	0.9359
Attention	0.0023	0.0149	0.1568	0.8754
Language	-0.0061	0.0143	-0.4300	0.6672
Memory	0.0060	0.0146	0.4089	0.6826
Spatial	0.0173	0.0101	1.7164	0.0861
Executive	-0.0331	0.0193	-1.7145	0.0864

***A univariate test was performed.** A value of $p<0.01$ represents statistical significance

4.5.1 Cognitive performance and Vascular Territory

In examining differences in cognitive function by vascular territory a profile analysis was conducted (Table 12), with vascular territory as the grouping variable and z scores across the individual domains of the S-NAB and additional tests (Figure 4). Looking at the specific domains within vascular territory, we identified that: MCA cases had significantly higher WCST scores (estimate = 0.08, *p*-value = 0.0186) and significantly lower language (estimate = -0.04, *p*-value =0.0149) compared to the other vascular territories. ACA had significantly higher language scores (estimate = 0.05, *p*-value = 0.0313) compared to the other vascular territories. PCA cases had near statistically significantly higher attention scores (estimate = 0.04, *p*-value = 0.0652) compared to the vascular regions.

Table 12. Profile analysis of Vascular Territory and cognitive domains

Vascular Territory			
MCA	**Estimate**	**SE**	***p*-value**
Intercept	1.43	2.51	0.5702
SDMT	-0.02	0.02	0.3130
WCST	0.08	0.03	**0.0186**
CTMT	0.00	0.01	0.5625
Attention	-0.01	0.02	0.3621
Language	-0.04	0.02	**0.0149**
Memory	0.02	0.02	0.2688
Spatial	0.00	0.01	0.6992
Executive	0.00	0.02	0.8032
PCA	**Estimate**	**SE**	***p*-value**
Intercept	-1.03	3.21	0.7475
SDMT	-0.01	0.03	0.6381
WCST	-0.04	0.03	0.2480
CTMT	0.00	0.01	0.7650
Attention	0.04	0.02	*0.0652*
Language	0.02	0.02	0.3487
Memory	-0.03	0.02	0.2358
Spatial	0.00	0.01	0.8226
Executive	-0.01	0.03	0.6922
PICA	**Estimate**	**SE**	***p*-value**
Intercept	-0.60	3.32	0.8571
SDMT	0.02	0.03	0.5121
WCST	-0.02	0.03	0.4771
CTMT	0.00	0.01	0.6401
Attention	-0.02	0.02	0.2877
Language	0.00	0.02	0.8930
Memory	-0.01	0.02	0.7680
Spatial	0.00	0.01	0.7322
Executive	0.02	0.03	0.5290
ACA/Unknown	**Estimate**	**SE**	***p*-value**
Intercept	-7.69	3.76	**0.0410**
SDMT	0.03	0.03	0.3912
WCST	-0.05	0.04	0.1595
CTMT	0.01	0.01	*0.0939*
Attention	0.00	0.02	0.8366
Language	0.05	0.02	**0.0313**
Memory	0.00	0.02	0.9808
Spatial	0.00	0.01	0.8955
Executive	-0.01	0.03	0.6804

*** A univariate test was performed.** A value of $p<0.01$ represents statistical significance

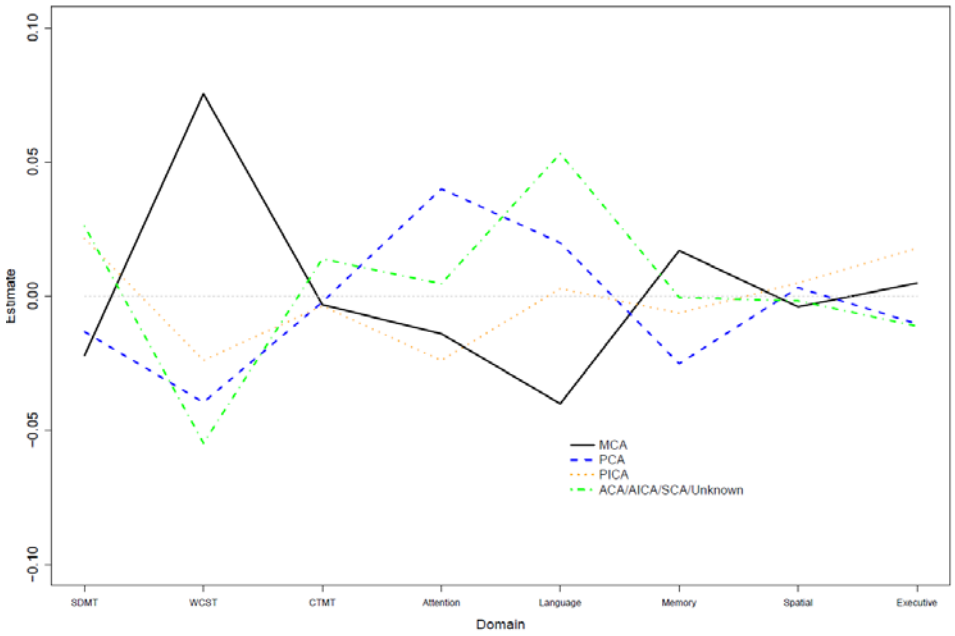

Figure 4. Performance on individual cognitive domains (z scores) by vascular territory

4.5.2 Cognitive performance by OCSP Stroke Subtype

In examining differences in cognition by OCSP classification, a profile analysis was performed (Table 13) with OCSP categories as the grouping variable and z scores across the individual domains of the S-NAB, SDMT, CTMT and M-WCST as dependent variables (Figure 5). LACI cases had significantly better spatial scores compared to the other sub-types (estimate = 0.03, *p*-value = 0.0135). PACI cases had a small but significantly better CTMT scores (estimate =0.01, *p*-value = 0.0353). PACI cases had significantly lower attention scores compared to other classifications (estimate =-0.04, *p*-value =0.0122). POCI cases had significantly lower WCST scores (estimate =-0.09, *p*-value =0.0163). POCI cases had borderline statistically significantly lower CTMT scores (estimate =-0.01, *p*-value =0.0881) and memory (estimate = -0.03, *p*-value = 0.0712) compared to the other subtypes. Those with TACI produced significantly lower spatial scores compared to all the other subtypes (estimate =-0.04, *p*-value = 0.0306).

Table 13. Profile analysis of OCSP and cognitive domains

	OCSP		
LACI	**Estimate**	**SE**	***p*-value**
Intercept	-7.58	3.23	**0.0187**
SDMT	0.00	0.02	0.9123
WCST	0.06	0.04	0.1431
CTMT	0.00	0.01	0.4650
Attention	0.03	0.02	0.1005
Language	-0.02	0.02	0.3084
Memory	0.01	0.02	0.6801
Spatial	0.03	0.01	**0.0135**
Executive	-0.01	0.02	0.8002
PACI	**Estimate**	**SE**	***p*-value**
Intercept	-3.99	3.15	0.2054
SDMT	-0.04	0.02	0.1276
WCST	0.06	0.04	0.1326
CTMT	0.01	0.01	**0.0353**
Attention	-0.04	0.02	0.0122
Language	0.01	0.02	0.3783
Memory	0.02	0.02	0.2078
Spatial	-0.01	0.01	0.4632
Executive	0.00	0.02	0.8188
POCI	**Estimate**	**SE**	***p*-value**
Intercept	2.92	2.74	0.2868
SDMT	0.02	0.02	0.3255
WCST	-0.09	0.04	**0.0163**
CTMT	-0.01	0.01	*0.0881*
Attention	0.03	0.02	0.1301
Language	0.03	0.02	0.1120
Memory	-0.03	0.02	*0.0712*
Spatial	0.00	0.01	0.9737
Executive	0.00	0.02	0.9967
TACI/uncertain/unknown	**Estimate**	**SE**	***p*-value**
Intercept	2.49	3.36	0.4586
SDMT	0.02	0.03	0.5478
WCST	-0.01	0.04	0.8680
CTMT	0.00	0.01	0.6267
Attention	-0.01	0.02	0.7909
Language	-0.03	0.02	0.1123
Memory	0.01	0.02	0.6304
Spatial	-0.04	0.02	**0.0306**
Executive	0.01	0.03	0.7335

*** A univariate test was performed.** A value of $p<0.01$ represents statistical significance.

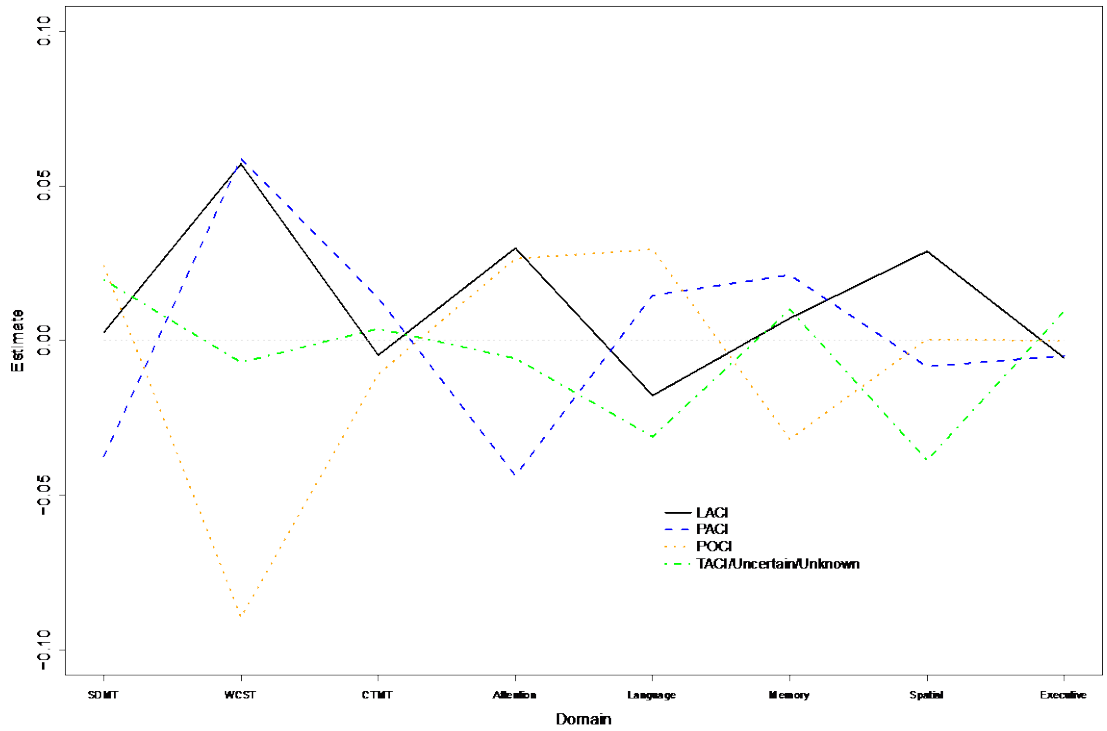

Figure 5. Performance on individual cognitive domains (z scores) by Oxfordshire stroke subtypes.

4.6 Discussion

This study profiled the demographic, stroke risk factor and cognitive characteristics of long-term stroke survivors. This study provided evidence of long-term cognitive impairment in a diverse population-based study, and identified factors associated with specific-domain related impairments. It is rare for population-based studies to examine specific cognitive profiles with long-term follow-up, usually reporting overall global cognitive impairment (Delavaran, Jonsson, et al., 2016; Douiri et al., 2013). Furthermore, this information provides more reliable estimates to the individual domains of cognition that remain affected in the long-term stages after stroke, and once identified can be targeted with cognitive rehabilitation.

At four-years after stroke, the majority (84%) of people with stroke experienced global cognitive impairment. This suggests that long-term cognitive impairment may be far more pervasive than previously reported in other population-based research. Overall, those who demonstrated lower mean MoCA scores tended to be older (>75), separated/divorced or widowed, retired and had not completed school and of Non-European ethnicity. Although the sample size for both Māori (n=13) and Pasifika (n=7) were small, consent rates were comparative to previous ARCOS studies (Feigin et al.,

2015). Additionally, age of stroke onset for Māori and Pasifika in this study was 56 and 57 years, respectively, which was considerably younger compared with Europeans (73 years). This is consistent with current national statistics reporting Māori and Pasifika groups experiencing stroke at a significantly younger age compared with Europeans (Ministry of Health, 2017). In terms of cognitive impairment, both, Māori and Pasifika had greater differences in overall mean MoCA (3 to 4 points lower) than Asians and Europeans. Similar results were found when examining the S-NAB, with Pasifika and Māori groups producing far lower scores on the total composite index score compared to European and Asians. While regression analysis found no significant relationships in terms of ethnicity, the overall lower MoCA scores highlight, that Māori and Pasifika people may be more affected by cognitive impairment long-term. Currently there is only limited available data on cognitive outcomes within the ethnically unique NZ population. For example: a 2016 study, examined neuropsychological outcome in NZ, one year after ischaemic stroke, but combined Māori, Pasifika and Asians as one group (Non-Europeans) for analysis due to small sample size (Barker-Collo et al., 2016). In a 2007 study, the same author examined cognitive profiles after ischaemic stroke, and although ethnicities were described consistent with this study, there was no mention of outcomes in terms of ethnicity (Barker-Collo, Feigin, Parag, et al., 2010). Considering there are significant ethnic disparities, in incidence in terms of age at onset and risk factors (Feigin et al., 2015; Ministry of Health, 2017), this relationship needs to be further explored in a larger data set.

Although the mean total index score on the S-NAB of 97, indicating overall cognitive function within the average range, it is important to consider that only 137 out of the 257 had the ability and capacity to complete the battery of tests. Generally, participants with a score of <18 (46%) on the MoCA did not complete the S-NAB battery. As demonstrated in regression analysis, older age was a significant predictor of failure to complete the S-NAB. Therefore, prevalence of the 137 participants who were assessed using the S-NAB may lead to underestimations. However, when examining the individual domains of the S-NAB, we found a different result, with a significant proportion of stroke survivors performing below average in domain specific tasks of the S-NAB. This was particularly true for tasks reliant on memory, attention, executive function and information processing speed. Persistence deficits in these domains are not uncommon, with deficits being reported up to 11 years post stroke (Nakling et al., 2017; Schaapsmeerders et al., 2013). A major observation is that there were differences in the

prevalence of cognitive deficits and domain-specific abilities among stroke subtypes, demographic groups and vascular territories, while no differences were reported between hemisphere and stroke location (subcortical and cortical).

Several studies have reported results that are consistent with this study (Barker-Collo et al., 2016; Hommel, Miguel, Naegele, Gonnet, & Jaillard, 2009; N. Karimian, K. Asgari, H. Neshat Doost, H. Oreizi, & M. Najafi, 2017; Middleton et al., 2014). For example, Jokinen and colleagues (2015), reported up to 50% of patients at 15 month follow-up were characterized with memory impairments than impairments in any other domains of cognition. However, a six-year follow-up study examining the trajectory of cognitive decline in 515 stroke survivors, found memory was not affected long-term (Levine et al., 2015). Determining the true prevalence of long-term memory impairment after stroke is further complicated by the influence of normal cognitive decline with increasing age and/or the lack of measuring pre-morbid cognitive function (Al-Qazzaz et al., 2014; Lo Coco et al., 2016). For example, faster memory decline before stroke has been shown to accelerate cognitive decline in older people after stroke (Rajan et al., 2014; Q. Wang et al., 2014).

Information processing speed was affected in the majority of this cohort. While there is considerable evidence that information processing speed is severely affected in the acute stage following stroke, (Ballard et al., 2003; Brand et al., 2014; Hurford et al., 2013) there is limited long-term data (> 1 year), which has examined the prevalence of impaired information processing speed (Barker-Collo et al., 2012; Narasimhalu et al., 2011). Despite its important contribution to cognitive function, the relationship between information processing speed and stroke remains ambiguous and largely un-investigated. This is further complicated by the fact that a number of processing speed measures require normal hand dexterity to facilitate performance (for example; the pegboard task). If motor performance is impaired this will affect reaction time in tasks which require a motor response (Low, Crewther, Ong, Perre, & Wijeratne, 2017). This is one advantage of using the SDMT, in that it includes both written and oral modalities and does not require normal hand dexterity (A. Smith, 1968). There has been some research into the effects of hemisphere lesion on information processing speed post stroke. Gerritsen and colleagues (2003), found adults with right hemisphere stroke performed worse on processing speed tasks compared to those with lesions in the left hemisphere (Gerritsen et al., 2003). However, in the current study no significant

differences were detected between hemisphere location and information processing speed.

A further complication is the contribution of natural ageing to processing speed. Collectively, slower processing speed is a phenomenon common to both older healthy people and those with neurological damage (Ebaid, Crewther, MacCalman, Brown, & Crewther, 2017; Manard, Carabin, Jaspar, & Collette, 2014). It is well known that information processing speed mediates the relationship between ageing and decline in other specific-domains of cognition. For example, several factors, proposed by Salthouse (1996) are thought to contribute to the relationship between processing speed, cognition and age: 1) limited time and 2) simultaneity. Salthouse suggested that as we age our ability to complete cognitive tasks in an allocated time frame diminishes, thereby reducing the amount of time available for later actions. Simultaneity occurs via a process by which slower processing speed leads to a displacement of previously presented information resulting in that information no longer being available for integrative higher-level processing (Salthouse, 1996). Thus, as we get older our ability to process information becomes slower, consequently disrupting a wide variety of cognitive abilities (Kerchner et al., 2012; Manard et al., 2014). Over 65% of this cohort was over the age of 65 and with no premorbid cognitive assessment, it makes it difficult to determine how much of results were confounded by ageing.

In this study it was important to identify those people with stroke who were most likely to suffer from ongoing cognitive deficits. Although males and females performed similarly on overall measures of global cognitive impairment, sex was a predictor of deficits in specific cognitive domains. Notably, males were more likely to have attentional and executive function deficits and greater impaired processing speed compared to females. In contrast, females were more likely than males to exhibit visuo-spatial impairments. Similar sex differences in attention, executive function and visuo-spatial task performance have been previously reported, with males out performing females in visuo-spatial tasks (Halpern, 2012; Kleinman et al., 2008) and females out performing males in attention and executive function tasks (Hua et al., 2014; Roivainen, 2011). However, Nakling and colleagues (2017), examination of 105 stroke patients found no differences in cognitive performance one year after stroke between males and females (Nakling et al., 2017).

Stroke survivors who were not employed were characterised by greater deficits in executive function compared to any other cognitive domain assessed in the current study. These findings were not surprising, with a number of studies reporting deficits in executive function significantly contributing to not working (Arauz, 2013; Kauranen et al., 2013; A. O'Brien & Wolf, 2010; Wang, Kapellusch, & Garg, 2014; Yeates et al., 2016). Considering executive function involves the orchestration and control of basic cognitive functions (planning, memory, problem solving, self-regulation), (Elliott, 2003), the ability to maintain certain vocational roles can be challenging and in some instances not sustainable (Y. Wang et al., 2014). Only a few studies have examined long-term executive dysfunction, with the consensus that persistent impairment is strongly associated with poor survival rates after stroke (Melkas et al., 2010; Wiberg, Kilander, Sundström, Byberg, & Lind, 2012). In a 14 year follow-up study of first ever stroke patients, poor performance in the Trail Making Test (TMT)-A at baseline was associated with post-stroke mortality (Wiberg et al., 2012). Likewise in a 12-year study, stroke patients with executive dysfunction had shorter survival rates than those with no executive dysfunction (6.4 versus 10.6 years) (Melkas et al., 2010).

Given the above, a plausible explanation for poor survival rates may be that when executive function is impaired, it has a detrimental effect on judgment abilities. For example, in a hospital-based study of War Veterans, Hinrichs and colleagues (2016), showed that intact executive functions were crucial for patients with brain injury for making appropriate decisions regarding their health and wellbeing. This suggests that executive functions play an important role in longevity and quality of life and therefore it is crucial to assess and manage executive deficits soon after stroke to mitigate longer-term adverse effects.

Those stroke survivors who were younger (aged <50 years) tended to experience more language impairment compared to older adults. This is in contrast to studies that have demonstrated associations between language impairment following stroke and older age (Gonzalez Mc et al., 2017; Naess, Hammersvik, & Skeie, 2009). Only a handful of studies have examined long-term language impairment in younger stroke patients with varying results. Cao et al, examined neuropsychological impairment in 40 ischaemic stroke patients aged 18 to 47 years and reported deficits in language and memory (Cao, Ferrari, Patella, Marra, & Rasura, 2007). Malmo et al, investigated cognitive impairment in 24 stroke patients aged 18 to 44 years at 12 months following stroke and found domains of working memory, information processing speed and cognitive

flexibility the most affected (Malm et al., 1998). Contrastingly, findings from a 2013 study in young (aged <50) adults with ischaemic stroke found below average performance in processing speed, attention and memory, 11 years after stroke, but no deficits in language (Schaapsmeerders et al., 2013).

Overall, there is very limited research which supports the current study's findings that language impairment is more prevalent in younger stroke patients, compared with other specific domains of cognition (Cao et al., 2007). One potential explanation for the difference between this study's results and the aforementioned studies, may be attributed to research design. For example, in comparison to this study the other studies were not population-based and comprised of small sample size (<100). This study was comparably larger, and was population-based, enabling the results to be inferred to a wider demographic than previous studies. Younger people with stroke tend to live longer with the effects of cognitive deficits, and language impairment is a major contributor to poorer long-term quality of life and the ability to return to work (Graham, Pereira, & Teasell, 2011; Kuluski, Dow, Locock, Lyons, & Lasserson, 2014; Lutski, Zucker, Shohat, & Tanne, 2017). Therefore, a better understanding of the factors which cause language impairment in younger stroke patients is needed. This will allow for the development of appropriate rehabilitation interventions, which either restore or compensate language deficits, to enable younger stroke survivors to adapt to living with long-term impairments.

This study also showed associations between stroke subtype, vascular territory and performance in specific cognitive domains. Those who were classified as having total anterior infarcts had the greatest cognitive impairment compared with the other subtypes, and also produced poorer scores on tasks of visuospatial functioning. This is congruent with previous research linking deficits in visuospatial ability to people with TACI (Barker-Collo et al., 2012). A five year follow-up reported adults with TACI performed significantly poorer on tasks requiring visual abstract reasoning compared to other domains of cognition (Barker-Collo et al., 2012). Those people with partial anterior infarcts, experienced greater deficits in the domain of attention which is comparable with prior research linking deficits in attention to anterior circulation regions (Tao, Liu, & Fisher, 2017). Those who had a LACI were more likely to have a language impairment compared to those who had POCI. This may be because the posterior vascular system is less definitively linked to language and executive tasks and more frequently causes visuospatial deficits, dysphagia and articulatory speech

difficulties (Tao et al., 2017; von Campe, Regli, & Bogousslavsky, 2003).

In fact, strokes in the posterior region (i.e.; POCI), resulted in less cognitive deterioration than the other OCSP classifications. This is in line with previous studies, and may indicate that strokes in posterior regions result in less disruption of brain areas involved in cognition (Kreiter et al., 2002). Additionally, people with strokes in the MCA territory were more likely to have language impairments compared with other vascular arteries. These results are consistent with recent findings (Rosemann, Brunner, Kastrup, & Fahle, 2017; W. Zhang et al., 2014). For example, Zhang and colleagues reported stroke which occurred in the MCA region were significantly correlated with language impairment ($p<0.05$) (W. Zhang et al., 2014).

4.7 Strengths and Limitations

The strengths of this study included the population-based study design, a reasonable sample size (n=257) and a broad cognitive test battery administered within a single study design. In addition, the long-term follow-up provided insight into the nature of long-term cognitive deficits which survivors of stroke continue to live with, well after their stroke event. Several limitations need to be acknowledged, first of all the inclusion of a control group would have strengthened the findings. A matched control sample, ideally would have undergone repeated assessments in order to define the size of any practice effects more precisely. However, this was not feasible within the time and financial constraints of this thesis. Second, an analysis of the individual tasks for each of the specific domains, such as digit span, block design, and cancellation tasks may have provided a more in-depth picture of cognition. Thirdly, loss to follow-up may have affected the results. For example, those who did not consent may have been more likely to have a greater disability, with a view that participation in research is more of a burden and less of a priority compared to their health. On the other hand, they may have fully recovered and therefore felt that they had nothing to contribute. This study presents one of the largest and most comprehensive studies assessing overall cognitive burden, profile and factors which affect domain-specific impairment in a post-stroke population. Like most observational studies, our findings may be limited for this reason and we identify that our study may not truly be representative of the stroke population.

4.8 Conclusion

To conclude, the pattern and prevalence of long-term cognitive impairment found in this study suggests that deficits are evident across most domains, rather than affecting one

specific domain. Male sex, older age, stroke subtype and vascular territory are the most dominant factors associated with impairment in specific cognitive domains. While ethnicity was not associated with specific domain impairments, Māori and Pasifika had lower scores on both cognitive assessments compared to Europeans. Additionally, the disparity in age between Māori, Pasifika and Europeans still reflects a 15-year difference in stroke onset. Given the projected increase in Māori, and Pasifika and the ageing population, as well as improved survival rates for people with stroke, it is crucial to implement effective cognitive rehabilitation and strategic planning for timely and targeted service provision to facilitate and promote cognitive recovery.

Chapter 5 Trajectory and Predictors of Long-Term Cognitive Impairment

5.1 Introduction

Stroke is common, costly and disabling. Globally, the epidemiological shift of disease burden towards long-term conditions such as stroke, means it is becoming increasingly important to understand the trajectory of these long-term outcomes. While people with language and hemi spatial neglect have improved recovery trajectories following stroke; for example, 95% of patients have almost full language recovery within 6 weeks of stroke, and within three months for hemi spatial neglect. Deficits that do not spontaneously resolve (i.e., cognitive deficits), contribute to the large number of patients requiring long-term care and management (i.e. rehabilitative therapy). Cognitive decline is a major cause of disability in stroke survivors, yet cognitive problems after stroke have received little attention. Further, stroke can expedite the onset of vascular dementia as well as accelerating already existing cognitive impairment. The onset of cognitive decline may become evident straight after the stroke event (Jacquin et al., 2014; Kalaria et al., 2016; Renjen et al., 2015), but quite often there is a delay in the development of cognitive deficits (Brainin et al., 2015). This delay can often be seen as a therapeutic time window for administering interventions in order to preserve cognition following stroke. Although it well recognised that stroke is associated with acute cognitive decline (Jacquin et al., 2014; Kalaria et al., 2016; Renjen et al., 2015), it is unknown whether stroke is related with decline over the long term. That is do stroke survivors have persistent decline years after the event?

A recent review suggested that stroke has a far more sinister effect on brain function compared with Alzheimer's Disease (AD) and therefore requires a more sustained approach to treatment (Gorelick et al., 2017). Current research of the trajectory of cognitive impairment has produced varying results, and as yet has failed to identify a consistent pattern of cognitive decline. Variability among studies is specifically related to design (Douven et al., 2016; Mellon et al., 2015), selection bias (Pendlebury et al., 2015) and poor choice of assessment tools (Nakling et al., 2017), with population-based studies yielding more consistent results (Barker-Collo, Feigin, Parag, et al., 2010; Barker-Collo et al., 2016; Barker-Collo et al., 2012; Crichton et al., 2016; Delavaran, Jonsson, et al., 2016).

For example, the long-term course of cognitive impairment after stroke may be underestimated due to selection bias in non-population-based research (Pendlebury et al., 2015). Often, patients with severe strokes and who experience aphasias are unable to complete cognitive assessments, therefore have to be excluded (e.g.; hospital-based studies (Pendlebury et al., 2015). The use of poor screening tools such as the Mini Mental State Examination (MMSE) to assess post-stroke cognitive function (which cannot detect mild cognitive impairment or assess executive function) (Pendlebury et al., 2010), and loss to follow-up, also likely contribute to the underestimation (Pendlebury et al., 2015).

The Lund Stroke Register Study (SLUR) examined cognitive impairment in ten-year follow-stroke survivors and showed that the odds of having severe cognitive impairment was higher among survivors of stroke compared to controls (Delavaran, Lövkvist, et al., 2016). The South London Stroke Register (SLSR) study examined long-term cognitive outcomes over a fifteen-year period. Prevalence rates for cognitive impairment at three years post stroke was reported at 32% (Patel et al., 2003), with cognitive impairment fluctuating up to the eight year time point, then steadily increasing at ten year follow-up (Wolfe et al., 2011). At the fifteen-year follow-up, prevalence of cognitive impairment was 30% (Crichton et al., 2016). It has been well documented that the MMSE is not sensitive enough as a cognitive screening tool to detect post stroke cognitive impairment (Y Dong et al., 2016; Pendlebury et al., 2010; Pendlebury et al., 2012), therefore the prevalence rates reported in both studies may have been under-estimated due to the use of the MMSE.

In comparison, other studies have shown that cognitive impairment following stroke does not necessarily decline over time and remains stable. For instance; A 2005 study, reported no changes in cognitive impairment two years following stroke (del Ser et al., 2005). While, a more recent population-based study reported improvements in cognitive functioning up to six months after onset of event, and found no further decline between six and 12 months (Barker-Collo et al., 2016).

The natural long-term (>12 months) course of cognitive deficits, and/or their relationship with other stroke-related, functional, psychological, clinical and socio-demographic outcomes is not well established. Risk factors and contributors to declining cognition post stroke include; older age (Chen et al., 2016), lower educational levels (Mirza et al., 2016), stroke location (Turunen et al., 2013), hemisphere (Mutai,

Furukawa, Houri, Suzuki, & Hanihara, 2017), vascular comorbidities (F Arba et al., 2017; Muela et al., 2017), and recurrent stroke (Kalaria et al., 2016). Additionally, 10% of stroke survivors will go on to develop dementia after their first stroke and over one third after recurrent stroke (Pendlebury & Rothwell, 2009). A 2016 study found baseline depression associated with cognitive deficits a year post stroke (Barker-Collo et al., 2016). Whereas, another study reported a diagnosis of previous cognitive impairment and older age, predictors of cognitive decline two years after stroke (del Ser et al., 2005). Alexandrova and colleagues, reported a history of diabetes mellitus, and being female associated with cognitive decline in the first year after stroke (Alexandrova & Danovska, 2016). Functional disability at baseline (measured by the mRS) was shown to be significantly associated with cognitive impairment six years after stroke in a cohort of young stroke survivors (Huang, Yang, & Jia, 2015). Evidence from the longitudinal Framingham Heart Study (Weinstein et al., 2014b), highlighted the influence of vascular risk (including hypertension, arrhythmia's, hypercholesterolemia and diabetes mellitus) factors on cognitive decline among a cohort of young stroke survivors (40 years on average), thus reinforcing the need for timely detection, stratification of risk factors and tailored interventions.

Variability in the range of baseline predictors selected among studies has resulted in a lack of consensus as to which factors truly influence the natural course of cognitive impairment (del Ser et al., 2005; Douven et al., 2017; Levine et al., 2015). Furthermore, there is a lack of longitudinal data greater than one year post stroke. A comprehensive range of baseline predictors is needed to more accurately determine predictors and trajectory of post stroke cognitive impairment. Therefore, the aim of this study was to evaluate the long-term course/trajectory and baseline predictors which influence cognitive decline. The overall hypothesis was that:

1) stroke-related risk factors and older age would contribute to persistent cognitive decline more than functional, psychological and stroke related factors
2) cognition will not recover but will continue to decline over time

5.2 Method

The sample and procedure have previously been described in the methods section in Chapter three (3.4, page 36). A brief overview of the MoCA and predictor variables will be described.

5.2.1 Cognitive Assessment

The MoCA was used to assess global cognition (Y Dong et al., 2010; Nasreddine et al., 2005). The MoCA has good psychometric properties and is a valid screening tool to detect cognitive impairment post-stroke (Burton & Tyson, 2015b). The MoCA is a pencil and paper test which takes 10 to 15 minutes to complete, with a total score of 30 points, and a cut off of ≤ 26 indicating cognitive impairment (Y Dong et al., 2010; Mai, Sposato, Rothwell, Hachiniski, et al., 2016; Pendlebury et al., 2012).

5.2.2 Potential Baseline Predictors

Covariate factors were measured at baseline and included demographics (age, gender, ethnicity, education level, marital status, and employment); stroke characteristics (OCSP classification, pathological subtype, vascular territory, lesion location, hemisphere); and stroke-related risk factors (hypertension, myocardial infarction, coronary artery disease, arrhythmia, hypercholesterolemia, and diabetes). Outcome measures collected at baseline and/or follow-ups included: clinical (Modified Rankin Scale), functional (Barthel Index), fatigue (Fatigue Visual Analogue Scale), mood (Hospital and Anxiety Scale), and cognition (MoCA). Diagnostic criteria for these covariates have been previously reported in the methods section: Chapter Three of this thesis.

5.2.3 Statistical Analyses

A general linear mixed-effects model was used to investigate changes in cognitive performance accounting for per-individual trajectories over the 5 follow-up time points. A univariate logistic repeated measures regression model was used to compare the trajectory of good outcomes (i.e., MoCA ≥26) vs. cognitively impaired (poor) MoCA (i.e., MoCA <26) **over time** to identify relevant time important statistical associations. For the purpose of this thesis we chose to analyse the MoCA as a binary variable (see Chapter Three, page 51) as it was more clinically relevant compared to analysing MoCA as a continuous variable. The effect of the continuous MoCA over time is reported in text. Demographic and stroke characteristics listed in Table 3 (Chapter three), comprised baseline covariates selected for the regression analyses to determine statistically significant predictors of long-term cognitive impairment ($p<0.05$). Significant predictors of cognitive functioning were retained in the multivariate logistic repeated measures regression models.

Covariates were considered as significant predictors, and retained in the multivariate logistic repeated measures regression model if p<0.10.

5.3 Results

Descriptive information for all participants has been previously described in Chapter Four Table 5. Mean age at four years was 71.2 ± 13.5 years. Age ranged from 28 years to 95 years.

5.3.1 Prevalence and Trajectory of Cognitive Impairment Post-Stroke

At four years post-stroke, a significant proportion of stroke survivors had global cognitive impairment assessed by the MoCA (MoCA < 26; N=216; 84%; *M*=19.5), compared to 41_stroke survivors who performed within the normal range (MoCA ≥ 26; 16%, *M* = 26.7). The number of the follow-up cases who completed MoCA at baseline was n= 113 (44%, *M* = 22.9 ± 4.55), 28 days N=179 (70%, *M* = 24.4 ± 3.84), six months n=194 (76%, *M* = 24.8 ± 3.7), 12 months, n=211 (82%, *M* = 24.7± 3.89), and four years n=257 (100%, *M* = 20.7, ± 4.70). Over 48 months, stroke survivors experienced a significant decline in global cognition, with total MoCA scores significantly decreasing (p<0.0001). In the time post-stroke, total MoCA scores increased by 0.85 points at 1-month (*p*-value = 0.953), by 1.26 points by 6-months (*p*-value = 0.0134), by 0.98 points by 12-months (*p*-value = 0.0488) but significantly declined by 2.8 points by 48-months (p<0.0001) compared to baseline.

5.3.2 Predictors of Long-term Cognitive Impairment

Univariate analysis (Table 14) identified that those aged over 75 years at the time of their stroke were 13.4 times likely to be cognitively impaired compared to someone aged ≤50 years at stroke onset (*p*<0.0001). Males were 2.5 times (95% CI 1.2-5.2) more likely to be cognitively impaired than females (*p*-value = 0.0171), whilst being single increased the odds of long-term cognitive impairment by 4.6 (95% CI 2.3-9.3, p<0.0001), being unemployed increased your odds of cognitive impairment by 13 (95% CI 5.1-33.4 p<0.0001), whereas individuals were more likely to be cognitively normal at four years if they completed school (*p*-value = 0.0293) or a post-school qualification (p<0.0001) compared to those who did not complete high school. The same set of statistically significant predictors of cognitive impairment where observed when analysing the MOCA as a continuous score (from 0 to 30 points) (Appendices Q and R).

There was a borderline significant result for SAH stroke survivors (*p*-value = 0.0931), with cognition improving over the four-year time period. All vascular risk factors were associated with cognitive impairment; the odds of being cognitively impaired at four years increased by 1.35 for those with high cholesterol, and 1.4 with hypertension although cholesterol and hypertension were not statistically significant. Having coronary heart disease was statistically significantly associated with increased odds of poor long-term cognitive impairment (OR=2.96, 95% CI 1.35-6.49, p=0.0070), as was arrhythmia (OR=2.21, 95% CI 1.07-4.57, p=0.0317) and diabetes mellitus (OR=1.14, 95% CI 1.02-1.28, p=0.0255).

Table 14. Results from univariate logistic regression repeated measures analyses identifying predictors of poor MoCA outcomes

Variable	**Intercept**	**OR**	**95% CI**		***p*-value**
Intercept		0.30	0.05	1.92	0.2040
Age at event		1.07	1.04	1.10	<0.0001
Time		0.90	0.71	1.15	0.4005
Intercept		6.33	1.75	22.93	0.0049
	51-64	2.70	0.77	9.50	0.1222
Age group	65-74	4.49	1.33	15.16	0.0155
	75+	13.43	4.11	43.93	<0.0001
Time		0.93	0.72	1.20	0.5771
Intercept		27.97	8.60	90.97	<0.0001
Sex	Male	2.46	1.17	5.16	0.0171
Time		0.88	0.65	1.20	0.4304
Intercept		29.29	9.02	95.07	<0.0001
Ethnicity	Non-European	1.48	0.62	3.49	0.3749
Time		0.99	0.72	1.36	0.9491
Intercept		13.72	4.91	38.29	<0.0001
Marital Status	Never married/Separated/ divorced/widowed	4.62	2.29	9.30	<0.0001
Time		0.98	0.75	1.29	0.9049
Intercept		4.36	1.43	13.32	0.0098
Employment status	Unemployed/Retired	13.09	5.13	33.45	<0.0001
Time		0.89	0.71	1.13	0.3410
Intercept		9.70	3.20	29.43	0.0001
Time since stroke		1.06	0.84	1.33	0.6378
Time		1.00	0.80	1.26	0.9840

Variable	Intercept	OR	95% CI		*p*-value
Intercept		140.22	36.94	532.34	<0.0001
Education	Completed school	0.32	0.12	0.89	0.0293
	Post-school qualification	0.14	0.06	0.32	<0.0001
Time		0.88	0.67	1.16	0.3541
Intercept		25.01	7.87	79.41	<0.0001
Recurrent stroke	Yes	2.20	0.90	5.39	0.0843
Time		1.02	0.74	1.39	0.9246
Intercept		48.39	13.45	174.06	<0.0001
Stroke Type	ICH	0.37	0.08	1.65	0.1919
	SAH	0.28	0.06	1.23	0.0925
Time		0.90	0.66	1.24	0.5217
Intercept		50.37	13.65	185.91	<0.0001
Stroke Type	HS vs. IS	0.32	0.10	0.98	0.0458
Time		0.90	0.66	1.24	0.5193
Intercept		22.19	6.48	75.98	<0.0001
Stroke OCSP	PACI	1.64	0.65	4.17	0.2969
	POCI	0.72	0.25	2.08	0.5486
	TACI/Uncertain/Unknown	1.57	0.52	4.74	0.4217
Time		1.07	0.76	1.51	0.7077
Intercept		36.83	11.33	119.79	<0.0001
Stroke hemisphere	Right	0.75	0.35	1.58	0.4437
	Brainstem/Uncertain	0.20	0.05	0.74	0.0159
Time		1.03	0.76	1.39	0.8378

Variable	Intercept	OR	95% CI		*p*-value
Intercept		38.62	12.32	121.10	<0.0001
Stroke Vascular territory	PCA	0.63	0.24	1.63	0.3375
	PICA	0.64	0.20	2.04	0.4538
	ACA/ Unknown	0.26	0.09	0.76	0.0141
Time		1.01	0.74	1.38	0.9687
Intercept		31.28	8.94	109.45	<0.0001
Stroke region	Cortical	1.02	0.44	2.37	0.9553
	Unknown	1.00	0.37	2.66	0.9973
Time		1.00	0.72	1.38	0.9781
Intercept		7.20	3.20	16.21	<0.0001
High Cholesterol	Yes	1.35	0.73	2.50	0.3326
Time		0.99	0.81	1.21	0.8941
Intercept		7.00	2.98	16.45	<0.0001
Hypertension	Yes	1.43	0.76	2.71	0.2669
Time		0.98	0.80	1.21	0.8790
Intercept		2.24	2.13	2.35	<0.0001
Diabetes	Yes	1.14	1.02	1.28	0.0255
Time		0.96	0.79	1.18	0.7191
Intercept		7.19	3.49	14.81	<0.0001
Coronary heart disease	Yes	2.96	1.35	6.49	0.0070
Time		0.97	0.80	1.19	0.7998
Intercept		7.51	3.58	15.78	<0.0001
Arrhythmia	Yes	2.21	1.07	4.57	0.0317
Time		0.97	0.79	1.19	0.7727

Variable	Intercept	OR	95% CI		*p*-value
Intercept		2.00	1.74	2.29	**<0.0001**
mRS Baseline		1.05	0.99	1.11	0.1092
Intercept		2.08	1.78	2.44	**<0.0001**
Fatigue Visual Analogue Scale		1.00	1.00	1.00	0.2795
Intercept		3.30	2.38	4.59	**<0.0001**
Barthel Baseline		0.98	0.96	1.00	**0.0140**
Intercept		2.21	1.95	2.51	**<0.0001**
HADS Anxiety		0.99	0.97	1.01	0.5860
Intercept		2.09	1.81	2.42	**<0.0001**
HADS Depression		1.00	0.98	1.03	0.7745
Intercept		5.49	3.76	8.01	**<0.0001**
MoCA Baseline		0.96	0.94	0.98	**<0.0001**

***** *A value of p<0.01 represents statistical significance*

Note: ISC=*ischaemic* stroke, ICH=intracerebral haemorrhage, SAH=subarachnoid haemorrhage,
LACI=lacunar infarct, PACI=partial anterior circulation infarct, POCI=posterior circulation infarct,
TACI= total anterior circulation infarct, MCA= middle cerebral artery, PCA=posterior cerebral artery,
PICA=posterior inferior cerebellar artery, ACA=anterior cerebral artery, mRS=Modified Rankin Scale,
HADS=Hospital Anxiety and Depression Scale, MoCA=Montreal Cognitive Assessment Scale.

Significant predictors of poor MoCA outcomes from the univariate analyses (Table 13 p<0.10) were entered into the multivariate analyses. Those variables that remained statistically significant at p<0.10 were retained in the final model and are presented in Table 15. Cognitive impairment was associated with males (OR = 2.9, 95% CI: 1.6-5.9); not in a relationship (OR=2.8, 95% CI: 1.4-5.5); and not working (OR=4.9, 95% CI: 1.9-12.1). Normal cognition was associated with completing high school (p=0.0413) or a post-school qualification (p=0.0001). Older age was predictive of poor MoCA and higher education levels were predictive of higher MoCA four years post-stroke. Cognitive improvement showed a trend of increasing over time (OR =0.8; 95% CI 0.7-1.0, p=0.0614), although this did not reach statistical significance. Cognitive impairment at baseline was significantly associated with declining cognition (OR =1.0; 95% CI 0.9-1.0, p=0.0001).

Table 15. Multivariate MoCA logistic regression. Predictors of progression of Global Cognitive Decline

Variable	**Category**	**OR**	**95% CI**		***p*-value**
	Intercept	5.61	1.42	22.07	0.0137
	51-64	1.77	0.59	5.27	0.3084
Age	65-74	1.45	0.47	4.47	0.5195
	75+	2.69	0.84	8.60	**0.0959**
Gender	Male	2.95	1.55	5.62	**0.0010**
Marital status	Never married/ Separated/divorced/widowed	2.76	1.39	5.47	**0.0036**
Employment status	Unemployed/Retired	4.85	1.95	12.06	**0.0007**
Education	Completed school	0.37	0.15	0.96	**0.0413**
	Post-school qualification	0.20	0.09	0.44	**0.0001**
Time		0.83	0.68	1.01	**0.0614**
MoCA	At Baseline	0.96	0.94	0.98	**0.0001**

***A multivariate test was performed.** A value of p<0.01 represents statistical significance.

5.4 Discussion

This study examined the baseline predictors and trajectory of cognitive impairment in a four-year population-based cohort of stroke survivors, using a commonly administered psychometric screening measure to assess global cognition. Findings from this study indicate global cognitive impairment continuing 1- year post-stroke onset and onwards. Socio-demographic, baseline cognitive impairment and stroke-related factors were associated with the greatest decline.

These findings are concordant with previous longitudinal research (Crichton et al., 2016; Levine et al., 2015), which have tracked post stroke cognitive impairment over multiple time-points. For example; the SLSR study examined cognitive impairment at 3 months, 1, 5, 10 and 15 years after stroke. Age-standardized prevalence of cognitive impairment ranged from 24% at 3 months, 22% at 5 years, 18% at 10 years and 22% at 15 years post stroke event (Douiri et al., 2013). At 3 months post stroke, cognition improved and then remained stable up to 15 years post stroke. However, the SLSR study used the Mini Mental State Examination (MMSE) to assess cognition. This tool has been shown to not be as sensitive as other measures in detecting cognitive impairment (Y Dong et al., 2010), therefore prevalence rates may have been underestimated. By comparison, our results showed cognition improving within the first 12-months, but then steadily deteriorated.

This study also found baseline cognitive impairment was associated with cognitive decline. Similar findings were reported in a prospective cohort study of 1369 stroke patients, where baseline cognitive impairment was associated with low MMSE scores <24 at 3.8 years after stroke (Rist et al., 2013a). However, these results should be interpreted with caution, as pre-morbid cognitive function was not assessed and this may have likely contributed to further decline.

In the present study, a major observation with our results was the influence of socio-demographic and stroke-related risk factors on long-term cognitive decline, with those who were male, aged >75, single/divorced or widowed, and not working more likely to have persistent declining cognition. Older age (greater than 75) is an accepted predictor of cognitive impairment following stroke (Akinyemi et al., 2014; T. Yang, Sun, Lu, Leak, & Zhang, 2017), but also confounded by other factors including pre-stroke cognitive impairment, hypertension, atrial fibrillation, diabetes and loneliness (Tilvis et al., 2004). Sex differences in post stroke cognitive impairment have been reported in other studies (Renjen et al., 2015), with males more likely to experience higher rates of age-related cognitive decline and memory impairment compared to females (Cho et al., 2014; Renjen et al., 2015). One explanation for this may be that males tend to be more susceptible to long-term cognitive impairment due to higher rates of vascular risk factors such as hypertension. For example, some data has shown that men with high systolic blood pressure have lower frontal lobe volumes (atrophy) resulting in poorer cognitive functioning, independent of age and other medical co-morbidities (Gianaros, Greer, Ryan, & Jennings, 2006; Jennings et al., 2017).

Consistent with previous research, stroke survivors who were single/widowed or divorced were significantly more likely to have persistent cognitive decline (Qu et al., 2015; Y. Wang et al., 2014; M. Wu, Lan, Chen, Chiu, & Lan, 2011). Increased loneliness and social isolation following a stroke can have detrimental effects on cognitive functioning and predicts well-being, especially in older persons (Ellwardt, Aartsen, Deeg, & Steverink, 2013; Mukherjee, Levin, & Heller, 2006). Of interest, social and emotional support following a stroke has been shown to act as a protective factor which may preserve cognitive functioning and buffer the effects of injury to the brain (Glymour, Weuve, Fay, Glass, & Berkman, 2008). Stroke survivors who are exposed to greater social support have better cognitive outcomes than those with the least support, with companionship mitigating the effects of disability, depression, increasing self-efficacy and promoting cognitive resilience (Volz, Möbus, Letsch, & Werheid, 2016).

Those stroke survivors who were not employed experienced persistent cognitive impairment. Several studies have shown that up to half of stroke survivors lose their ability to return to prior employment, contributing to the overall burden of stroke, especially in terms of the socioeconomic impact (Arauz, 2013; Hofgren, Bjorkdahl, Esbjornsson, & Sunnerhagen, 2007; Kauranen et al., 2013; Y. Wang et al., 2014). Employment has been shown to enhance cognition, through regular participation in cognitively demanding activities or tasks (Leist, Glymour, Mackenbach, van Lenthe, & Avendano, 2013). Time away from work following a stroke can predict later cognitive decline, due to the reduction in engaging in these activities. Additionally, employment is a significant contributor to social networking after stroke, (Vincent-Onabajo, Muhammad, Ali, & Masta, 2015) with failure to return to work resulting in isolation and negative health outcomes (Harris, 2014). Therefore, returning to work may mediate the relationship between social support and cognition. However, it is important to note, employment status prior to stroke was not known, and therefore causality cannot be inferred.

Contrary to previous reports which have shown recurrent stroke to be a major risk factor for cognitive decline (Pendlebury & Rothwell, 2009) we found no association. However, stroke-related risk factors including coronary artery disease, arrhythmia and diabetes mellitus were significantly associated with cognitive decline, these findings have been supported in other studies (Alexandrova & Danovska, 2016; Sahathevan, Brodtmann, & Donnan, 2012; Singh-Manoux et al., 2017). The role of heart disease and

progressive cognitive decline has been well documented (de Bruijn & Ikram, 2014; Marengoni, Qiu, Winblad, & Fratiglioni, 2011; Mohd Zulkifly et al., 2016). However, the association has not been consistent across studies. Further, is not clear whether cognitive impairment in the context of arrhythmia and heart disease is solely mediated through stroke or whether other factors are responsible (Kaffashian et al., 2013).

Hypertension at stroke onset, was independently associated with declining cognition over the four-year time period. Although the relationship between hypertension and impaired cognitive performance has been previously investigated in normal populations (Aronow, 2017; Iadecola et al., 2016; Muela et al., 2017; Tadic, Cuspidi, & Hering, 2016), there is limited research within stroke populations (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013; Sahathevan et al., 2012). This is further complicated by evidence which suggests hypertension may interact with diabetes to exacerbate cognitive decline (Kaffashian et al., 2011; Qiu & Fratiglioni, 2015). Therefore, further research needs to explore this relationship more in-depth.

An encouraging finding of this research was that stroke survivors who had a high level of education returned to normal cognitive functioning at 4 years post-stroke. This may be attributed to a higher cognitive reserve in those stroke survivors who have higher education levels and therefore higher tolerance to neurodegenerative pathology and cognitive decline (Mirza et al., 2016). It is also possible that those with higher levels of education had higher socioeconomic status, more access to resources, and financial support than those with lower education (Marshall et al., 2015).

Although this study found no statistical significant difference between pathological stroke types and declining cognition, there was a borderline significant result for SAH stroke survivors, with cognition improving over the four year time period. These results were surprising considering up to 50% of stroke patients experience persistent cognitive sequelae following SAH (Zweifel-Zehnder et al., 2015). Age is a contributing factor of poorer cognitive dysfunction following SAH, with significantly poorer outcomes after the age of sixty (le Roux & Wallace, 2010). As our SAH cohort had a mean age of 55, this may have contributed to improved cognition over time and the majority had returned to work. These findings are encouraging, but need to be viewed with caution owing to the small sample size of the SAH cohort (n=18).

Overall the findings from this longitudinal study demonstrated that companionship (having a partner versus being single or not married), working, and having a higher

education can improve cognition after stroke. A potential explanation for the variances in socio-demographic contributors of long-term cognitive decline following stroke is the theory of cognitive reserve (CR). Active stimulation of the brain throughout the life span, through social support, working and learning, strengthens cognitive reserve (MacPherson et al., 2017). After stroke CR can offset or compensate progressive cognitive decline (Willis & Hakim, 2013). Further, CR is influenced by education level, employment and exposure to enriched environments such as social participation. These factors may mitigate the effects of faster cognitive decline by having a protective role, with stroke survivors who have a higher cognitive reserve being more resilient to the effects of cognitive impairment (MacPherson et al., 2017).

5.5 Limitations and Strengths

Our study had several limitations, such as the lack of a control group-which would have strengthened the study and allowed comparisons of determinants to non- stroke people. The baseline sample size was less than half the size of the sample at four years, with participant numbers steadily increasing over time. There is a potential that the additional participants in later time points are somehow different in their demographic/stroke make up to baseline which may explain the changes in MoCA scores. We did not amend the MoCA score by adding an extra 1-point for those participants with less than 12 years education, which has been suggested in other studies (Horstmann et al., 2014). Pre-stroke cognitive status was not assessed in the parent study, therefore we could not determine pre-existing cognitive impairment prior to stroke. Other limitations include the use of a screening measure to assess cognition versus a comprehensive neuropsychological battery. Thus, we could only assess global cognition rather than specific domains of cognition which may have potentially yielded different results. The strengths of this study included the population-based design, good sample size and inclusion of an extensive range of baseline covariates, which have not been considered in previous population-based studies (Douiri et al., 2013; Levine et al., 2015).

5.6 Conclusion

This population-based study is one of the few which has provided evidence that cognitive impairment following stroke does not resolve and/or remain stable but changes over time. However, an important finding was that cognitive recovery was possible for some people within the first year following the stroke, but declined from

this time point on. This is a crucial finding, as it means there may be a window of opportunity to intensify cognitive rehabilitation within the first year for those who are more at risk. Socio-demographic and stroke-related risk factors play an important role in the progression of cognitive deterioration following stroke. While some of these factors can be modified (through primary prevention strategies), others are more complex and require further research. Although the relationship between cognitive decline and stroke remains complex, maintaining active stimulation of the brain throughout the life span, to increase brain resilience may mitigate the effects of faster cognitive decline by having a protective role. Moreover, engaging in early cognitive rehabilitation could accelerate, potentiate and enhance cognitive recovery. From a clinical perspective survivors of stroke need to have regular cognitive assessments in order to ensure that cognitive decline is noticed early on. Known risk factors which have been identified in this study which are associated with cognitive decline, could be incorporated into risk scores to ensure prompt detection of post stroke cognitive decline. Recommendations for rehabilitation should include interventions which use a more holistic multidimensional approach to facilitate health and wellbeing in order to optimize, maintain and/or restore brain health, to mitigate further progression of cognitive decline following a stroke.

Chapter 6 Cognitive Assessment in Stroke: The Accuracy of a Screening Tool to Detect Persistent Domain-Specific Cognitive Impairment in Stroke Patients

6.1 Introduction

Targeting ways to improve and/or manage changes in cognition, has been identified as the number one research priority for people with stroke, caregivers and health professionals (Pollock, St George, Fenton, & Firkins, 2012, 2014). A first step in the management of post stroke cognitive impairment is to detect and diagnose the problem; given that identification and monitoring of cognitive changes can reveal specific patterns of dysfunction and track the course of cognitive recovery through-out the stroke journey (Burton & Tyson, 2015b; Jaillard et al., 2010; Lees et al., 2017). However, cognitive dysfunction is left undiagnosed in a significant number of cases, as assessment is not routinely carried out in clinical settings (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009; McDonnell et al., 2011; R Stolwyk, 2016).

While comprehensive neuropsychological testing has previously been the gold standard method to detect and characterize domain specific impairment (R Stolwyk, 2016), they are often considered too lengthy, impractical, expensive and require specialist administration. For instance, neuropsychological testing often takes more than one session to administer, for some patients experiencing severe symptoms post stroke this is often not feasible nor appropriate (de Vries et al., 2017; Hinkle et al., 2017; Nakling et al., 2017). For example; a comprehensive neuropsychological assessment can require two to three sessions to complete and often three to four hours to administer per session (de Koning, 2009). Moreover, comprehensive neuropsychological assessment often requires trained neuropsychologists, who do not routinely see all patients (Han et al., 2014; Quinn, Elliott, & Langhorne, 2018). In most clinical settings assessment is often underutilized; due to no standardized method of assessment (Burton & Tyson, 2015b; Burton, Tyson, & McGovern, 2013; R Stolwyk, 2016). A systematic review of cognitive assessment following stroke revealed only 6% (488 out of 8826) of studies included cognitive assessment (Lees, Fearon, Harrison, Broomfield, & Quinn, 2012). Additionally, assessment tools were highly variable, with 367 different measures among studies. In reality, the lack of resources and training available to health professionals to conduct a comprehensive assessment is a common situation, and therefore they can only perform assessments which require minimal time and training.

In an attempt to improve the detection of cognitive deficits, and mitigate the expense, practicality and often burden on patients, national stroke clinical guidelines now recommend the use of cognitive screening tools for all patients prior to discharge (see Figure 6) (Hebert et al., 2016; Intercollegiate Stroke Working Party, 2016; NHS Improvement, 2016; Ntaios et al., 2015; Powers et al., 2018; Stroke Foundation, 2017).

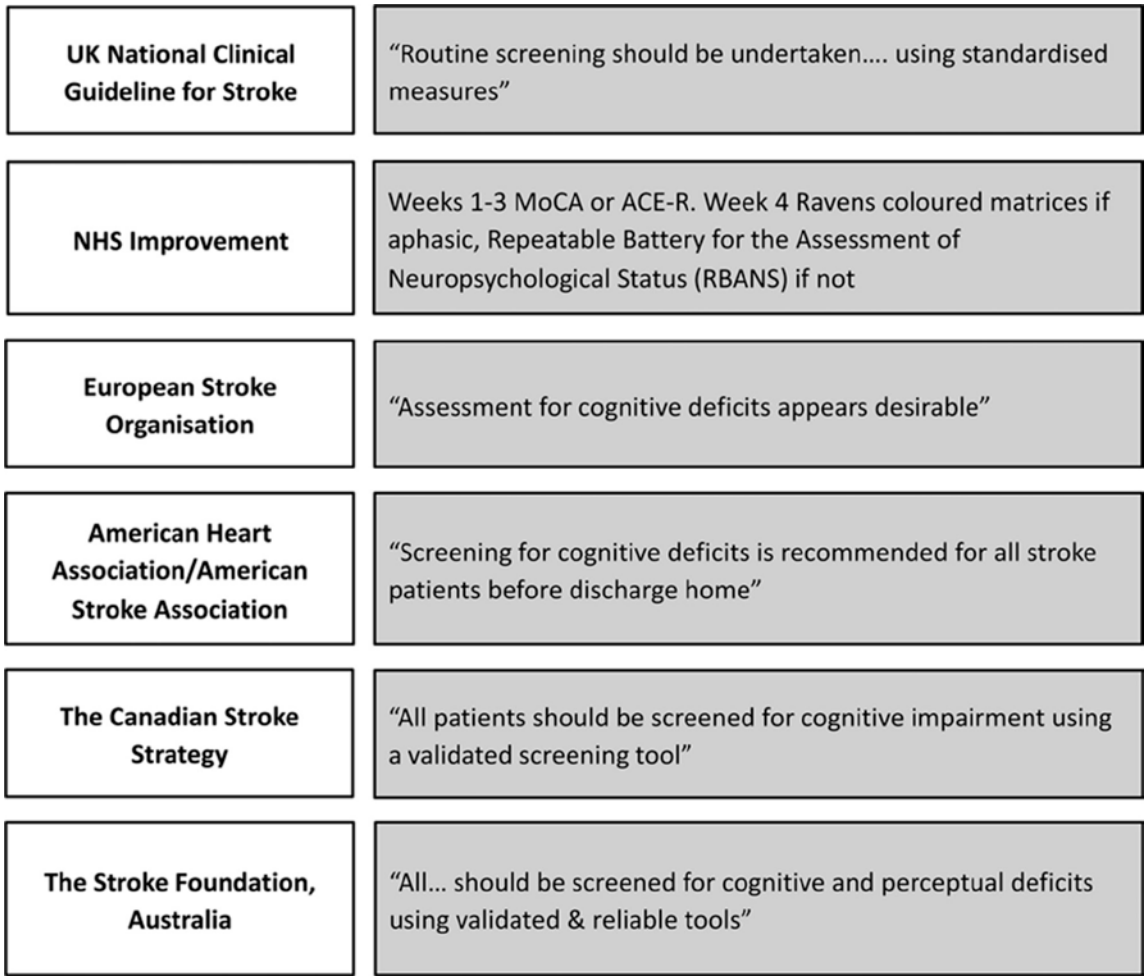

Figure 6. National clinical guidelines on cognitive assessment in stroke.
ACE-R indicates Addenbrookes Cognitive Assessment Revised.
Note: Reprinted from *Cognitive and Mood Assessment Tools for Use in Stroke* (p 2), by Quinn, Elliot & Langhorne, 2018, Glasgow, United Kingdom. Copyright (2018) by Wolters Kluwer Health, Inc. Reprinted with permission (Appendix P) (Quinn et al., 2018)

The Montreal Cognitive Assessment (MoCA) is one the most extensively used screening tools to detect mild to moderate cognitive impairment in patients with stroke (Chiti & Pantoni, 2014; Nasreddine et al., 2005). The MoCA sub-sections assess, attention, language, executive functioning, visuospatial ability and memory and are similar to those in more comprehensive neuropsychological batteries (Waldron-Perrine & Axelrod, 2012). Compared with another widely used screening tool; the Mini Mental Status Examination (MMSE), the MoCA has consistently demonstrated its superiority, due to its higher sensitivity to detect executive dysfunction (Fu et al., 2017; Mai,

Sposato, Rothwell, Hachiniski, et al., 2016; Markwick et al., 2012; O'Driscoll & Shaikh, 2017; Pendlebury et al., 2010; Salvadori et al., 2013). The MoCA has also shown dominance as a global screening tool compared to other brief measures (Y Dong et al., 2016) and a good predictor of cognitive and functional outcomes post-stroke (Toglia et al., 2017; Toglia et al., 2011). Toglia and colleagues (2011), reported lower sub-scores on visuo-executive items on the MoCA were associated with fewer decreased functional gains in self-care and mobility (Toglia et al., 2011).

Several studies have questioned the reliability of the MoCA to detect global and domain specific post stroke cognitive impairment. For example; a 2016 study reported the MoCA was less sensitive compared with the Oxford Cognitive Screen (OCS), 78% versus 86% respectively (Demeyere et al., 2016). Another study found the MoCA underestimated memory in acute stroke survivors when compared with a comprehensive battery (Chan et al., 2014). A more recent study by the same authors reported the MoCA had poor sensitivity to detect executive and attention deficits patients with right hemisphere lesions (Chan et al., 2017). However, these findings are debatable as the authors did not calculate the sub-domains as recommended by published criteria (Nasreddine et al., 2005), therefore there is some ambiguity surrounding these results. For example; visuo-spatial and executive domains were added together, instead of being calculated separately, therefore reducing sensitivity.

The extent to which overall cognitive performance on the MoCA relates to cognitive performance using a more comprehensive neuropsychological battery has been previously examined, providing evidence of good convergent and criterion validity and comparable constructs as those measured by a more detailed battery (Brenkel, Shulman, Hazan, Herrmann, & Owen, 2017; Lam et al., 2013; R. Paul et al., 2011; Shopin et al., 2013; Tan et al., 2017; Vogel et al., 2015). Earlier studies have compared the sensitivity and specificity of the overall MoCA score to impaired performance on a neuropsychological battery and reported good concurrent validity for the MoCA (Godefroy et al., 2011; Markwick et al., 2012). However, it is unclear how sensitive and specific the MoCA is at classifying impairment within individual domains due to the paucity of available data (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015). Currently, the MoCA is used to assess global cognitive impairment and not by specific domains of cognition. Considering that acute inpatient, outpatient and community rehabilitation services are often under resourced and do not have access to/or the appropriate training to administer a comprehensive neuropsychological battery,

there would be benefit in knowing the reliability of the MoCA subsections to identify domain-specific impairments.

Recent stroke clinical guidelines for Australia and New Zealand (Stroke Foundation, 2017), emphasize the need to assess multiple domains of cognition following stroke. Specifically, prompt detection of cognitive sub-domains is crucial as it can provide valuable prognostic information and assist in planning over the course of cognitive recovery. The effectiveness and quality of rehabilitation programmes, can be facilitated by short generalized global screening tools, which can accurately predict global cognitive impairment and domain-specific impairments for people with stroke. The purpose of this study was to determine the predictive value of the MoCA and sub-domains (determined by sensitivity and specificity) compared to a more in-depth comprehensive computerized neuropsychological battery in an existing cohort of stroke survivors. Detailed comparison may identify differences in the capacity of different psychometric measures to accurately detect cognitive deficits in stroke patients. Based on previous evidence it was hypothesized that:

1) The MoCA would demonstrate high sensitivity and specificity compared to a comprehensive neuropsychological battery
2) The sub-sections of the MoCA could accurately predict domain-specific impairment

6.2 Methods

6.2.1 Justification of using CNS-VS instead of S-NAB

Originally the analyses were to investigate the predictive validity of the MoCA against the S-NAB, however given the low specificity (see Table 16) CNS-VS is being used instead of S-NAB as a more comprehensive battery. As previously mentioned in chapter three, the CNS-VS was administered at baseline and/or 1, 6 and 12 month follow-up in the ARCOS-IV parent study. At the four-year follow-up, the CNS-VS was not used as the sample comprised of a large number of older participants (29% aged 65-74, and 42% aged >75). From the experience of the ARCOS-IV parent study, administering the CNS-VS was not feasible for this thesis, as there was low uptake of the computerized assessment tool in this sample. Therefore, we used the most-recent and largest sample available (collected at12-months) for the analyses here, comprised of MoCA (n=228) and CNS-VS (n=146).

Table 16. Sensitivity and Specificity results MoCA versus the S-NAB at 48 months Post Stroke

	AUC	Lower bound	Upper bound	*p*-value	Cut-off point MoCA [S-NAB]	Total points per section	Sensitivity %	Specificity %	PPV %	NPV %
Global	0.601	0.548	0.654	0.0386	≤26 [85]	30	96.6	23.6	29.6	95.4
Executive	0.636	0.597	0.674	0.9930	≤3 [73]	4	100.0	27.1	31.4	100.0
Visuospatial	0.602	0.568	0.637	0.9960	≤3 [74]	4	100.0	20.5	29.5	100.0
Memory	0.516	0.501	0.531	0.9940	≤4 [75]	5	100.0	3.1	25.6	100.0
Language	0.787	0.745	0.829	0.9960	≤4 [75]	5	100.0	57.5	43.9	100.0
Attention	0.623	0.522	0.725	0.0272	≤5 [74]	6	69.2	55.4	34.1	84.4

ROC, receiver operating characteristic, AUC, area under the curve, MoCA, Montreal Cognitive Assessment, S- NAB, screening module, neuropsychological assessment battery, SE, standard error, P, probability value, SEN, sensitivity, SPEC, specificity, PPV, positive predictive value, NPV, negative predictive value

6.2.2 Sample

The cohort for this study comprised of stroke survivors (Figure 7), drawn from the ARCOS-IV sample who agreed to be contacted. Full methods, including case ascertainment and ethical approval for the ARCOS-IV study have been previously described in Chapter Three of this thesis. Consented participants for this study completed cognitive assessments at baseline and/or 12 months post stroke.

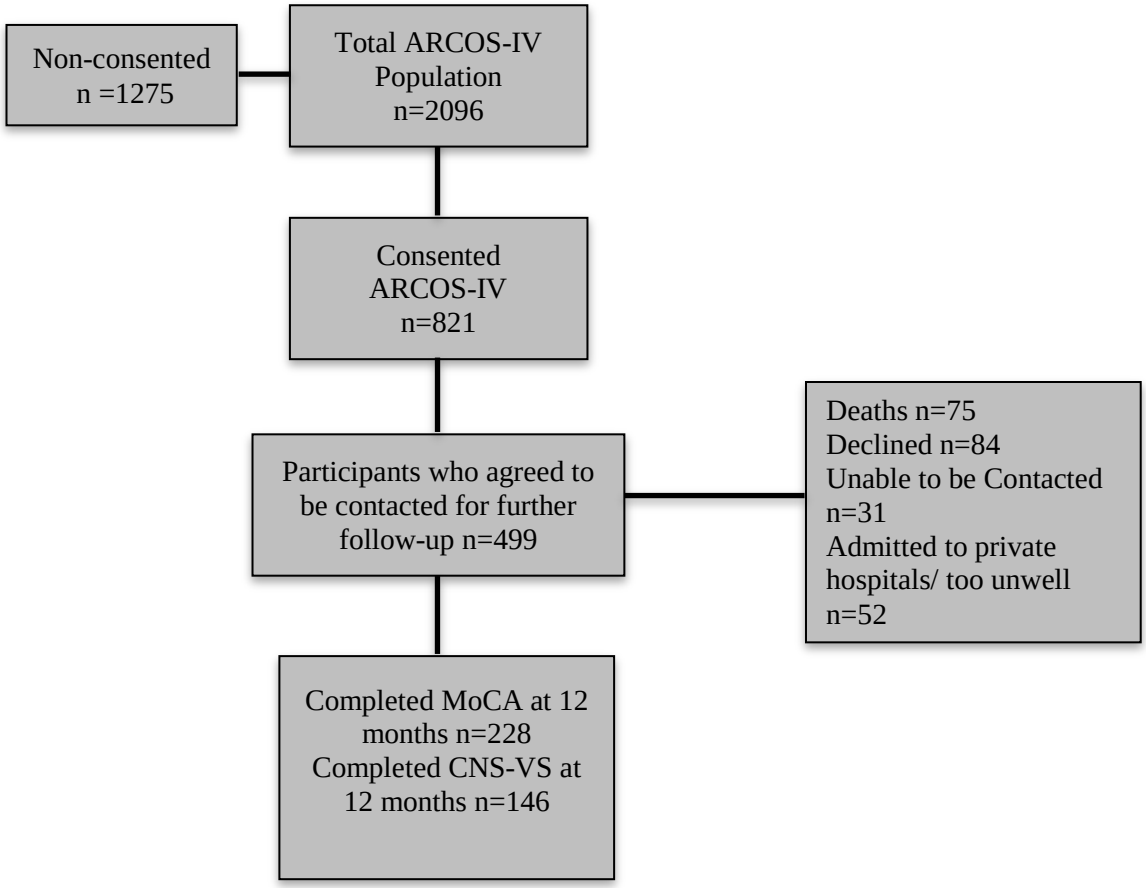

Figure 7. Flow Chart of Participant Recruitment

6.2.3 Procedure

Once written informed consent was obtained, face-to-face assessments were conducted at the participant's primary place of residence with the researcher. Two types of cognitive assessments were administered, a comprehensive computerised neuropsychological battery (CNS-VS) (N=146) and the MoCA (N=228). Previous time-points were examined (1 and 6 months) where participants had completed both cognitive assessments, however the 12 month time-point had the largest sample who had completed both the CNS-VS and MoCA, therefore this data was used for the sensitivity and specificity analysis. All baseline demographic and clinical stroke

characteristics were extracted from the ARCOS-IV database. Definitions for the cognitive measures have been previously described in Chapter Three, with the exception of the CNS-VS.

CNS-Vital Signs Test (CNS-VS)

The CNS-VS is a self-administered, computerised neuropsychological test for ages 8 to 89 (T. Gualtieri & L. Johnson, 2006; Gulatieri, Johnson, & Benedict, 2004). CNS-VS has been used to assess cognitive status in patients with traumatic brain injury (T. Gualtieri & Johnson, 2008), mild cognitive impairment (T. Gualtieri & Johnson, 2005) and stroke (Barker-Collo et al., 2016). The test takes approximately 45 minutes to administer, assesses memory (verbal, visual and working), reaction time, visuospatial ability, psychomotor speed, attention and executive functioning. Scoring is automatically and calculated by the computer programme. An overall individual performance score is generated (Neurocognitive Index) from the average of the five domain scores. Each of the domains scores has a normal distribution, with a mean of 100 and standard deviation of 10. Cut-off scores of <80 for each of the domains are considered low average (T. Gualtieri & L. Johnson, 2006). The CNS-VS has age-corrected normative data, ranging from 7 to 90 years, although a recent study suggested socio-demographic factors such as; gender and education should also be considered and performance based on solely on American normative data should be interpreted with caution (Rijnen et al., 2017).

6.3 Statistical Analysis

A sensitivity and specificity analysis was performed to determine if the MoCA was able to predict whether a participant had cognitive impairment in the corresponding sub-domains of a computerized neuropsychological battery (CNS-VS). Sensitivity was determined by the number of people with cognitive impairment who are correctly identified by the MoCA (referred to as poor) (Appendix R). In comparison, specificity was determined by the number of people who are correctly identified as not having any cognitive impairment by the MoCA (referred to as good) (Parikh, Mathai, Parikh, S, & Thomas, 2008). The analysis involved calculating the receiver operating characteristics (ROC) statistic and calculate area under the curve (AUC), positive predictive values (PPV) and negative predictive values (NPV).

The area under the curve (AUC) was calculated using a generalised logistic model (assessing how CNS-VS and MoCA are associated with each other), entering MoCA as

the dependent (predictor variable) and CNS-VS as the independent variable; i.e. determining how well MoCA is predictive of determining cognitive impairment in the corresponding sub-domains versus CNS-VS. Lower and upper bounds were generated through DeLong's Confidence Intervals for AUC (Verzani, 2014). Using the receiver operating characteristic (ROC) curve, we then determined the optimal cut off for diagnostic accuracy, sensitivity, and specificity of each subsection (Appendix Q). Data analysis for this study was conducted using Statistical Package R version 3.4.3 (Verzani, 2014). Sample size estimate: This study required approximately 228 participants to be powered at 80 % (alpha = 0.05) to assess if the MoCA is representative of the CNS-VS, given that the sensitivity of the MoCA to be around 70 % (Cumming, Churilov, et al., 2013) and the CNS around 80 % (Gulatieri et al., 2004).

6.4 Results

6.4.1 Descriptive Results

Table provides a summary of the demographic characteristic of the sample. Two hundred and twenty eight stroke survivors (mean age of 69.0 ± 13.5 years, ranging from 31-94 years) completed the MoCA at one year after stroke. 146 out of 228 completed the CNS-VS. Most of the sample were married (62%) and not working (75%). Recruited participants were mostly NZ European (80.5%), followed by Asian (11%), Maori (5%) and Pacific Island (2%). There were more males, n=122 (53.5%) compared to females n=106 (46.5%). Looking at stroke characteristics, the majority of the sample experienced ISC (87%), in sub cortical regions (60%). Using OCSP classification, there was a fairly even distribution of LACI (30%), PACI (30%) and POCI (28%) stroke sub-types, with fewer people having TACI's (5%). Slightly more people had right hemisphere strokes compared to left (47.4% versus 43.4%). Using the proposed cut-off score of ≤ 26 for the total MoCA, 64.5% of stroke survivors were cognitively impaired at one year. The mean score was 24.5 ± 4.18.

Table 17. Demographic and Stroke Characteristics of Sample at 12 month follow-up

Descriptive	N	%
Gender		
Female	106	46.5
Male	122	53.5
Ethnicity		
NZ European	207	91.0
Maori	11	4.8
Pacific People	5	2.2
Asian	5	2.0
Marital status		
Married, civil union or defacto	187	82.0
Never married/Not specified/ Separated, divorced, or widowed	85	37.3
Employment		
Employed	48	21.1
Not specified/ Retired/ Unemployed	180	78.9
Education Level		
Did not complete school	62	27.2
Completed school	49	21.5
Post-school qualification	117	53.1
Stroke Type		
IS	199	87.3
ICH	12	5.3
SAH	17	7.5
Stroke Sub-type		
LACI	68	29.8
PACI	69	30.3
POCI	63	27.6
TACI	11	4.8
Unknown	17	17.5
Hemisphere of Lesion		
Left	99	43.4
Right	108	47.4
Both/Brainstem/Uncertain	21	9.2

Descriptive	N	%
Stroke Vascular territory		
MCA	121	53.1
PCA	46	20.2
PICA	33	14.5
ACA	9	3.9
SCA	2	0.9
Unknown	17	7.5
Location of Lesion		
Cortical	60	26.3
Subcortical	137	60.1
Unknown	31	13.6
Medical co-morbidities		
High cholesterol	122	53.5%
Hypertension	150	65.8%
Diabetes	46	20.2%
Coronary heart disease present	48	21.1%
Arrhythmia present	57	22.0%
	Mean	**(SD)**
Age	69.1	(13.5)
Time since stroke	1.3	(0.23)

6.4.2 Comparison of the Predictive Accuracy of the MoCA and CNS-VS to Detect Global Impairment

ROC analysis was conducted to quantify the accuracy of the MoCA (Table 18) to determine if the stroke survivors had global cognitive impairment, and impairment in any of the five sub-domains; executive, visuospatial, memory, language and attention of the CNS-VS (Table 19). Using a cut-off of less than or equal to 26, for global cognitive impairment, we found an acceptable diagnostic accuracy (67%), level of sensitivity 68.2% and specificity 65.6%. At one year post stroke, the MoCA (≤ 26) identified more individuals as being cognitively impaired compared to the CNS-VS (<80) ($p = 0.001$). This is reflected with the low PPV (39.8%) and high NPV (86.1%) showing that the MoCA classifies many of the CNS-VS classed cognitively intact patients as cognitively impaired. This was observed consistently across all of the sub-domains (NPV ranging from 78.3% to 90.0%).

Table 18. Calculation of sensitivity and specificity

Reference		"True" CNS-VS	
"Predicted" MoCA		"Event" =Poor	"No Event" =Good
	"Event" = Poor	A	B
	"No Event" = Good	C	D

Sensitivity = A/ (A+C) *Specificity* = D/ (B+D)

6.4.3 Comparison of the Domain-Specific Impairments: MoCA versus CNS-VS

The results showed MoCA sub-domains of executive function and visuospatial ability ($p<0.05$) significantly predict cognitive impairment in the corresponding domain of the CNS-VS, with higher rates of sensitivity (84.2% and 70% respectively), again have high NPV rates (90.0% and 85.1%).

The executive sub-domain demonstrated diagnostic accuracy of 66%, good sensitivity (84.2%) but low specificity (47.3%) and with a PPV of 34.8% and NPV of (90.0%). Again, this indicates that the MoCA classified many of the participants as being impaired in executive function domains (indicated by a high NPV and low specificity) where the CNS-VS classified them as not impaired. When looking at the memory domain, we found good sensitivity (80%) and NPV (81.6%) but low specificity (29.6%) and PPV (27.5%), and diagnostic accuracy (55%). Similar to the previous domains, with good sensitivity indicating the MoCA was correctly classifying people as being cognitively impaired in memory when the CNS-VS says they are not impaired. Conversely, the low specificity shows that the MoCA was classing more people who were cognitively intact whereas according to the CNS-VS they were cognitively impaired. Additionally, the visuospatial sub-domain had an acceptable level of sensitivity (70%), high NPV (85.1%) with lower specificity (56.9%) and PPV (35.1%), with a diagnostic accuracy of 64%. Lastly, the language and attention domains had lower sensitivity (43.8%, 50% respectively), but higher specificity (67.6% versus 62.5% respectively) and the lowest diagnostic accuracy (56% each). Both showed high NPV (78.3% and 78.9% respectively), but low PPV (31.0% and 30.8%) (Table 19).

Table 19. ROC analysis of MoCA sub-domains at 12 Month Follow-up

Variable	**AUC**	**Lower Bound**	**Upper Bound**	**SE**	***p*-value**	**Cut-off MoCA (CNS-VS)**	**Total Points per domain**	**SEN %**	**SPEC %**	**PPV %**	**NPV %**
Global	0.669	0.553	0.785	0.528	0.0076*	≤26 (80)	30	68.2	65.6	39.8	86.1
Executive	0.658	0.556	0.760	0.671	0.0196*	≤ 3 (80)	4	84.2	47.3	34.8	90.0
Visuospatial	0.635	0.517	0.753	0.543	0.0379*	≤3 (80)	4	70.0	56.9	35.1	85.1
Memory	0.548	0.443	0.653	0.617	0.4001	≤ 4 (80)	5	80.0	29.6	27.5	81.6
Language	0.557	0.420	0.693	0.562	0.3900	≤ 4 (80)	5	43.8	67.6	31.0	78.3
Attention	0.563	0.448	0.677	0.469	0.2767	≤ 5 (80)	6	50.0	62.5	30.8	78.9

*ROC, receiver operating characteristic, AUC, area under the curve, MoCA, Montreal Cognitive Assessment, SE, standard error, P, probability value, SEN, sensitivity, SPEC, specificity, PPV, positive predictive value, NPV, negative predictive value

6.5 Discussion

This study compared the use of the MoCA against the CNS-VS to determine its accuracy (strengths and limitations) in determining cognitive deficits in chronic stroke survivors. The MoCA is of particular interest in stroke, as it is widely used to identify global cognitive impairment in both clinical and research settings. Specifically, the sub-section domains of the MoCA are relevant to the neuropsychological sequelae commonly associated with stroke. The main findings of this study found the MoCA can accurately predict cognitive impairment at one year following stroke as well as a more comprehensive neuropsychological battery.

Overall the global MoCA score demonstrated a fair level of both sensitivity and specificity at the recommended cut-off of ≤ 26, correctly classifying a good number of stroke survivors as being cognitively impaired, which supports its usefulness as a clinical diagnosis tool to screen for cognitive impairment. Furthermore, our results are in line with past studies which have demonstrated the MoCA's accuracy using a cut-off ≤ 26 (Blackburn et al., 2013; Chiti & Pantoni, 2014; Pendlebury et al., 2013; Schweizer et al., 2012; Shopin et al., 2013; Toglia et al., 2011; G. Wong et al., 2013). While the sensitivity of the global MoCA score was not as high as previous studies, this difference may be attributed to a lack of long-term data. For example, Cumming and colleagues (2013), reported the MoCA had high sensitivity (0.92) compared to the MMSE (0.82) three months after stroke, where-as Demeyere et al., reported sensitivity at 78%, within three weeks of stroke, and a French Study at 0.94% specificity within one month of stroke compared to a more comprehensive battery of neuropsychological tests (Godefroy et al., 2011). However, these studies had short-term follow-up and did not calculate the sub-sections according to the published criteria (for example; the executive and visuo-spatial domains were added together), therefore limiting the validity of their conclusions.

Consistent with previous work, the sub-domains revealed a varied range of sensitivity and specificity, indicating that the MoCA may be better at identifying certain domains of impairment than the comprehensive battery. For instance; we found the executive function sub-domain of the MoCA was highly sensitive when compared to the same construct on the CNS-VS. These findings correspond well to a more recent study, where the executive function subsection showed the highest sensitivity (Hendershott et al., 2017). This may also suggest that the executive subsection of the MoCA, could be used

as a screening tool for research aimed at investigating this specific domain in stroke population.

Similar to previous research, this study found the MoCA demonstrated high sensitivity in identifying visuospatial impairment followed by good sensitivity in the memory subsection, but with limited specificity in both domains (Hendershott et al., 2017). Comparatively, we found the MoCA was not very sensitive or specific in identifying impairments in language and attention sub-sections, with similar findings previously reported (Hendershott, Zhu, Llanes, & Poston, 2016). This suggests that the language and/or attention sub-sections of the MoCA may not be suitable to for specific domain screening in people with stroke.

The overall results for this study (indicated by high NPV and low PPV) may suggest that the thresholds for the CNS-VS were too high (i.e. may need to be dropped below 80) or alternatively the optimal cut-offs for domain-specific impairments should have been lower for the MoCA. For example, the cut-off points for maximum sensitivity in each domain were only reduced by one point, (i.e., executive function ≤ 5 was lowered to ≤ 4) which may indicate a likely ceiling effect. Secondly although, some of the MoCA sub-section tasks overlap with tests neuropsychological batteries (i.e., naming, trail making test B, phonemic fluency and digit span), there are major differences in scoring and length of tasks that potentially influence the subdomain categorization which may have affected sensitivity. For instance, in the CTMT, the number sequencing task and the alternating number-letter sequencing task is longer (1-A-2-B-3-C-4-D…. L-13), in addition to the amount of time taken to complete the tasks. Therefore, the comprehensive test (CTMT) includes variables specific to working memory and attention, whereas the Trail Making Test on the MoCA is untimed, shorter and only includes a short version alternating number-letter sequencing task)1-A-2-B-3-C-4-D-5-E). Similarly, the MoCA's digit span task trail sequence is much shorter (only recall 5 numbers; 2-1-8-5-4) than the full digit span task used in the neuropsychological battery (recall up to 9 numbers 3-6-2-8-1-7-5-4).

However, taking into account the majority of publications have reported excellent sensitivity and specificity for the MoCA when compared to other neuropsychological assessments, another explanation for these results may be that perhaps the CNS-VS (not the MoCA) is not as reliable to detect cognitive impairment (Y Dong et al., 2010; Fu et al., 2017; Hendershott et al., 2017; Jaywant, Toglia, Gunning, & O'Dell, 2017; Lees et

al., 2017; Lu & Lam, 2017; Markwick et al., 2012; Nasreddine et al., 2005; O'Driscoll & Shaikh, 2017; Schweizer et al., 2012; Toglia et al., 2017). This is supported by the fact that the existing limited research regarding the validity and predictive value of the CNS-VS is largely unfavourable (Arrieux, Cole, & Ahrens, 2017; Quinn et al., 2018). For example, one study reported the CNS-VS was weakly correlated in most cognitive domains compared to traditional batteries to detect cognitive impairment (T Gualtieri & Hervey, 2015). Overall, the results from this study should be interpreted with caution and suggest that although screening tools such as the MoCA can provide information as to the presence of global cognitive impairment, in the ideal clinical or research setting any screening measure should be followed up by a more comprehensive gold standard assessment to establish domain-specific impairments.

6.6 Limitations and Strengths

There were several limitations in this study. First, not all of the domains of the CNS-VS could be tested against the MoCA because, the MoCA does not assess language impairment, visual acuity, apraxia, writing and reading ability which are all assessed by the CNS-VS measure (Demeyere et al., 2016). Second, performance on certain tasks can be influenced by other stroke neuropsychological sequelae. For example, all of the sub-sections of the MoCA require a level of verbal ability (non-language domains such as memory recall, naming), thus people with language impairments may score low because of language impairment (Beanie et al., 2015). A final limitation, was that we did not have data for S-NAB to compare against CNS-VS. CNS-VS was recorded at 1, 6 and 12 months in ARCOS-IV, and we only MoCA data available at these times (and no S-NAB which was only recorded at 48-months). Therefore, we were only able to analysis MoCA versus S-NAB and MoCA versus CNS-VS but not S-NAB versus CNS-VS, which would have allowed a more comprehensive analysis.

The strengths of this study included the sample size and the design. Population-based data is gold standard compared to hospital data. To the best of my knowledge, and comprehensive literature review (in chapter 2) this is the first study to report the accuracy of the MoCA sub-sections (scored according to published criteria) with regard to specific cognitive sequelae related to stroke. While the sub-sections of the MoCA were not intended to be individually assessed the same way as the domains of a comprehensive battery, this study has provided unique evidence to suggest the contrary. However, is important to acknowledge that the MoCA is a screening tool and therefore when appropriate, formal diagnoses may be required to fully investigate specific post

stroke cognitive impairments. Although poor specificity in some sub-domains may preclude the use of the MoCA as a clinical diagnostic tool, the acceptable level of sensitivity strengthens the view that the MoCA is a valuable screening tool that can be used to inform cognitive rehabilitation interventions and to help determine when more comprehensive neuropsychological testing would be appropriate or available. Finally, a total MoCA score of ≤ 26 is predominately used as an inclusion/exclusion criteria for recruitment in research targeting post stroke cognitive impairment; this can lead to a highly heterogeneous group, with people who have non-overlapping domain impairments. As an alternative, it may be more helpful for future studies to use domain-specific cut-offs as described in this study in order to identify and recruit a more comprehensive cohort of people with varying domain impairments

6.7 Conclusion

Overall this study has provided evidence that the MoCA can be used in the diagnosis of cognitive impairment following stroke. Although a comprehensive battery can be useful for classifying specific cognitive profiles, it is not mandatory for a diagnosis of post stroke cognitive impairment. The utility of the MoCA to predict domain-specific impairment was not well established in this study, this may be because of the validity and reliability of the CNS-VS, therefore further investigation is warranted using a more validated comprehensive neuropsychological battery. Future research is needed in larger population-based cohorts. Considering the MoCA is available in 46 different languages and dialects, cross-cultural meta-analyses would allow for comparisons amongst a wide range of cohorts.

Chapter 7 Integrated Discussion

The primary aim of this thesis was to expand the current knowledge of the long-term impact stroke has on cognitive recovery. Chapters One and Two, reviewed existing evidence on stroke, cognition and neuropsychological assessment. The current gaps in the literature were used to inform the studies in Chapters Four, Five and Six. A quantitative research approach was employed to examine the long-term profiles, and level of cognitive impairment and predictors, which resulted in cognitive decline over time. Additionally, the accuracy of the MoCA and sub-domains to determine cognitive impairment was investigated compared to a more in-depth neuropsychological assessment battery.

Overall, this thesis highlighted that cognitive impairment is frequent nearly four-years after the initial stroke event, and contrary to prior research recovery of cognitive function does not occur in the majority of survivors. Cognitive recovery was evident in a select group of survivors, for example; those who had post-graduate education and those people who had SAH strokes (although this was a small sample of only 18 people). Specifically, regarding poor cognitive outcomes, we found that socio-demographic and vascular factors have an integral role in declining cognition. The four main objectives of this thesis were addressed, with the findings from Chapter Five (Study 2) published in the journal of Neuroepidemiology (Mahon et al., 2017), supporting the quality of research, which is presented within this thesis. Emphasis was also placed on cognitive assessment, with the MoCA and a number of sub-domains of the MoCA demonstrating good accuracy and high sensitivity to detect domain-specific impairments. A brief summary of the studies is further explained below.

The findings from the first study (Chapter Four), found that specific domains of cognition remain impaired well after the stroke event. It was also revealed that cognitive function did not improve in the majority of participants (84%), with many experiencing persistent cognitive deficits at the four-year follow-up. The high prevalence of long-term cognitive impairment found in this study is consistent with previous population-based research (Crichton et al., 2016; Delavaran, Jonsson, et al., 2016), however these studies were both limited by the use of the MMSE to measure cognition. Although the sample of Māori and Pasifika stroke survivors was small, this study showed that the level of cognitive impairment may be higher in these groups, on both the MoCA and S-NAB compared to Europeans. But there is a paucity of long-term data on cognitive

outcomes for people in which to compare the findings from this study. Statistics NZ, population growth projections (2013-2028), indicate that Māori and Pacific populations will continue to grow faster than Europeans (Ministry of Health, 2017). Considering, ethnic inequalities in stroke incidence and outcomes have worsened over the past decade (Fink, 2016), these results emphasize the need for more in-depth research to better understand and prevent further decline in cognitive outcomes for Māori and Pasifika.

Of note, my publication in Neuroepidemiology examined ethnicity by comparing NZ European versus Non-European, as without the breakdown into individual ethnic groups (Māori, Pasifika and Asian), as I have done in my thesis. This was for two reasons (1) due to small sample size in the three other ethnic groups it was not possible to analyse the data based on individual ethnicities, and (2) the publication was addressed to an international audience, where reporting on small numbers by individual ethnicities was less relevant. However, I acknowledge that it is important to examine individual outcomes in terms of ethnicity, particularly for Māori and Pasifika in the NZ context and I have addressed this in my thesis.

It should be acknowledged that premorbid cognitive performance was not known in this study. A previous history of cognitive impairment is a major contributor to cognitive decline following stroke, therefore pre-existing cognitive impairment may have potentially lead to the higher prevalence we found in this study (Tang et al., 2018; Wagle et al., 2010). This highlights the importance of screening for pre-morbid cognitive function upon presentation to hospital, and/or primary healthcare clinics. The inclusion of a pre-stroke assessment screen such as the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1996), and a detailed medical history may provide invaluable information regarding premorbid functioning prior to the stroke event.

Although a large number of participants had deficits in attention and executive functioning, which is consistent with previous research, this study also found impaired information processing speed was present in the majority of survivors. This strengthens the evidence that impaired information processing speed is highly prevalent after stroke and can persist for many years after onset. Although it is important to acknowledge, no causal inference could be made from these findings, the results complement the limited research available on the impact of stroke on information processing speed. Therefore, it

seems plausible that consideration should be given to include information processing speed in the typical “post stroke cognitive profile” alongside executive function, memory and attention. Moreover, it is crucial that rehabilitation should focus on early interventions, which can promote and/or restore or compensate for recovery of information processing speed.

This study also extended existing knowledge on the influence of stroke related-characteristics such as vascular territory and stroke sub-type on long-term domain-specific impairment. Strokes, which occurred in the middle cerebral artery, were significantly associated with long-term language impairment. Considering the MCA supplies a large volume of blood to Broca’s and Wernicke’s areas (responsible for language reproduction and expression), these findings were not surprising (W. Zhang et al., 2014). However, the long-term association of strokes in the MCA region with language impairment has not been evidenced in previous research. These results may suggest that either people could have been overlooked and underdiagnosed at discharge, and therefore did not receive an adequate intervention, and/or the prognosis of strokes in MCA regions is unfavourable towards language recovery over the long term.

After identifying the level and predictors of global and domain specific cognitive impairment, the longitudinal course of cognitive function was examined in Study 2 (chapter 5). Although cognitive function did improve for those with a post-graduate education, a significant number of people still experienced persistent global cognitive impairment. Specifically, those who were older, were male, not working, or in a relationship, were more likely to experience cognitive decline over time. This supports previous research findings on predictors for post stroke cognitive impairment (Mackowiak-Cordoliani, Bombois, Memin, Henon, & Pasquier, 2005; Teasell & Hussein, 2016).

Specific vascular risk factors were also associated with declining cognition over the four year time period. While hypertension is a known risk factor for cognitive deterioration in normal populations (Vicario, Martinez, Baretto, Casale, & Nicolosi, 2005; Yasar, Ko, Nothelle, Mielke, & Carlson, 2011), the relationship between high blood pressure, stroke and cognitive decline has been inconclusive (Levine et al., 2013; Vaughan, Bushnell, Bell, & Espeland, 2016). In contrast, the evidence presented in this study suggests the development of cognitive decline related to the presence of hypertension is greatly augmented by the presence of stroke. This supports recent recommendations,

which state that modifiable vascular risk factors such as vascular should be targeted through the implementation of primary prevention strategies to significantly decrease both the risk of stroke and further deterioration of cognition post-stroke (Stroke Foundation, 2017).

The findings from Study two, also revealed the influence of socio-demographic factors on progressive post-stroke cognitive decline. Specifically, those stroke survivors who were not working/retired and separated/divorced or widowed experienced greater cognitive decline compared to other socio-demographic factors (i.e. ethnicity, education level). A lack of mentally challenging activities following early retirement and/or loss of employment after stroke, is known to exacerbate the loss of cognitive function (Westerlind, Persson, & Sunnerhagen, 2017; Xue et al., 2017). Additionally, social networks are often not maintained which can also result in social isolation, and loneliness which contributes to further cognitive decline (Zhong, Chen, Tu, & Conwell, 2017). The relationship between not working after stroke and cognitive decline needs to be further explored as there may be underlying factors such as loss of social networks, loneliness and isolation which may influence cognitive function (Ellwardt et al., 2013; Yeates et al., 2016).

Although the majority of stroke survivors experienced long-term cognitive impairment, cognitive recovery was possible for those people who had experienced SAH strokes and with post-graduate education. While it is has been well documented that higher education may mitigate or buffer the long-term effects of stroke on the brain and preserve cognitive reserve, the lesser is known about cognitive recovery in SAH (Mirza et al., 2016). One potential explanation could be that SAH survivors tend to spend longer time in inpatient rehabilitation, and therefore have access to early intervention. This supports previous research which has demonstrated that early rehabilitation following SAH has been shown to be a predictor of good cognitive outcome following stroke (Shukla, 2017). While this relationship was not examined in this thesis, further exploration may identify the efficacy of early rehabilitation on cognitive recovery.

The final study (3) aimed to examine the accuracy of the MoCA to detect both global and domain-specific impairment compared to a more in-depth neuropsychological assessment battery. Findings from this study showed that the MoCA demonstrated an acceptable level of specificity and sensitivity to detect global cognitive impairment compared to the CNS-VS. Levels of sensitivity and specificity were lower than those

previously reported (Fu et al., 2017; Jaywant, Toglia, Gunning, & O'Dell, 2017; Tsai et al., 2016). The results for domain-specific impairment were varied, and overall suggest that while the MoCA is a reliable tool for assessing global cognitive impairment, it may not be as reliable to detect individual domains of impairment. These results were in contrast to prior research, which has shown the sub-domains of the MoCA can accurately predict domain-specific impairment (Hendershott et al., 2017; Hurford et al., 2013; Vogel et al., 2015). The discrepancy in these findings may be explained by the inaccuracy of the CNS-VS as a valid battery to predict domain-specific impairment. On the other hand, there is enough evidence to support the CNS-VS as an appropriate neuropsychological battery specific to stroke populations. In comparison, and as highlighted through-out this thesis, there is a plethora of research, which has consistently demonstrated the high sensitivity of the MoCA to predict both global and domain-specific impairment. Therefore, the findings related to the domain-specific impairment should be interpreted with caution and need further investigation using a more reliable and valid battery. In spite of the mixed results in this study, the fact that all 257 participants were able to complete the MoCA four years after their stroke, demonstrates the feasibility and ease of the MoCA to assess global cognitive function at a longitudinal level. While the MoCA is useful for initial assessment of cognition at the acute stage (inpatient), and for monitoring longitudinal changes, it should be supplemented alongside a more comprehensive battery, if global function is below the threshold for impairment.

7.1.1 Key Points

- At four-years following stroke, more than two thirds of stroke survivors experienced cognitive impairment
- Longitudinal changes in global cognitive function occur
- Risk of cognitive decline is dependent on sociodemographic, stroke-related and vascular risk factors
- Impairments of executive function, attention, information processing speed and memory appear to be a consistent pattern with other long-term research
- While cognitive recovery may be possible within the first 6 months, many patients will experience further decline past the first year.
- Increasing age, being male, not working nor in a relationship was associated with further cognitive decline over time.

- Vascular risk factors, such as hypertension, diabetes mellitus and arrhythmia contributed to cognitive decline over time more than psychological, functional, physical and stroke-related factors.
- As a screening tool to detect post stroke cognitive impairment, the MoCA provides reliable diagnosis for global cognitive impairment, but is limited in its ability to detect domain-specific impairments.
- The MoCA is a feasible and easy screening tool to detect cognitive impairment

7.1.2 Added Value of Thesis to the Research Literature

This thesis has added to current literature by helping to further identify the impact stroke has on longitudinal changes in cognitive function. While it is well documented that cognitive impairment is highly prevalent following stroke, there is limited long-term population-based data (Crichton et al., 2016; Delavaran, Jonsson, et al., 2016). Specifically, there is a lack of data that has examined the impact of vascular risk factors (hypertension, diabetes mellitus, arrhythmia etc.) as predictors of progressive cognitive decline after stroke. This new information provides some new insight into specific predictors of decline such as vascular risk factors, which can be easily targeted through compliance of medications, and through regular monitoring of cognitive function. Specifically, the results in Chapter Five have already been published (Mahon et al., 2017), and extends existing international knowledge on the trajectory and predictors of cognitive impairment after stroke. The findings of this research highlight the importance of conducting detailed investigations of prognostic factors identified in this study at stroke onset, and using this information to tailor rehabilitation and recovery goals for stroke survivors.

The longitudinal changes in cognitive function have been well demonstrated in this research, and not investigated in previous stroke research in NZ to this extent. This research has identified the severity of cognitive impairment after stroke and this evidence needs to be used to inform current stroke management pathways in NZ. While newly released stroke clinical guidelines, propose compulsory screening of all stroke patients prior to discharge home, this is yet to be implemented in NZ (Stroke Foundation, 2017). As a result, it has become apparent there is a need for a systematic review on current cognitive rehabilitation interventions, offered both in NZ and internationally in order to identify gaps in the current evidence base. This review is currently underway.

Due to the influence of vascular risk factors on post-stroke cognition identified within this thesis, pharmacological and psychological interventions, targeting behaviour changes (compliance to medication, diet, exercise) may be ideally placed to address these factors either in hospital, inpatient rehabilitation, and/or prior to discharge home. An analysis of their effectiveness would therefore provide important information to inform current management of risk factors and cognitive impairment.

7.1.3 Thesis Limitations and Recommendations for Future Research

Limitations specifically relating to the three studies have been previously discussed within the relevant chapters. However, there are some general limitations which should be considered.

Participant Attrition

From the original cohort of consented participants (n=821/2096), only 499 participants were approached as they were recorded at their last follow-up (12 months), of agreeing to participate in further research. It is possible that people were either not asked, or if they declined. As a large number of people did not complete 12-month follow-up in the consented sample, this may suggest they were not asked, as a result 322 people (39%) were not approached for follow-up. In addition, there may have also been a selection bias, as patients who had were too unwell, and experienced, aphasia nor unable to speak English (especially in Pacific Island groups) may not have been approached for consent. Therefore, the prevalence of long-term cognitive impairment may have been underestimated in this thesis. While, attrition rates may be seen as a limitation, loss to follow-up is a commonly reported occurrence in longitudinal population-based stroke research (Delavaran, Jonsson, et al., 2016; Patel et al., 2003), especially in terms of recurrent stroke, declining health, and mortality between follow-up periods.

However, of the 499 participants who could be contacted, we achieved a 52% consent rate, this was including a 15% mortality rate which occurred between 12-month and four year follow-up. Three participants who had completed assessments in the four-year follow-up passed away over the study period. To ensure the sample of stroke survivors in this thesis was representative of the total ARCOS-IV cohort, chi-squared tests were conducted. While, no significant differences were found between the two samples, in terms of stroke characteristics, there was a significant difference in ethnicity. In terms of ethnic representation, there were more Europeans, compared to Māori Pasifika and Asian in this study compared to the total ARCOS-IV cohort. These figures indicate that

Europeans were over represented and Māori and Pasifika underrepresented in this study. Reasons for these differences are unclear. A further study is currently being planned to examine outcomes for the entire cohort up to four years, using information obtained from Ministry of Health data. This information may provide some evidence to ethnic differences in stroke outcomes and augment the findings from this thesis.

Pre-Morbid Cognitive Function

Another limitation to consider, was the lack of pre-morbid cognitive function data. Pre-existing cognitive impairment is a known risk factor for cognitive deterioration post stroke (Mijajlović et al., 2017). However, this was not possible to collect during the initial baseline assessments. As a result, it is unknown whether or not previous deficits in cognitive function may have potentially contributed to the higher rates of impairment reported in this thesis. A recent review of post stroke cognitive deficits, revealed that premorbid cognitive impairment can significantly affect the brain's cognitive reserve (CR) and capacity to recover following stroke (MacPherson et al., 2017; Umarova, 2017). As previously discussed in Chapter four, damage to the brain is mitigated or buffered by the level of cognitive reserve, with higher CR associated with formal education level, high intelligence, life experience and occupation. This seems a plausible explanation, considering that stroke patients who had completed post-graduate education were more likely to recover compared to those who did not over the four-year time period.

Future research needs to include the collection of pre-morbid function, via informant questionnaires and medical records. This information, may be able to paint a clearer picture of the level of cognitive function at the time of stroke and be used to target intensive cognitive rehabilitation, for those who are more likely to progress with further decline.

Influence of Fatigue

Fatigue is an incredibly debilitating symptom of stroke and often not taken into consideration in approaches to stroke management. One of the aims of this thesis was to look at **baseline predictors** and the association of time on cognition. While a preliminary correlational analysis showed that cognitive impairment was significantly associated ($p= 0.05$) with fatigue (measured by the FFS at four years), there was no association with baseline fatigue and long-term cognitive decline. However, it is important to note there was a large number of missing baseline fatigue data. The

relationship between cognitive impairment and fatigue is further complicated by the influence of sleep disturbances, medication, mood and older age (Drummond et al., 2017; MacIntosh et al., 2017). For example, as we age our ability to sustain attention and concentrate becomes more difficult, and our thinking processes become slower, these factors combined may contribute to decreased mental energy (construct of fatigue). When a stroke is added into this mix, it becomes difficult to decipher the true relationship. Therefore, there is a need for more rigorous and comprehensive longitudinal research, to investigate the complex interactions between cognitive impairment and fatigue and the multitude of factors which interplay with both. This information may be used to inform current management strategies and the development of appropriate treatment and interventions.

Comprehensive Cognitive Profiles

Although the studies within this thesis explored long-term cognitive impairment both at a global level and domain specific level, a more in-depth analysis of the specific types of functionality related to each of the cognitive domains was not explored. For example; there are different types of memory such as; short term memory (phone numbers, post code etc.), long-term memory (episodic and semantic), procedural memory and working memory (verbal, visual, concentration and attention) (Al-Qazzaz et al., 2014). These memory types, once impaired can have varying effects on a stroke survivor's quality of life. For instance; procedural memory is used to complete everyday tasks such as remembering to take medications on time, getting the children from school, or remembering to pick up certain groceries from the supermarket. When this is impaired, it can significantly impact the ability to complete everyday tasks, reducing a person's independence (Hogan, Fleming, Cornwell, & Shum, 2016).

While, the screening neuropsychological assessment battery used in thesis does broadly measure specific types of memory, for the purposes of this thesis, it was not feasible to carry out this additional analysis. However, it may be worthwhile to use this data for a small project exploring how stroke affects individual types of memory long-term. This additional knowledge may be used to optimize rehabilitation interventions to improve memory impairment after stroke.

Access to Cognitive Rehabilitation

The findings in this thesis have identified for the first time in a NZ population, that cognition remains highly impaired in the long-term following a stroke. These results are

concerning and highlight a major gap in current stroke services, which suggest that assessment of cognitive function is currently not being addressed adequately enough and/or overlooked prior to discharge. Access to rehabilitation was not assessed in this thesis. This information would have greatly augmented the overall theme of this thesis, by highlighting the disparity between prevalence and access to current rehabilitation services. Irrespective of this data being collected as part of the 4-year follow-up, it would not have affected the outcome of this research as there is no evidence to suggest that cognitive rehabilitation is routinely offered in NZ. A review is currently underway by myself, to identify what is being offered in terms of cognitive rehabilitation and types of intervention in NZ, compared to other countries. This evidence will be used to disseminate to clinicians working directly with stroke patients, General Practitioners and other community health providers, the Stroke Foundation and Stroke Network. This may potentially lead to the formation of a working group to develop a new pathway for cognitive rehabilitation in NZ.

Pilot Study to Test a Computerised Cognitive Rehabilitation Intervention

The survival and trajectory of recovery are dependent on the effectiveness of rehabilitation/treatment, thus highlighting the importance of appropriate interventions to improve outcomes for all stroke survivors. While the recovery of physical function post-stroke has been the primary focus of rehabilitation research, with evidence demonstrating significant improvements following physical rehabilitation, considerably less attention has been given to post-stroke cognitive impairment (Gillespie et al., 2015). Of equal importance, the cost-benefits of cognitive rehabilitation in the acute phase of stroke can be significant in terms of functional gains, increased productivity (return to work, reduced dependence) and reduction in levels of care and financial burden in the longer-term (Oddy & da Silva Ramos, 2013). There is mounting evidence that computer-based cognitive rehabilitation training (CCRT) is an effective method for improving cognitive and functional recovery in patients with stroke. Computer-based training provides a structured standardised approach to rehabilitation by either restoring function or compensating for loss of function, in order to assist adaptation and facilitate independence (Cicerone et al., 2011b). Several studies have shown promising results after only 4 to 6 weeks of CCRT, by improvement in cognitive and functional deficits after stroke (Modden et al., 2012). Additionally, CCRT offers the choice of applying cognitive rehabilitation in the comfort of home while patient adherence and performance can be monitored remotely online. This reduces the burden on the patient

and their families, is significantly less resource intensive and provides greater access for a larger number of stroke patients (Cogollor et al., 2018). However, there is a lack of robust evidence on the effectiveness of CCRT as a cognitive rehabilitation intervention for stroke patients in NZ. As cognitive impairment after stroke is complex, a feasible approach that addresses cognitive impairment is vital in order for stroke patients to improve their ability to perform everyday activities and consequently enhance their quality of life.

Although there is evidence supporting cognitive rehabilitation in stroke (das Nair et al., 2017; Gillespie et al., 2015; Shigaki et al., 2014), a gap remains between basic research and stroke rehabilitation, which limits the efficacy of interventions and opportunities available for cognitive rehabilitation. After consultation with Stroke specialists (geriatricians, neurologists, neuropsychologists, stroke nurse specialists, rehabilitation managers) at three Auckland-based stroke units, there is a strong consensus that there is a huge gap in services currently offered, with *most patients receiving no form of cognitive rehabilitation*. Additionally, there is agreement that the implementation of a cognitive rehabilitation is long overdue, and an intervention of this kind would be feasible in both the hospital/rehabilitation setting and home. For the reasons listed above, a pilot trial is currently underway to test the effectiveness of intensive cognitive rehabilitation to improve functional recovery, in order to provide evidence that cognitive and functional recovery after stroke can occur through specialised cognitive rehabilitation training.

7.1.4 Implications for Practice

Due to the relatively high prevalence of persistent cognitive impairment, the following recommendations are suggested for clinical practice.

The development of an Approach to Cognitive Assessment Pathway for Stroke

Recommendations for practice include a feasible and practical approach to cognitive assessment (Figure 8). This needs to be implemented in both acute, subacute and outpatient settings and should include; a) compulsory screening for pre-morbid cognition, using the Informant Questionnaire on Cognitive Decline (IQCODE), and a detailed medical history and b) compulsory screening of cognition at various time-points in order to monitor changes in cognitive function. The recent development of the Oxford Cognitive Screen in 2015, may supersede the use of the MoCA, as was shown to more accurately predict domain-specific profile designed specifically for stroke

survivors (Demeyere et al., 2015; Mancuso et al., 2018). Further, the OCS assesses aphasia and neglect, which are not evaluated in the MoCA. However, at this stage there is limited data on the validity and accuracy of the OCS and therefore, further population-based longitudinal research needs to be conducted to support the use of the OCS in stroke populations. In addition, to the screening tools, the inclusion of the NINDS-CNS 30 minute protocol (as recommended by current stroke clinical guidelines) (Stroke Foundation, 2017) within the inpatient rehabilitation setting should be conducted. This will provide a clearer picture for those who have exhibited global impairment determined by a MoCA of < 26 or OCS. Other outcomes, including sleep, fatigue, mood, function, stroke severity, social participation, quality of life and impact specific to stroke should also be measured and monitored (see Figure 8). This information can be used as part of an annual stroke review to track changes over time.

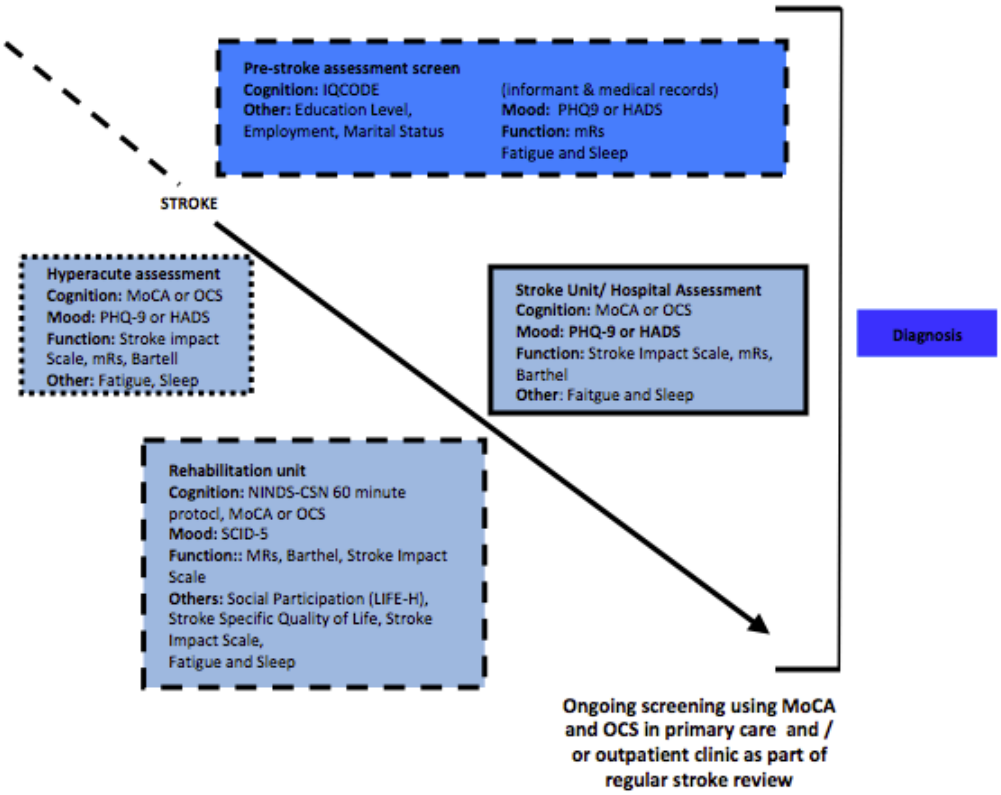

Figure 8. Schematic Illustrating Proposed Pathway for Cognitive Assessment

7.2 Conclusion

Cognitive impairment following a stroke can affect all aspects of a person's life, often resulting in increased dependence on others and reduced quality of life. The key contributions to knowledge reflected in this thesis; are that cognitive impairment is

highly prevalent well after the stroke event, and affects most domains of cognition, but is more specific to memory, attention, executive function and information processing speed. Further, it was found that declining cognition is linked to vascular and sociodemographic factors. Specifically, hypertension, diabetes and arrhythmia contributed to persistent cognitive decline, as well as those who were not working or married. Cognitive recovery was possible for those people who had higher levels of education. This thesis also highlighted that a brief screening cognitive assessment tool, can accurately predict global cognitive impairment compared to a more in-depth neuropsychological assessment battery.

While, there is continued research into the relationship between stroke and cognitive function, the findings from this research have important implications for treatment. Behavioural interventions which target the management of vascular risk factors, such as hypertension and diabetes may lessen the further development of cognitive decline. Additionally, interventions which focus on maintaining or increasing social networks, and participation for those who are on their own and/or not working, should form an integral part of treatment to strengthen cognitive reserve.

Assessment of pre- and post-morbid cognitive function in the acute phase after stroke, may offer vital information by identifying specific cognitive deficits which may impede recovery. Cognitive interventions which are tailored to domain-specific impairment are required and once implemented may change the trajectory of recovery for stroke survivors who are experiencing significant deficits. Early rehabilitation may reduce the long-term burden of stroke-related cognitive impairment, and improve functional outcomes, and quality of life. Moreover, regular monitoring of cognitive function (annually) through-out the stroke journey will assist in recognising any changes over time. The combination of assessment, intervention and monitoring can have a substantial impact on the burden of cognitive impairment and improve overall outcomes for people with stroke and their families.

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Abbreviations

ABI	Atherothrombotic Brain Infarct
AF	Atrial Fibrillation
ARCOS-IV	Auckland Stroke Community Outcomes Study
AUC	Area Under the Curve
BI	Barthel Index
BP	Blood Pressure
CBF	Cerebral Flow Blood
CNS-VS	Computerized Neurocognitive Assessment Software-Vital Signs
CT	Computed tomography scan
CTMT	Comprehensive Trail Making Test
DALYS	Disability-Adjusted Life Years
DV	Delayed Vasospasm
EQ-5D	European Quality of Life- 5 Dimensions
FFS	Fatigue Severity Scale
GBD	Global Burden of Disease
GCS	Glasgow Coma Scale
HADS	Hospital Anxiety and Depression Scale
HDEC	Health Disability Ethics Council
HRC	Health Research Council
ICC	Intraclass Correlation
ICH	Intracerebral Haemorrhage
ICP	Intracranial Pressure
ICU	Intensive Care Unit
ISH	Ischaemic
IVH	Intraventricular Haemorrhage
LACI	Lacunar Circulation Infarct
M-WCST	Modified Wisconsin Card Sorting Test
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
NPV	Negative Predictive Value
NZ	New Zealand
OCSP	Oxfordshire Community Stroke Project

PACI	Partial Anterior Circulation Infarct
POCI	Posterior Circulation Infarct
PPV	Positive Predictive Value
PSCI	Post-stroke Cognitive Impairment
ROC	Receiver Operating Characteristic
RR	Relative Risk
S-NAB	Screening Module Neuropsychological Assessment Battery
SAH	Subarachnoid Haemorrhage
SDMT	Symbol Digit Modalities Test
SES	Socioeconomic Status
TACI	Total Anterior Circulation Infarct
TOAST	Trial of Org 10172 in Acute Stroke Treatment
VCI	Vascular Cognitive Impairment
VFAS	Visual Fatigue Analogue Scale

Appendices

Appendix A: Letter of Ethical Approval Health and Disability Ethics Committee (HDEC)

Health and Disability Ethics Committees

Health and Disability Ethics Committees
Ministry of Health
C/- MEDSAFE, Level 6, Deloitte House
10 Brandon Street
PO Box 5013
Wellington
6011

0800 4 ETHICS
hdecs@moh.govt.nz

24 April 2014

Professor Valery L. Feigin
National Institute for Stroke and Applied Neurosciences
90 Akoranga Drive
AUT University
Northcote 0627
Auckland 0627

Dear Professor Feigin

Re:	**Ethics ref:**	**NTX/10/09/090/AM07**
	Study title:	Auckland Regional Community Stroke Study: Measuring and reducing stroke in New Zealand

I am pleased to advise that this amendment has been *approved* by the Northern A Health and Disability Ethics Committee. This decision was made through the HDEC Expedited Review pathway.

Please don't hesitate to contact the HDEC secretariat for further information. We wish you all the best for your study.

Yours sincerely,

Dr Brian Fergus
Chairperson
Northern A Health and Disability Ethics Committee

Encl: appendix A: documents submitted
appendix B: statement of compliance and list of members

Appendix A
Documents submitted

Document	Version	Date
PIS/CF: Patient Information Sheet and Consent Form for ARCOS IV 3 year follow-up study.	1	30 March 2014
Protocol: Protocol Version 1 for ARCOS IV 3 year follow-up study	1	20 March 2014
Survey/questionnaire: Participant Questionnaire for ARCOS IV 3 year follow-up	1	15 April 2014
Survey/questionnaire: Stroke Proxy questionnaire ARCOS IV 3 year follow up	1	15 April 2014
Survey/questionnaire: TIA participant questionnaire	1	15 April 2014
Post Approval Form	1	15 April 2014

Appendix B
Statement of compliance and list of members

Statement of compliance

The Northern A Health and Disability Ethics Committee:

- is constituted in accordance with its Terms of Reference
- operates in accordance with the *Standard Operating Procedures for Health and Disability Ethics Committees*, and with the principles of international good clinical practice (GCP)
- is approved by the Health Research Council of New Zealand's Ethics Committee for the purposes of section 25(1)(c) of the Health Research Council Act 1990
- is registered (number 00008714) with the US Department of Health and Human Services' Office for Human Research Protection (OHRP).

List of members

Name	*Category*	*Appointed*	*Term Expires*
Dr Brian Fergus	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Dr Karen Bartholomew	Non-lay (intervention studies)	01/07/2013	01/07/2016
Ms Susan Buckland	Lay (consumer/community perspectives)	01/07/2012	01/07/2015
Ms Shamim Chagani	Non-lay (health/disability service provision)	01/07/2012	01/07/2014
Dr Christine Crooks	Non-lay (intervention studies)	01/07/2013	01/07/2015
Mr Kerry Hilni	Lay (consumer/community perspectives)	01/07/2012	01/07/2014
Dr Etuate Saafi	Non-lay (intervention studies)	01/07/2012	01/07/2014
Ms Michele Stanton	Lay (the law)	01/07/2012	01/07/2014

http://www.ethics.health.govt.nz

Appendix B: Letter of Ethical Approval AUT University Ethics Committee (AUTEC)

AUT UNIVERSITY

AUTEC SECRETARIAT

13 May 2014

Valery Feigin
Faculty of Health and Environmental Sciences

Dear Valery

Re: Ethics Application: **11/297 Auckland Regional Community Stroke Study (ARCOS IV). Measuring and reducing the stroke burden in New Zealand. Part 1: ARCOS IV incidence and outcomes study (2010-2013)**

Thank you for your request for approval of an amendment to your ethics application.

I have approved a minor amendment to your ethics application allowing a 3 year follow up with participants who had previously agreed to be approached.

I remind you that as part of the ethics approval process, you are required to submit the following to the Auckland University of Technology Ethics Committee (AUTEC):

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 31 October 2014;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 31 October 2014 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Rita Krishnamurthi; Kathryn McPherson; Max Abbot; Sue Mahon

Auckland University of Technology Ethics Committee
WA505F Level 5 WA Building City Campus
Private Bag 92006 Auckland 1142 Ph: +64-9-921-9999 ext 8316 email ethics@aut.ac.nz

Appendix C: Participant Information and Consent Form

Registration Number:	Participant Initials:	Date of Birth:

ARCOS IV: 4 Year Post-Stroke Follow-Up

Participant Information Sheet

An invitation

You are invited to take part in this research study because you agreed to be contacted for future studies as a participant in the ARCOS IV stroke study. This study is conducted by the National Institute for Stroke and Applied Neurosciences, AUT University in Auckland.

Your participation is entirely voluntary (your choice). You do not have to take part in this study. If you choose not to take part, any care or treatment that you are currently receiving will not be affected. If you do agree to take part, you are free to withdraw from the study at any time, without having to give a reason. Withdrawing at any time will in no way affect your future health care. You may take as much time as you like to consider whether or not to take part.

What are the aims of this study?

The main aim of the study is to determine the impact of stroke on cognitive performance (such as thinking, memory, attention and reasoning) and other stroke related outcomes (health and wellbeing and quality of life) which may influence recovery following stroke.

What types of people can be in the study?

The study will include all people in the Greater Auckland Region who sustained a stroke between 1st March 2011 and 29th February 2012, participated in the ARCOS IV study and who consented to being contacted for future research.

How many people will be in the study?

We estimate about 400 people will be involved in this study.

What happens if I do decide to take part?

If you decide to take part, the researcher will contact you by telephone and arrange a suitable time to complete the assessments. The assessment will take place face to face at home. The face to face assessment will take place at home and involves completing some cognitive tests which will take about 60-90 minutes of your time. You will be able to take a break during the assessment if you wish. The researcher conducting the assessment has been specifically trained for this project.

Some of the results of this study will also be collected and used for a PhD study (student name Susan Mahon, Auckland University of Technology). The PhD study is looking at cognitive outcomes after stroke. The results may be also be used for other related sub-studies.

Registration Number:	Participant Initials:	Date of Birth:

What is the time-span for the study?

The study is expected to start on 1st June 2014 and will continue until 31st May 2016.

How will the study affect me?

Taking part in this study will take some of your time and require you to answer a series of questions in a single assessment. There are no known risks caused by this study. Your usual medical care will not be affected in any way by participating in the study, or by deciding not to take part in the study or withdrawing from the study at any stage. Your participation in this study will be stopped if any harmful effects appear or if the doctor feels it is not in your best interests to continue.

There is no direct benefit to you from being involved in this study, however the study may help others with stroke in future.

Reimbursement/koha

For all study participants a $20 food/fuel voucher will provided after the assessments have been completed in appreciation of your time.

Confidentiality

The study files and all other information that you provide will remain strictly confidential. No material that could personally identify you will be used in any reports on this study. Upon completion of the study your records will be stored for 16 years in a secure place at the central coordinating centre in Auckland. All computer records will be password protected. All future use of the information collected will be strictly controlled in accordance with the Privacy Act.

Compensation

In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation, and Compensation Act 2001. ACC cover is not automatic, and your case will need to be assessed by ACC according to the provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors, such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses, and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators.

If you have any questions about ACC, contact your nearest ACC office or the investigator.

You are also advised to check whether participation in this study would affect any indemnity cover you have or are considering, such as medical insurance, life insurance and superannuation.

Registration Number:	Participant Initials:	Date of Birth:

If you have any queries or concerns regarding your rights as a participant in this study, you may wish to contact an independent Health and Disability Advocate. This is a free service provided under the Health and Disability Commissioner Act:

Free phone: 0800 555 050
Free fax: 0800 2787 7678 (0800 2 SUPPORT)
Email: advocacy@hdc.org.nz

Finally

This study has received Ethical Approval from the Health and Disability Ethics Committee. Ref: NTX/10/09/090/AM07 and AUTEC (Auckland University of Technology Ethics Committee) Ref: 11/297.

If you would like some more information about the study please feel free to contact the Susan Mahon on 09-921-9999 ext 7438 or email smahon@aut.ac.nz at the National Institute for Stroke and Applied Neurosciences (NISAN), AUT University.

Alternatively, you can contact:

Dr Rita Krishnamurthi, Senior Research Fellow, NISAN, AUT University on 09-921-9999 ext. 7809 or email: rita.krishnamurthi@aut.ac.nz

Study Investigators

The principle investigator for this study is: **Professor Valery Feigin** Tel: (09) 921 9166
National Institute for Stroke and Applied Neurosciences (NISAN), AUT University,
Private Bag 92006, Auckland 1142

Please keep this brochure for your information.
Thank you for reading about this study

Registration Number:	Participant Initials:	Date of Birth:

CONSENT FORM

1. I have read/had explained to me, and understand, the Information Sheet for participants taking part in the 3 year ARCOS IV follow-up study. I have had the opportunity to discuss this study. I am satisfied with the answers I have been given.
2. I understand that taking part in this study is voluntary (my choice). I realise the study involves an interview with medical and lifestyle questions, that I may choose not to answer any questions or choose to withdraw from the study at any time and this will in no way affect my future health care.
3. I have had the opportunity to use family/whānau support or a friend to help me ask questions and understand the study.
4. I agree to an approved auditor appointed by either the ethics committee, or the regulatory authority or their approved representative, and approved by the Northern Regional X Ethics Committee reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.
5. I give my approval for information regarding my medical condition in the past three years to be obtained from medical records, including medical records kept by my GP. A copy of this signed consent form will be sent to your GP, if requested.
6. I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.
7. I understand the compensation provisions for this study.
8. I have had time to consider whether to take part.
9. I know whom to contact if I have any questions about the study.
10. I agree to being contacted for further follow-up. yes ☐ no ☐
11. I agree to the information I provide being used for future relevant sub-studies. All data will be anonymised and no individual data will be reported. yes ☐ no ☐

Appendix D: Participant Questionnaire

IKURA RORO AKO O T E ROHE O T AMAKI MAKAURAU WHANUI

ARCOS IV

Auckland Regional Community Outcome Stroke

ARCOS-IV 4 Year Follow-up: Stroke

(For ALL Participants)

Information to be obtained from interview

Registration Number

Participant Initials

Date Of Birth

Day Month Year

Date of first stroke during ARCOS-IV period

Day Month Year

Data entered

Signed

Day Month Year

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number	Participant Initials	Date Of Birth
		Day Month Year

Answer all questions. DO NOT LEAVE BLANK SPACES. Tick circles, write numbers in boxes.

If the data are unavailable put an asterisk '*' and clearly note reason and date on form.

If the data are not applicable put a dash '-' and clearly note reason and date on form.

Yes/No Responses: for each question, please mark 'Yes' or 'No

1.0 Patient Details

1.1 [ ][ ][ ] Date of birth
Day Month Year

1.2 Gender: ○ Male ○ Female

2.0 Assessment Details

2.1 [ ][ ][ ] Date of assessment
Day Month Year

2.2 Date of first stroke during ARCOS-IV period (2011-2012): [ ][ ][ ]
Day Month Year

2.3 Signed informed consent to study participation obtained for ARCOS-IV 3 year follow up.

Yes ○ No ○ If No, note reason for decline and stop here. [ ]

2.4 If Yes, who signed consent form?

○ Patient

Note: For proxy assessments (stroke only) use Proxy form.

3.0 Baseline Demographic Information

3.1 What is your current marital status? (tick one only)

○ Married, civil union or defacto relationship
○ Never married
○ Separated, divorced, or widowed

3.2 Has this changed since your stroke?

○ Yes ○ No

3.3 What is your current living status? (tick one only)

○ Living with partner / family
○ Living with others
○ Living alone

ARCOS IV Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number	Participant Initials	Date Of Birth
		Day Month Year

3.4 What is your current dwelling place?

- ○ Own home
- ○ Rented accommodation
- ○ Living with family or friends
- ○ Retirement village
- ○ Rest home or private hospital
- ○ Other

3.5 What is your current employment status?

- ○ Employed
- ○ Unemployed
- ○ Retired

3.5.1 If employed, what is your current occupation?

3.5.2 In what industry or organisation?

4.0 Medical History since February 2012

Note: if more than one event of any type since February 2012, enter date of earliest event first.

4.1 Have you had a new stroke since February 2012?

Yes No If No, go to 4.2

4.1.1 If Yes, date: Day Month Year

4.1.2 Did your diagnosis take place at:

○ Hospital GP ○ If other, specify:

4.1.3 If hospital, which:

4.1.4 Supporting evidence attached (e.g. discharge summary) Yes No N/A

4.1.4 Dates of any other stroke events:

4.2 Have you had a TIA since February 2012?

Yes No If No, go to 4.3

4.2.1 If Yes, date: Day Month Year

4.2.2 Did you seek medical advice from:

○ Hospital ○ GP only ○ None ○ Other, specify:

4.2.3 If hospital, which:

4.1.4 Supporting evidence attached (e.g. discharge summary) Yes No N/A

4.2.4 Dates of any other TIA events:

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day Month Year)

4.3 Have you had a heart attack/myocardial infarction since February 2012?

○ Yes ○ No 4.3.1 If Yes, date: ___ ___ ___ (Day Month Year) If No, go to 4.4

4.3.2 Did your diagnosis take place at:

○ Hospital ○ GP ○ If other, specify: _____

4.3.3 If hospital, which: _____

4.1.4 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No ○ N/A

4.3.4 Dates of any other MI events: _____

Have you had any of the following procedures conducted since February 2012?

4.4 Carotid endartectomy ○ Yes ○ No If No, go to 4.5

4.4.1 If Yes, date: ___ ___ ___ (Day Month Year)

4.4.2 Where was procedure performed? _____

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.5 Carotid artery stenting ○ Yes ○ No If No, go to 4.6

4.4.1 If Yes, date: ___ ___ ___ (Day Month Year)

4.4.2 Where was procedure performed? _____

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.6 Coronary artery bypass graft ○ Yes ○ No If No, go to 4.7

4.4.1 If Yes, date: ___ ___ ___ (Day Month Year)

4.4.2 Where was procedure performed? _____

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.7 Coronary artery stenting ○ Yes ○ No If No, go to 4.8

4.4.1 If Yes, date: ___ ___ ___ (Day Month Year)

4.4.2 Where was procedure performed? _____

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

4.8 Peripheral vascular revascularisation procedure ○ Yes ○ No If No, go to 4.9

4.4.1 If Yes, date: ___ ___ ___ (Day Month Year)

4.4.2 Where was procedure performed? _____

4.4.3 Supporting evidence attached (e.g. discharge summary) ○ Yes ○ No

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

Since February 2012, have you had a **new** diagnosis of any of the following:

	Yes	No		Hospital only: if Yes, daignosis confirmed?
4.9	○	○	Elevated blood lipids (cholesterol)	○
4.10	○	○	Hypertension, elevated blood pressure	○
4.11	○	○	Diabetes	○
4.12	○	○	Coronary artery disease, angina	○
4.13	○	○	Irregular pulse (arrhythmia), atrial fibrillation, valvular heart disease	○
4.14	○	○	Heart disease	○
4.15	○	○	Peripheral vascular disease (pain in legs when walking)	○
4.16	○	○	Epilepsy/seizures	○
4.17	○	○	Any other diagnosis?	○

4.17.1 If yes, specify: _____

5.0 Lifestyle

5.1 What is your current smoking status?

- ○ Never smoked (If never smoked, go to 5.2)
- ○ Ex-smoker
- ○ Current smoker (smoked within past month)

5.1.1 If ex-smoker or current smoker, has your smoking changed since your first stroke event during the ARCOS period (2011-2012)?

○ Yes ○ No

5.1.2 If yes, what changes have you made?

- ○ Stopped smoking successfully
- ○ Reduced smoking
- ○ Smoking more often

5.2 Do you regularly drink any type of alcohol?

○ Yes ○ No (If No, go to 5.2.2)

5.2.1 If Yes, which of the following best describes how often have you drank in the past three months?

- ○ All day
- ○ Four or more times a day
- ○ Two or three times a day
- ○ Once a day
- ○ Every 2 days
- ○ Every 3 or 4 days
- ○ Every 5 or 6 days
- ○ Once a week
- ○ Every 10 days
- ○ Once a fortnight
- ○ Once a month

ARCOS IV Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number	Participant Initials	Date Of Birth
		Day / Month / Year

5.2.2 Have you made any changes to your drinking since your first stroke event during the ARCOS period (2011-2012)?

○ Yes ○ No

5.2.3 If yes, what change have you made?

○ Stopped drinking
○ Reduced amount of drinking
○ Increased amount of drinking

5.3 How would you rate your current diet or eating habits?

Very healthy — Mostly healthy
A mixture of healthy and unhealthy — Mostly unhealthy

5.4 On average how many servings of vegetables and fruit do you eat per day?

○ None ○ Less than one ○ One
○ Two ○ Three ○ Four or more

5.5 How often do you add salt to your food?

○ Never ○ Rarely ○ Sometimes
○ Regularly ○ Always ○ Don't know

5.6 How often do you remove fat from your food or choose low fat options?

○ Never ○ Rarely ○ Sometimes
○ Regularly ○ Always ○ Don't know

5.7 Have you made any changes to your diet since your first stroke event during the ARCOS period (2011-2012)?

Yes No

5.7.1 If yes, what changes have you made?

○ Smaller amounts of food ○ More fruit and/or vegetables
○ Reduced fat ○ Less healthy diet
○ Reduced salt ○ Other:

5.8 During the past month, on how many days per week did you engage in at least 30 minutes of moderate exercise or activity that made you breathe harder than normal?

○ None ○ 1 day ○ 2 days ○ 3 days
○ 4 days ○ 5 days ○ 6 days ○ 7 days

5.7 Are there any lifestyle areas you would like to change to reduce your risk of recurrent stroke?

○ Yes ○ No

5.7.1 If Yes, what changes would you like to make?

Appendix E: Barthel Index

ARCOS IV

Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

7.0 Rehabilitation

7.1 Did you receive inpatient rehabilitation following your stroke?

○ Yes ○ No

7.1.1 If yes, specify length of stay

7.2 Did you receive community rehabilitation following your stroke?

○ Yes ○ No

7.2.1 If yes, which service?

7.2.2 How often did you receive community rehabilitation?

○ Once per week ○ Once per fortnight ○ Once per month ○ Once per 6 months Other:

8.0 Barthel Index

Guidelines for Completion

a. *The index should be used as a record of what a participant does, not as a record of what a participant, could do.*

b. *The main aim is to establish the degree of independence from any help, physical or verbal, however minor or for whatever reason.*

c. *The need for supervision renders the participant not independent.*

d. *A participant's performance should be established using the best available evidence. Asking the participant, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However, direct testing is not needed.*

e. *Usually the participant's performance over the proceeding 24-48 hours is important, but occasionally longer periods will be relevant.*

f. *Middle categories imply that the patient supplies over 50 percent of the effort.*

g. *Use of aids to be independent is allowed.*

Choose the scoring point for the statement that most closely corresponds to the patient's current level of ability for each of the following 10 items. Record actual, not potential, functioning. Information can be obtained from the patient's self-report, from a separate party who is familiar with the patient's abilities (such as a relative), or from observation.
Refer to the Guidelines section for detailed information on scoring and interpretation.

8.1 Feeding (tick one only)

2 ○ Independent: Able to use any necessary device; feeds in a reasonable time; able to cut up food, use condiments, spread butter etc. on his/her own. Food may be placed within reach.

1 ○ Needs help: e.g. with cutting or spreading butter.

0 ○ Dependent: Needs to be fed.

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

8.2 Bathing (tick one only)

1 ○ Independent: Able to wash self all over; may be by using shower, a full bath or standing and sponging all over. Includes getting into and out of bath, or shower room.

0 ○ Dependent: Needs some help.

8.3 Grooming (tick one only)

1 ○ Independent: Doing all personal activities, e.g. washing hands and face, combing hair. Includes shaving and teeth. Not to need any help, except.

0 ○ Dependent: Needs some help.

8.4 Dressing (tick one only)

2 ○ Independent: Able to dress, includes (buttons, zip, laces) getting clothes out of closet/drawers. No needed at all, may use rail for stabilising.

1 ○ Needs help: Needs minor help verbal or physical managing clothes and balancing.

0 ○ Dependent: Unable to dress without major assistance.

8.5 Bowels (tick one only)

2 ○ Continent: If needs enema, suppository, must manage him/herself.

1 ○ Occasional accident: Rare (under once a week); needs help with enema.

0 ○ Incontinent

8.6 Bladder (tick one only)

2 ○ Continent: Able to use any device (e.g.catheter) if necessary.

1 ○ Occasional accident: Maximum once per 24 hours; needs help with device.

0 ○ Incontinent or catheterized and unable to manage.

8.7 Toilet (tick one only)

2 ○ Independent: Able to handle clothes, wipe self, flush toilet, empty commode completely unaided. Able to get on and off alone.

1 ○ Needs help: Able to manage with minor help balancing, handling clothes or toilet paper. However, still able to use toilet.

0 ○ Dependent: Unable to manage without major assistance.

8.8 Chair/Bed Transfers (tick one only)

3 ○ Independent: No help; includes locking wheelchair if necessary.

2 ○ Minimal help: Includes verbal supervision and minor physical help such as might be given by a not very strong spouse.

1 ○ Major help: Able to sit unaided, but needs much help (two people).

0 ○ Dependent: Unable to manage without major assistance.

Continued...

Appendix F: Modified Rankin Scale

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

8.9 Mobility (tick one only)

3 ○ Independent: May use any aid; speed is not important. Able to mobilise about house.

2 ○ Needs help: Verbal or physical supervision, including help up into walking frame or other help standing.

1 ○ Independent in wheelchair: Must be able to negotiate corners alone.

0 Immobile: Including being wheeled by another.

8.10 Stairs (tick one only)

2 ○ Independent: Must carry walking aid if used.

1 Needs help: Physical or verbal supervision, carrying aid etc.

0 Unable: Needs lift (elevator), or cannot negotiate stairs.

8.11 Total Barthel Score

9.0 Modified Rankin Scale

How would you describe your current symptoms or disability?

	SCORE	DESCRIPTION
○	0	No symptoms at all
○	1	No significant disability despite symptoms; able to carry out all usual duties and activities
○	2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
	3	Moderate disability; requiring some help, but able to walk without assistance
○	4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
	5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
○	6	Dead

9.1 MRS Score

ARCOS IV
Auckland Regional Community Outcome Stroke

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

10.0 Health related Quality of life

Instructions: *By placing one tick only in each question, please indicate which statements best describe your health today.*

10.1 Mobility (tick one only)

- ○ I have no problems walking about
- ○ I have some problems walking about
- ○ I am confined to bed

10.2 Self-Care (tick one only)

- ○ I have no problems with self-care
- ○ I have some problems washing or dressing myself
- ○ I am unable to wash or dress myself

10.3 Usual Activities (e.g. work, study, housework, family or leisure activities) (tick one only)

- ○ I have no problems with performing my usual activities
- ○ I have some problems with performing my usual activities
- ○ I am unable to perform my usual activities

10.4 Pain/Discomfort (tick one only)

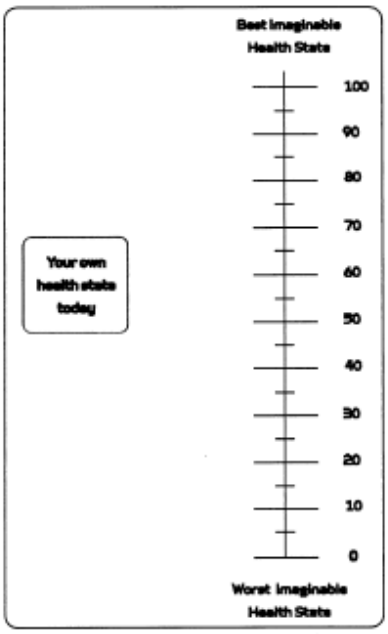
- ○ I have no pain or discomfort
- ○ I have moderate pain or discomfort
- ○ I have extreme pain or discomfort

10.5 Anxiety/Depression (tick one only)

- ○ I am not anxious or depressed
- ○ I am moderately anxious or depressed
- ○ I am extremely anxious or depressed

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



10.6 Health state score: ____

Appendix G: Fatigue Visual Analog Scale and Fatigue Severity Scale

ARCOS IV
Auckland Regional Community Outcome Stroke

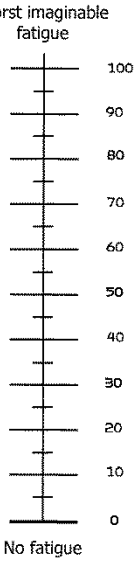
ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day Month Year)

11.0 Fatigue Visual Analogue Scale

On a scale of 0 to 100, with 100 representing maximum fatigue and 0 representing no fatigue, how much fatigue have you experienced since your stroke?

Please put a line on the scale that represents how much fatigue you have experienced.



(Office Use only)

11.1 Fatigue score

[ ] If zero, go to 13.0

12.0 Fatigue Severity Scale

Please circle the number between 1 and 7 which you feel best fits the following statements. This refers to your usual way of life within the last week. 1 indicates "strongly disagree" and 7 indicates "strongly agree."

Read and circle a number.	Strongly disagree						Strongly agree
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

12.1 Total fatigue score: [ ]

Appendix H: Hospital Depression and Anxiety Scale

ARCOS - IV 4 Year Follow - Up: Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

Complete remaining sections in Part A at ALL assessments (ALL Participants)

Hospital Anxiety and Depression Scale (HADS)

Please indicate which of the following options best describes how you have been feeling during the last week.

I feel tense or wound up

- ○ 3 - Most of the time
- ○ 2 - A lot of the time
- ○ 1 - From time to time, occasionally
- ○ 0 - Not at all

I still enjoy the things I used to enjoy

- ○ 0 - Definitely as much
- ○ 1 - Not quite as much
- ○ 2 - Only a little
- ○ 3 - Hardly at all

I get a sort of frightened feeling as if something awful is about to happen

- ○ 3 - Very definitely and quite badly
- ○ 2 - Yes, but not too badly
- ○ 1 - A little, but it doesn't worry me
- ○ 0 - Not at all

I can laugh and see the funny side of things

- ○ 0 - As much as I always could
- ○ 1 - Not quite so much now
- ○ 2 - Definitely not as much now
- ○ 3 - Not at all

Worrying thoughts go through my mind

- ○ 3 - A great deal of the time
- ○ 2 - A lot of the time
- ○ 1 - From time to time, but not too often
- ○ 0 - Only occasionally

15.6 I feel cheerful (tick one only)

- ○ 3 - Not at all
- ○ 2 - Not often
- ○ 1 - Sometimes
- ○ 0 - Most of the time

15.7 I can sit at ease and feel relaxed (tick one only)

- ○ 0 - Definitely
- ○ 1 - Usually
- ○ 2 - Not often
- ○ 3 - Not at all

15.8 I feel as if I am slowed down (tick one only)

- ○ 3 - Nearly all the time
- ○ 2 - Very often
- ○ 1 - Sometimes
- ○ 0 - Not at all

15.9 I get a sort of frightened feeling like 'butterflies' in the stomach (tick one only)

- ○ 0 - Not at all
- ○ 1 - Occasionally
- ○ 2 - Quite often
- ○ 3 - Very Often

15.10 I have lost interest in my appearance (tick one only)

- ○ 3 - Definitely
- ○ 2 - I don't take as much care as I should
- ○ 1 - I may not take quite as much care
- ○ 0 - I take just as much care as ever

15.11 I feel restless as if I have to be on the move (tick one only)

- ○ 3 - Very much indeed
- ○ 2 - Quite a lot
- ○ 1 - Not very much
- ○ 0 - Not at all

15.12 I look forward with enjoyment to things (tick one only)

- ○ 0 - As much as I ever did
- ○ 1 - Rather less than I used to
- ○ 2 - Definitely less than I used to
- ○ 3 - Hardly at all

15.13 I get sudden feelings of panic (tick one only)

- ○ 3 - Very often indeed
- ○ 2 - Quite often
- ○ 1 - Not very often
- ○ 0 - Not at all

15.14 I can enjoy a good book or TV programme (tick one only)

- ○ 0 - Often
- ○ 1 - Sometimes
- ○ 2 - Not often
- ○ 3 - Very seldom

Anxiety Subscore	
Depression Subscore	
15.15 **Total HADS Score**	

Appendix I: Montreal Cognitive Assessment

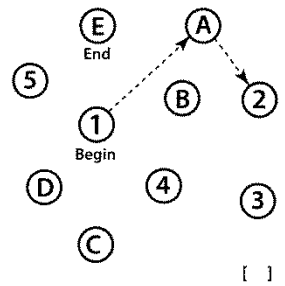
ARCOS IV — ARCOS - IV 3 Year Follow - Up Stroke

Registration Number | Participant Initials | Date Of Birth (Day / Month / Year)

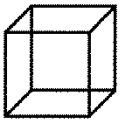
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

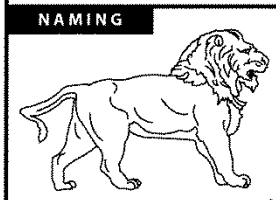
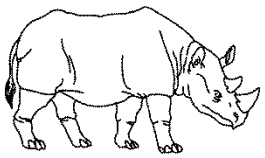
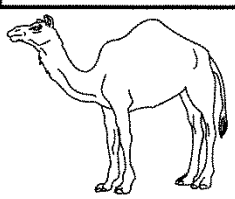


[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING

[ ] [ ] [ ] ___/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) ___/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	___/5
Optional	Category cue							
	Multiple choice cue							

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

© Z.Nasreddine MD **www.mocatest.org** Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

MOCA Test Scores

(Instructions for RA: please use the information and sub-scores above to complete the following section)

18.1 MOCA (tick one only)

(Instruction: If Not Done, go to section 10)

- ○ Full test
- ○ Short test, reason: _____
- ○ Not done, reason: _____

18.2 ☐☐ : ☐☐ Start Time
hh mm

18.3 ☐☐ : ☐☐ Finish Time
hh mm

18.4 ☐ Visuospatial/executive

18.5 ☐ Naming

18.6 ☐ Attention

18.7 ☐ Language

18.8 ☐ Abstraction

18.9 ☐ Delayed recall

18.10 ☐ Orientation

18.11 ☐ Total MOCA Score

Please record the following additional information from the MoCA during testing:

18.12 ☐☐ **Verbal fluency**

Number of words beginning with f generated in the first 15 seconds

18.13 ☐☐ **Delayed recall (category cue)**

Number of words recalled with category cue (if patient does not spontaneously recall all the words)

18.14 ☐☐ **Delayed recall (multichoice cue)**

Number of words recalled with a multichoice cue (if patient fails to recall the words with a category cue)

Appendix J: Screening Neuropsychological Assessment Battery

Neuropsychological Assessment Battery®

By

Robert A. Stern, PhD, and Travis White, PhD

Screening Module Score Report

Developed By

Travis White, PhD, Robert A. Stern, PhD, and PAR Staff

Patient Information

Patient Name:	C SMI
Patient ID:	101099
Date of Birth:	15/09/1924
Age:	89
Sex:	Male
Ethnicity:	Caucasian
Handedness:	Right
Education:	-Not Specified-

Testing Information

Date of Examination:	12/08/2014
Normative Sample:	U.S. Census-Matched Sample

This report is confidential and is intended to be used by qualified individuals only, as defined in the *NAB Administration, Scoring, and Interpretation Manual* (Stern & White, 2003). The report should only be released to individuals who are qualified to interpret the results. NAB test scores should be interpreted within the context of the examinee's individual presentation and history. Although standardized scores provide the examiner with an important and necessary understanding of the individual's test performance compared with a normative group, they do not on their own lead to accurate diagnosis or treatment recommendations. Please refer to the *NAB Administration, Scoring, and Interpretation Manual* for guidance in the interpretation and meaning of NAB scores.

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Version: 1.10 (2.20.036)

Screening Domain Score Summary Table

Screening Domain Score	Standard Score	Percentile Rank	Confidence Interval 95%	Interpretive Category
Screening Attention Domain (S-ATT)	76	5	67 - 85	Mildly-to-moderately impaired
Screening Language Domain (S-LAN)	129	97	109 - 149	Superior
Screening Memory Domain (S-MEM)	108	70	95 - 121	Above average
Screening Spatial Domain (S-SPT)	79	8	63 - 95	Mildly impaired
Screening Executive Functions Domain (S-EXE)	96	39	85 - 107	Average
Total Screening Index (S-NAB)	96	39	83 - 109	Average

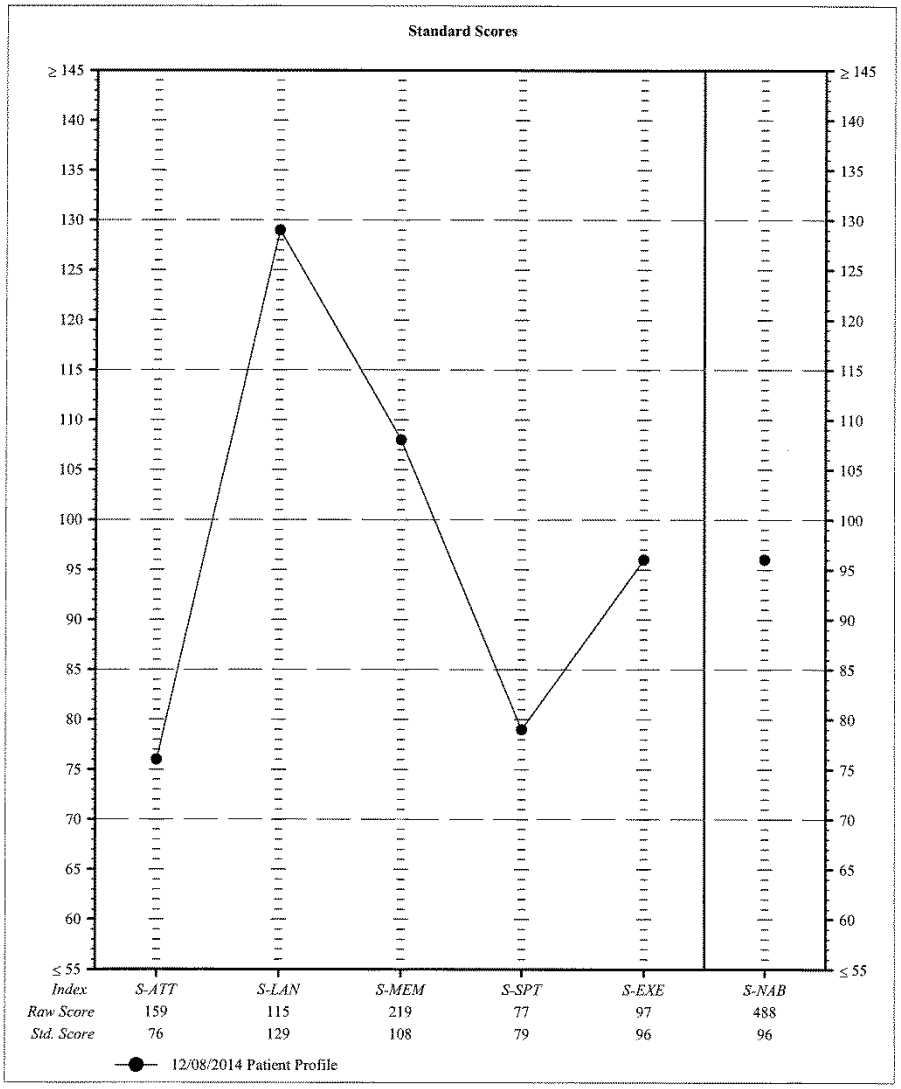
Recommendations for Administration of Main NAB Modules

Screening Domain Score	Score Range	Patient's Score	Administration Recommendation for Main Module
Screening Attention Domain (S-ATT)	45-74		☐ Do not administer NAB Attention Module
	75-113	76	☑ Administer NAB Attention Module
	114-155		☐ Do not administer NAB Attention Module
Screening Language Domain (S-LAN)	45-75		☐ Do not administer NAB Language Module
	76-125		☐ Administer NAB Language Module
	126-155	129	☑ Do not administer NAB Language Module
Screening Memory Domain (S-MEM)	45-75		☐ Do not administer NAB Memory Module
	76-118	108	☑ Administer NAB Memory Module
	119-155		☐ Do not administer NAB Memory Module
Screening Spatial Domain (S-SPT)	45-74		☐ Do not administer NAB Spatial Module
	75-119	79	☑ Administer NAB Spatial Module
	120-155		☐ Do not administer NAB Spatial Module
Screening Executive Functions Domain (S-EXE)	45-73		☐ Do not administer NAB Executive Functions Module
	74-114	96	☑ Administer NAB Executive Functions Module
	115-155		☐ Do not administer NAB Executive Functions Module

Screening Recommendations Caveats

Screening recommendations were developed to assist clinicians with interpreting NAB Screening Domain scores for purposes of selecting main NAB module(s) for subsequent administration after the Screening Module. A detailed discussion of the methodology used to determine the screening recommendations is contained in the *NAB Psychometric and Technical Manual* (White & Stern, 2003). These screening recommendations are merely guidelines for those users who may wish to follow them. Many referral questions and applications of the NAB will no doubt require administration of the entire NAB or select NAB modules, and professional clinicians should use their judgment when determining the need for administration of the entire NAB or select NAB modules.

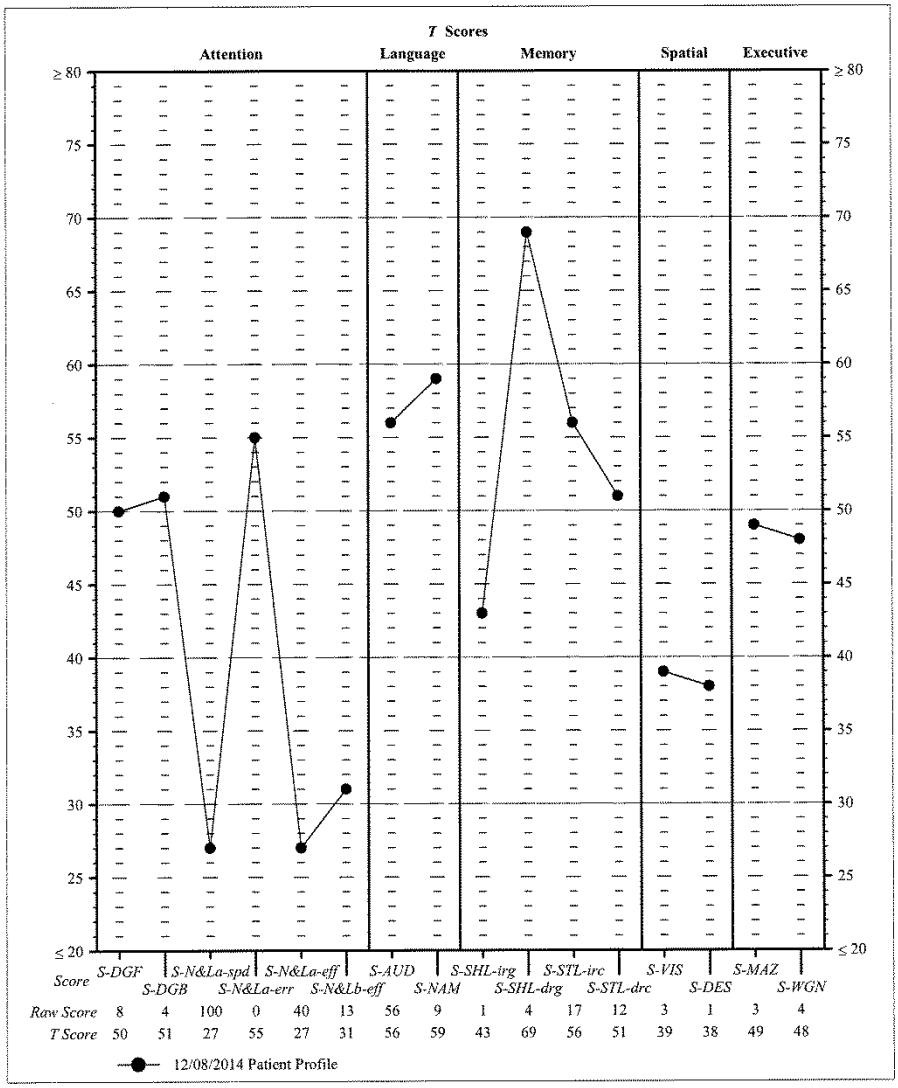
Screening Domain / Index Score Profiles



Patient: C SMI
Patient ID: 101099

Test Date: 12/08/2014
Page 4 of 8

Screening *T* Score Profiles



Screening Attention Score Table

Form 1

Score	Raw Score	*z* Score	*T* Score	%ile	Cum. %age	Interpretive Category
Screening Orientation (S-ORN)	29			50		Average
Screening Orientation to Self (S-ORN-slf)	14				100.00	
Screening Orientation to Time (S-ORN-tim)	10				100.00	
Screening Orientation to Place (S-ORN-plc)	4				100.00	
Screening Orientation to Situation (S-ORN-sit)	1				100.00	
Screening Digits Forward (S-DGF)	8	-0.08	**50**	50		Average
Screening Digits Forward Longest Span (S-DGF-spn)	7			75		Above average
Screening Digits Backward (S-DGB)	4	0.05	**51**	54		Average
Screening Digits Backward Longest Span (S-DGB-spn)	4			21		Below Average
Screening Numbers & Letters Part A Speed (S-N&L$_A$-spd)	100	-2.75	27	1		Moderately impaired
Screening Numbers & Letters Part A Errors (S-N&L$_A$-err)	0	-0.13	55	69		Above average
Screening Numbers & Letters Part A Efficiency (S-N&L$_A$-eff)	40	-2.65	**27**	1		Moderately impaired
Screening Numbers & Letters Part B Efficiency (S-N&L$_B$-eff)	13	-2.33	**31**	3		Mildly-to-moderately impaired

Qualitative Features

Screening Digits Forward Qualitative Features:
☐ Reversals ☐ Omissions ☐ Perseverations

Screening Digits Backward Qualitative Features:
☐ Reversals ☐ Omissions ☐ Perseverations

Screening Attention Domain Score Table

Score	Sum of *T* Scores	S-ATT Standard Score	Percentile Rank	Confidence Interval 95%
Screening Attention Domain (S-ATT)	159	76	5	67 - 85

Screening Language Score Table

Form 1

Score	Raw Score	*z* Score	*T* Score	%ile	Cum. %age	Interpretive Category
Screening Auditory Comprehension (S-AUD)	56	-0.74	**56**	73		Above average
Screening Auditory Comprehension Colors (S-AUD-col)	13				100.00	
Screening Auditory Comprehension Shapes (S-AUD-shp)	22				100.00	
Screening Auditory Comprehension Colors/Shapes/Numbers (S-AUD-csn)	21				100.00	
Screening Naming (S-NAM)	9	-0.13	**59**	82		Above average
Screening Naming Percent Correct After Semantic Cuing (S-NAM-sem%)	---				---	
Screening Naming Percent Correct After Phonemic Cuing (S-NAM-pho%)	---				---	

Note. "---" indicates a score that could not be calculated due to missing data.

Qualitative Features

Screening Auditory Comprehension Colors Qualitative Features:

☐ Pointing problems ☐ Perseverations ☐ Sequencing problems

Screening Auditory Comprehension Shapes Qualitative Features:

☐ Pointing problems ☐ Perseverations ☐ Sequencing problems

Screening Auditory Comprehension Colors/Shapes/Numbers Qualitative Features:

☐ Pointing problems ☐ Perseverations ☐ Number problems

Screening Naming Qualitative Features:

☐ Perceptual errors ☐ Perseverations ☐ Semantic paraphasias
☐ Phonemic paraphasias

Screening Language Domain Score Table

Score	Sum of *T* Scores	S-LAN Standard Score	Percentile Rank	Confidence Interval 95%
Screening Language Domain (S-LAN)	115	129	97	109 - 149

Screening Memory Score Table

Form 1

Score	Raw Score	*z* Score	*T* Score	%ile	Interpretive Category
Screening Shape Learning Immediate Recognition (S-SHL-irg)	1	-0.58	**43**	24	Below Average
Screening Shape Learning Delayed Recognition (S-SHL-drg)	4	1.64	**69**	97	Above average
Screening Shape Learning Percent Retention (S-SHL-%rt)	200			90	Above average
Screening Story Learning Immediate Recall (S-STL-irc)	17	0.08	**56**	73	Above average
Screening Story Learning Delayed Recall (S-STL-drc)	12	-0.50	**51**	54	Average
Screening Story Learning Percent Retention (S-STL-%rt)	71			25	Average

Delayed Recall Intervals

Screening Shape Learning: 1425 minutes.

Screening Story Learning: 1425 minutes.

Screening Memory Domain Score Table

Score	Sum of *T* Scores	S-MEM Standard Score	Percentile Rank	Confidence Interval 95%
Screening Memory Domain (S-MEM)	219	108	70	95 - 121

Screening Spatial Score Table

Form 1

Score	Raw Score	*z* Score	*T* Score	%ile	Interpretive Category
Screening Visual Discrimination (S-VIS)	3	-0.95	**39**	14	Mildly impaired
Screening Design Construction (S-DES)	1	-1.41	**38**	12	Mildly impaired

Screening Spatial Domain Score Table

Score	Sum of *T* Scores	S-SPT Standard Score	Percentile Rank	Confidence Interval 95%
Screening Spatial Domain (S-SPT)	77	79	8	63 - 95

Screening Executive Functions Score Table

Form 1

Score	Raw Score	*z* Score	*T* Score	%ile	Interpretive Category
Screening Mazes (S-MAZ)	3	-0.67	**49**	46	Average
Screening Word Generation (S-WGN)	4	-0.41	**48**	42	Average
Screening Word Generation Perseverations (S-WGN-psv)	1			7	Mildly impaired

Screening Executive Functions Domain Score Table

Score	Sum of *T* Scores	S-EXE Standard Score	Percentile Rank	Confidence Interval 95%
Screening Executive Functions Domain (S-EXE)	97	96	39	85 - 107

End of Report

Appendix K: Computerized Neuropsychological Vital Signs Test

CNS Vital Signs Neurocognitive Testing Report

Billing Codes 96111, 96116, 96118, 96119, 96120 and more...

Find CNS Vital Signs Reimbursement & Brief Interpretation Guides at www.CNSVS.com

CNS Vital Signs Report				Test Date: March 28, 2015 11:20:03				
Patient ID: PatientExample				Administrator: Technician				
Age: 50				Language: English (United States)				
Total Test Time: 34:07 (min:secs)			CNSVS Duration: 26:16 (min:secs)		Version 4.0.86			
Patient Profile:	Percentile Range			> 74	25 - 74	9 - 24	2 - 8	< 2
	Standard Score Ran	2	1	> 109	90 - 109	80 - 89	70 - 79	< 70
Domain Scores	Subject Score	Standard Score	Percentile	VI**	Above	Average	Low Average	Low	Very Low
Neurocognition Index (NCI)	NA	78	7	Yes			X		
Composite Memory	94	93	32	Yes		X			
Verbal Memory	52	99	47	Yes		X			
Visual Memory	42	90	25	Yes		X			
Psychomotor Speed	127	69	2	Yes					X
Reaction Time*	751	87	19	Yes	3		X		
Complex Attention*	16	70	2	Yes		X		X	
Cognitive Flexibility	22	70	2	Yes				X	
Processing Speed	29	64	1	Yes					X
Executive Function	28	77	6	Yes				X	
Simple Visual Attention	40	107	68	Yes		X			
Motor Speed	98	84	14	Yes			X		

Domain Dashboard: Above average domain scores indicate a standard score (SS) greater than 109 or a Percentile Rank (PR) greater than 74, indicating a high functioning test subject. Average is a SS 90-109 or PR 25-74, indicating normal function. Low Average is a SS 80-89 or PR 9-24 indicating a slight deficit or impairment. Below Average is a SS 70-79 or PR 2-8, indicating a moderate level of deficit or impairment. Very Low is a SS less than 70 or a PR less than 2, indicating a deficit and impairment. Reaction times are in milliseconds. An * denotes that "lower is better", otherwise higher scores are better. Subject Scores are raw scores calculations generated from data values of the individual subtests.
VI - Validity Indicator:** Denotes a guideline for representing the possibility of an invalid test or domain score. "No" means a clinician should evaluate whether or not the test subject understood the test, put forth their best effort, or has a clinical condition requiring further evaluation.

Verbal Memory Test (VBM)	Score	Standard	Percentile	
Correct Hits - Immediate	13	104	61	The **VBM** test measures how well a subject can recognize, remember, and retrieve words e.g. exploit or attend literal representations or attribute. Subjects have to remember 15 words and recognize them in a field of 15 distractors. There are two parts to this test, Immediate and Delayed. The delayed part is presented at the end of the battery. "Correct Hits" refers to the number of target words recognized. Low scores indicate verbal memory impairment.
Correct Passes - Immediate	14	96	40	
Correct Hits - Delay	9	93	32	
Correct Passes - Delay	15	110	75	
Visual Memory Test (VIM)	**Score**	**Standard**	**Percentile**	
Correct Hits - Immediate	12	101	53	The **VIM** test measures how well a subject can recognize, remember, and retrieve geometric figures e.g. exploit or attend symbolic or spatial representations. Subjects have to remember 15 geometric figures, and recognize them in a field of 15 distractors. There are two parts to this test, Immediate and Delayed. The delayed part is presented at the end of the battery. "Correct Hits" refers to the number of target figures recognized. Low scores indicate visual memory impairment.
Correct Passes - Immediate	11	98	45	
Correct Hits - Delay	9	86	18	
Correct Passes - Delay	10	95	37	
Finger Tapping Test (FTT)	**Score**	**Standard**	**Percentile**	
Right Taps Average	50	86	18	The **FTT** is test of motor speed and fine motor control ability. There are three rounds of tapping with each hand. The FTT test measures the speed and the number of finger-taps with each hand. Low scores indicate motor slowing. Speed of manual motor activity varies with handedness. Most people are faster with their preferred hand but not always.
Left Taps Average	48	85	16	
Symbol Digit Coding (SDC)	**Score**	**Standard**	**Percentile**	
Correct Responses	29	64	1	The **SDC** test measures speed of processing and draws upon several cognitive processes simultaneously, such as visual scanning, visual perception, visual memory, and motor functions. Errors may be due to impulsive responding, misperception, or confusion.
Errors*	0	110	75	
Stroop Test (ST)	**Score**	**Standard**	**Percentile**	
Simple Reaction Time*	231	102	55	The **ST** measures reaction times, inhibition / disinhibition, mental flexibility or directed attention. The ST is a classic test of impulsivity and inhibitor control. Prolonged reaction times indicate cognitive slowing / impairment. Errors may be due to impulsive responding, misperception, or confusion.
Complex Reaction Time Correct*	542	91	27	
Stroop Reaction Time Correct*	568	87	19	
Stroop Commission Errors*	6	33	1	
Shifting Attention Test (SAT)	**Score**	**Standard**	**Percentile**	
Correct Responses	38	77	6	The **SAT** measures executive function or how well a subject reacts to set shifting (mental flexibility) and manages multiple tasks simultaneously. Subjects have to adjust their responses to randomly changing rules. The best scores are high correct responses, few errors and a short reaction time. Normal subjects may be slow but accurate, or fast but not so accurate. Attention deficit may be apparent.
Errors*	10	84	14	
Correct Reaction Time*	1360	77	6	
Continuous Performance Test (CPT)	**Score**	**Standard**	**Percentile**	
Correct Responses	40	103	58	The **CPT** measures sustained attention or vigilance and choice reaction time. Most normal subjects obtain near-perfect scores on this test. A long response time may suggest cognitive slowing and/or impairment. More than 2 errors (total) may be clinically significant. More than 4 errors (total) indicate attentional dysfunction.
Omission Errors*	0	103	58	
Commission Errors*	0	107	68	
Choice Reaction Time Correct*	491	83	13	

Appendix L: Published Paper from Results from Study Two (Chapter 5)

Original Paper

Neuro epidemiology

Neuroepidemiology 2017;49:129–134
DOI: 10.1159/000484606

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Published online: November 16, 2017

Determinants, Prevalence, and Trajectory of Long-Term Post-Stroke Cognitive Impairment: Results from a 4-Year Follow-Up of the ARCOS-IV Study

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Keywords
Stroke · Neuropsychology · Cognitive Impairment · Long term · Prevalence · Trajectory · Determinants

Abstract

Background: The long-term (>12 months) prevalence, predictors, and trajectory of post-stroke cognitive deficits are not well established, especially at a community level. This study investigated the longitudinal course and prevalence of cognitive impairment in an incidence cohort, identifying factors associated with declining cognition. ***Methods:*** Two hundred fifty-seven participants (mean age = 67.93 ± 13.59) of first-ever stroke survivors, completed cognitive assessments within 2 weeks post stroke, and/or 1, 6, 12, and 48-month. Multivariate linear and logistic models were used to identify baseline predictors (reported as OR with 95% CI) and trajectory of cognitive impairment. ***Results:*** Cognitive functioning significantly declined by 2.8 points by 4 years post stroke. Eighty-four percent of stroke survivors had cognitive impairment indicative of post-stroke dementia (mean Montreal cognitive assessment = 20 ± 4.7) at 4-year. There were significant associations between progressive cognitive decline and the following factors: male gender (OR 2.9, 95% CI 1.6–5.9, $p = 0.0171$), coronary artery disease (OR 2.96, 95% CI 1.35–6.49, $p = 0.0070$), arrhythmia (OR 2.21, 95% CI 1.07–4.57, $p = 0.0317$), not in a relationship (OR 2.8, 95% CI 1.4–5.50, $p < 0.0001$), and not employed (OR 4.9, 95% CI 1.9–12.1, $p < 0.0001$). ***Conclusions:*** Cognitive deficits remain highly prevalent at 4-year post stroke. Early identification of those at higher risk of declining cognition is vital to target rehabilitation interventions at the acute stage and improve overall outcomes.

Introduction

Stroke has a significant deleterious affect on cognition, and this is a major cause of post-stroke disability. Acute post-stroke cognitive impairment (PSCI) is reported in up to 70% of patients [1]. While these deficits may improve within weeks/months after onset, over half of stroke survivors experience persisting long-term deficits, which can affect the daily functioning and quality of life [2]. There is also evidence that 10% of stroke survivors develop dementia after their first stroke and over one third after recurrent stroke [3]. Risk factors and contributors to PSCI vary; these factors could be older age (>65), lower educational levels, stroke location, vascular comorbidities, and recurrent stroke [4]. The true prevalence of PSCI

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may be underestimated in non-population-based research due to selection bias [5], with exclusion of non-hospitalized stroke patients (e.g., hospital-based studies) and patients with more severe strokes or with aphasias who are unable to complete cognitive assessments. The use of inadequate psychometric screening tools such as the Mini Mental State Examination (MMSE) to assess cognitive function (often missing mild cognitive impairment and executive functioning), and loss to long-term follow-up, also likely contribute to the underestimation of PSCI [6]. Furthermore, variability in the range of baseline predictors selected among studies has resulted in a lack of consensus as to which factors truly influence the natural course of cognitive impairment [7, 8]. Therefore, a comprehensive range of baseline predictors and a reliable tool is needed to evaluate PSCI more accurately. The aim of this study was to evaluate the prevalence of PSCI and predictors of persistent PSCI.

Methods

Study Population

This study was a follow-up of the fourth Auckland Stroke Regional Outcomes Study (ARCOS-IV), a prospective population-based study, in New Zealand [9]. ARCOS-IV was a register of all new stroke cases (n = 2,096; Fig. 1) registered between March 2011 and February 2012. Full methods for ARCOS-IV study have been previously described [9]. The cohort comprised 257 stroke patients who completed assessments at baseline, and/or 1, 6, and 12-month and 4 years post stroke. Informed consent was obtained at baseline and again at 4 years post stroke. In brief, case ascertainment used multiple sources of information to obtain both hospitalized and non-hospitalized cases. Stroke was defined on the basis of World Health Organization standard diagnostic criteria [10] and was divided into pathological types (ischemic, intracerebral, subarachnoid, undetermined) according to standard clinical and CT/MRI/necropsy findings (97% cases were identified according to this criteria). Potential participants who previously consented to be contacted about future research at the 12-month follow-up were invited to take part in the 4-year follow-up study. These analyses included all ARCOS-IV cases who (1) provided written informed consent, (2) agreed to be contacted for further follow-up, and (3) had outcome data for at least one follow-up assessment.

Ethical Approval

Ethical approval was obtained from the New Zealand Northern Y Regional Ethics Committee (NTX/10/90/090).

Assessment

Cognitive Assessment

With its high sensitivity to detect PSCI, the Montreal cognitive assessment (MoCA) was used to assess global cognition [11, 12]. The MoCA has good psychometric properties and is a valid screening tool to detect post-stroke cognitive impairment [13]. Although a recent study [14] questioned the accuracy of the MoCA to assess attention and executive function by stroke lateralization, the majority of studies have shown the MoCA to be superior compared to other screening measures such as the MMSE [11, 15, 16]. While primarily considered a screening tool, the MoCA has been used as a cognitive outcome measure in longitudinal studies where lengthy neuropsychological testing is not often feasible.

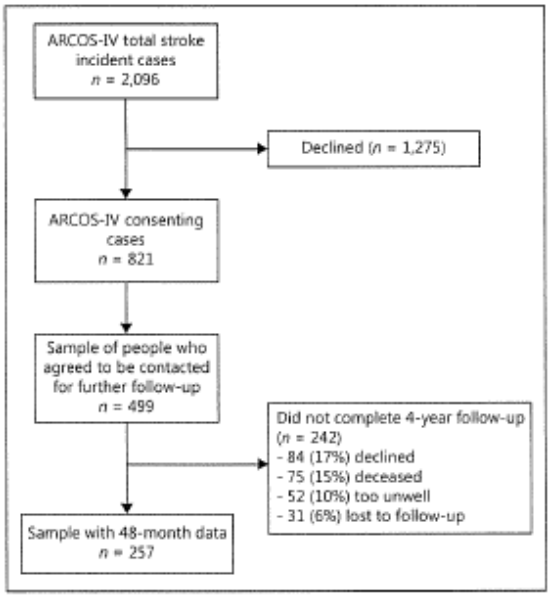

Fig. 1. Study recruitment summary.

Potential Predictors

Covariate factors measured at baseline included demographics (age, gender, education level, marital status, employment); stroke characteristics (subtype, vascular territory, lesion location, hemisphere); and vascular risk factors (hypertension, myocardial infarction, coronary artery disease, arrhythmia, hypercholesterolemia, and diabetes). Outcome measures collected at follow-ups included clinical (Modified Rankin Scale), functional (Barthel Index), fatigue (Fatigue Visual Analogue Scale), health-related quality of life (European Quality Life-5 dimensions), mood (Hospital and Anxiety Scale), and cognition (MoCA, as described above) [9]. Diagnostic criteria for these covariates are reported elsewhere [9].

Statistical Analyses

A general linear mixed-effects model was used to investigate changes in cognitive performance over the 5 follow-up time points. A univariate logistic repeated measures regression model was used to compare the trajectory of cognitively intact (i.e., MoCA ≥26) vs. cognitively impaired MoCA (i.e., MoCA

Table 1. Demographic and clinical features of participants

Descriptive	*n* (%)
Age groups	
<50	33 (13)
51–64	58 (23)
65–74	79 (31)
75+	87 (33)
Gender	
Female	121 (47)
Male	136 (53)
Ethnicity	
European	207 (81)
Non-European	50 (19)
Marital status	
Married	157 (61)
Never married/separated, divorced, or widowed	100 (39)
Employment	
Employed	50 (19)
Retired/unemployed	207 (81)
Education level	
Did not complete school	69 (27)
Completed school	51 (21)
Post-school qualification	132 (52)
Recurrent stroke	
Yes	44 (17)
Stroke type	
IS	224 (87)
ICH	15 (6)
SAH	18 (7)
Stroke sub-type	
LACI	74 (29)
PACI	78 (30)
POCI	69 (27)
TACI	18 (7)
Unknown	18 (7)
Hemisphere of lesion	
Left	116 (45)
Right	118 (46)
Brainstem	8 (3)
Both	14 (5.5)
Uncertain	1 (0.5)
Stroke vascular territory	
MCA	137 (53)
PCA	51 (20)
PICA	36 (14)
ACA	9 (4)
SCA	3 (1)
Unknown	21 (8)
Location of lesion	
Cortical	66 (26)
Subcortical	139 (54)
Unknown	52 (20)
Vascular risk factors	
High cholesterol	137 (54)
Hypertension	166 (65)
Diabetes	49 (19)
Coronary heart disease present	54 (21)
Arrhythmia present	65 (26)
Age, years, mean (SD)	67.93 (13.59)
Time since stroke, mean, (SD)	3.98 (5.60)

ISH, ischemic stroke; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage; LACI, lacunar infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct; TACI, total anterior circulation infarct; MCA, middle cerebral artery; PCA, posterior cerebral artery; PICA, posterior inferior cerebellar artery; ACA, anterior cerebral artery.

<26) over time to identify relevant time-important statistical associations (online suppl. Table 4; for all online suppl. material, see www.karger.com/doi/10.1159/000484606). For the purpose of this manuscript, we have chosen to analyze the MoCA as a binary variable, as it is more clinically relevant compared to analyzing MoCA as a continuous variable. The effect of the continuous MoCA over time is reported in text. Demographic and stroke characteristics listed in Table 1 comprised covariates selected for the regression analyses to determine statistically significant predictors of long-term cognitive impairment ($p < 0.05$). Significant predictors of cognitive functioning were retained in the multivariate logistic repeated measures regression models. Covariates were considered significant predictors and retained in the multivariate logistic repeated measures regression model if $p < 0.10$. The representativeness of the 4-year follow-up sample against the total ARCOS-IV incidence sample at stroke onset on demographic and stroke characteristic was evaluated using chi-square tests (online suppl. Table 3).

Results

Descriptive information for all participants is presented in Table 1. The mean age at 4 years was 67.93 ± 13.5 years. In terms of representativeness to the ARCOS-IV total stroke sample cohort, there were no significant differences between most characteristics, with the exception of stroke type, ethnicity, and high cholesterol.

Prevalence and Trajectory of Cognitive Impairment Post Stroke

At 4-years post stroke, a significant proportion of stroke survivors had global cognitive impairment assessed by the MoCA (MoCA <26; *n* = 217; 84%, m = 19.5), compared to 40 stroke survivors who performed within the normal range (MoCA ≥26; 16%, m = 26.7). The number of cases

Table 2. Multivariate MoCA logistic regression. Predictors of progression of global cognitive decline

Variable category	OR	95% CI	*p* value
Intercept	5.61	1.42–22.07	0.0137
Age, years			
51–64	1.77	0.59–5.27	0.3084
65–74	1.45	0.47–4.47	0.5195
75+	2.69	0.84–8.60	0.0959
Gender			
Male	2.95	1.55–5.62	0.0010
Marital status			
Never married/separated/ divorced/widowed	2.76	1.39–5.47	0.0036
Employment status			
Unemployed/retired	4.85	1.95–12.06	0.0007
Education			
Completed school	0.37	0.15–0.96	0.0413
Post-school qualification	0.20	0.09–0.44	0.0001
Time	0.83	0.68–1.01	0.0614

who completed MoCA at each time point was as follows: at baseline $n = 113$ (44%, m = 22.9 ± 4.55), at 28 days $n = 179$ (70%, m = 24.4 ± 3.84), at 6 months $n = 194$ (76%, m = 24.8 ± 3.7), at 12 months, $n = 211$ (82%, m = 24.7 ± 3.89), and at 4 years $n = 257$ (100%, m = 20.7 ± 4.70).

Over time, stroke survivors experienced a significant decline in global cognition, with total MoCA scores significantly decreasing ($p < 0.0001$). In the years post stroke, total MoCA scores increased by 0.85 points at 1 month ($p = 0.953$), by 1.26 points by 6 months ($p = 0.0134$), by 0.98 points by 12 months ($p = 0.0488$) but significantly declined by 2.8 points by 48 months ($p < 0.0001$) compared to baseline.

Predictors of Long-Term Cognitive Impairment

Univariate analysis (online suppl. Table 4) identified that older age (≥75 years) was associated with 13.4 times the risk of being cognitively impaired compared to someone aged ≤50 years at stroke onset ($p < 0.0001$). Males were 2.5 (95% CI 1.2–5.2) times more likely to be cognitively impaired than females ($p = 0.0171$), while being single increased the odds of cognitive impairment by 4.6 (95% CI 2.3–9.3, $p < 0.0001$) and being unemployed increased your odds of cognitive impairment by 13 (95% CI 5.1–33.4 $p < 0.0001$). However, individuals were more likely to be cognitively normal if they completed school ($p = 0.0293$) or had a post-school qualification ($p < 0.0001$). There was a borderline significant result for SAH stroke survivors ($p = 0.0931$), with cognition improving over the 4-year time period (online suppl. Table 4). All vascular risk factors were associated with cognitive impairment; the odds of being cognitively impaired increased by 1.35 for those with high cholesterol, by 1.4 for those with hypertension, and by 1.9 for those with diabetes – although these were not statistically significant. Having coronary heart disease was statistically significantly associated with increased odds of cognitive impairment (OR 2.96, 95% CI 1.35–6.49, $p = 0.0070$), as was arrhythmia (OR 2.21, 95% CI 1.07–4.57, $p = 0.0317$). The same set of statistically significant predictors of cognitive impairment were observed when analyzing the MOCA as a continuous score (from 0 to 30 points).

Multivariate analysis (Table 2) presents an analysis of adjusting for all variables identified as statistically significant predictors from the univariate analysis (online suppl. Table 4). Cognitive impairment was associated with being male (OR 2.9, 95% CI 1.6–5.9); unmarried, widowed, or divorced (OR 2.8, 95% CI 1.4–5.5); and unemployed/retired (OR 4.9, 95% CI 1.9–12.1). Normal cognition was associated with completing high school ($p = 0.0413$) or possessing a post-school qualification ($p = 0.0001$). Cognitive improvement showed a trend of increasing over time (OR 0.8; 95% CI 0.7–1.0, $p = 0.0614$), although this did not reach statistical significance.

Discussion

The main objective of this study was to determine the predictors, prevalence, and trajectory of PSCI in a cohort of stroke survivors 4 years post stroke. Our findings show that a significant proportion of stroke survivors exhibited cognitive deficits, with global cognitive impairment continuing 1 year after the onset of stroke. Sociodemographic and cardiovascular factors were associated with the highest decline.

Our findings challenge the results of previous research indicating that cognitive deficits post stroke can improve and/or remain stable over time [17]. For example, a previous longitudinal study [17] reported that 3 months post stroke, cognition improved and remained stable up to 15 years post event. By comparison, our results showed that cognition improved within the first 12 months, but then steadily deteriorated. However, the aforementioned study used the MMSE to assess cognition, which is an insensitive tool to detect cognitive impairment; therefore, prevalence rates may have been underestimated.

Contrary to previous reports, which have shown recurrent stroke to be a major risk factor for PSCI compared to first-ever stroke survivors, we found no differ-

ence between groups [3, 18]. Our data are concordant with data of previous population-based research, which has shown that patients with cardiovascular disease and arrhythmias are at higher risk of increased cognitive decline [19]. The role of heart disease, cardiovascular risk factors, and progression to PSD has been well documented [20], and may potentially have contributed to higher prevalence rates of PSD.

In terms of sociodemographic factors, gender, marital status, and employment were significantly associated with declining cognition. Gender differences in PSCI have been reported in other studies [21], with males more likely to experience age-related cognitive decline compared to females. One explanation for this may be that males tend to be more susceptible to PSCI because they are likely to experience higher rates of vascular risk factors such as hypertension compared to women [22].

Consistent with the findings of previous research, stroke survivors who were single/widowed or divorced were significantly more likely to have persistent cognitive decline [23]. Increased loneliness and social isolation following a stroke can have detrimental effects on cognitive functioning [24]. In comparison, social and emotional support following a stroke is a protective factor, which may preserve cognitive functioning, with companionship mitigating the effects of disability and depression, increasing self-efficacy, and promoting cognitive resilience.

An encouraging finding of this research was that stroke survivors who had a high level of education returned to normal cognitive functioning at 4 years post stroke. This may be attributed to a higher cognitive reserve in those stroke survivors who have higher education levels and therefore, higher tolerance to neurodegenerative pathology and cognitive decline [25]. It is also possible that those with higher education had higher socioeconomic status and more access to resources and financial support than those with lower education [26].

An additional positive finding in this study was a borderline significant result for SAH stroke survivors, with cognition improving over the 4-year time period. These results were surprising, considering that up to 50% of stroke patients experience persistent cognitive sequelae following SAH [27–32]. Age is a contributing factor of poorer cognitive dysfunction following SAH, with significantly poorer outcomes after the age of 60 [33]. As our SAH cohort had a mean age of 55, this may have contributed to improved cognition over time and the majority had returned to work. While these positive findings are encouraging, they need to be viewed with caution owing to the small sample size (n = 18).

Our study had several limitations; the inclusion of a control group would have strengthened the study and allowed comparisons of determinants to non-stroke people. The baseline sample size was less than half of the sample at 4 years, with numbers steadily increasing over time. There is a potential that the additional participants included at later time points are somehow different in their demo/stroke make up, which could be the reason for these changes in MoCA scores. We did not amend the MoCA score by adding an extra 1 point for those participants with less than 12 years education, which has been suggested in other studies [34]. Pre-stroke cognitive status was not assessed; therefore, we could not determine preexisting cognitive impairment prior to stroke. Other limitations include the use of a screening measure to assess cognition versus a comprehensive neuropsychological battery. Thus, we could only assess global cognition rather than specific domains of cognition, which may have yielded different results. The strengths of this study included the population-based design, good sample size, and inclusion of an extensive range of baseline covariates, which have not been considered in previous population-based studies [17, 35].

Conclusion

Our population-based study is one of the few that has provided strong evidence that cognitive impairment following stroke does not resolve and/or remain stable but changes over time. Sociodemographic and cardiovascular factors play an important role in the prevalence and progression of cognitive deterioration following stroke. While some of these factors can be modified (through primary prevention strategies), others are more complex and require further research. Although the relationship between cognitive decline and stroke remains complex, maintaining active stimulation of the brain throughout the life span to increase brain resilience may mitigate the effects of faster cognitive decline by having a protective role. Recommendations for rehabilitation should include interventions at the acute stage of stroke, which use a more holistic multidimensional approach to facilitate good health and well-being for those stroke survivors who are more at risk of cognitive decline.

Disclosure Statement

All the authors declare that they have no conflicts of interest to disclose.

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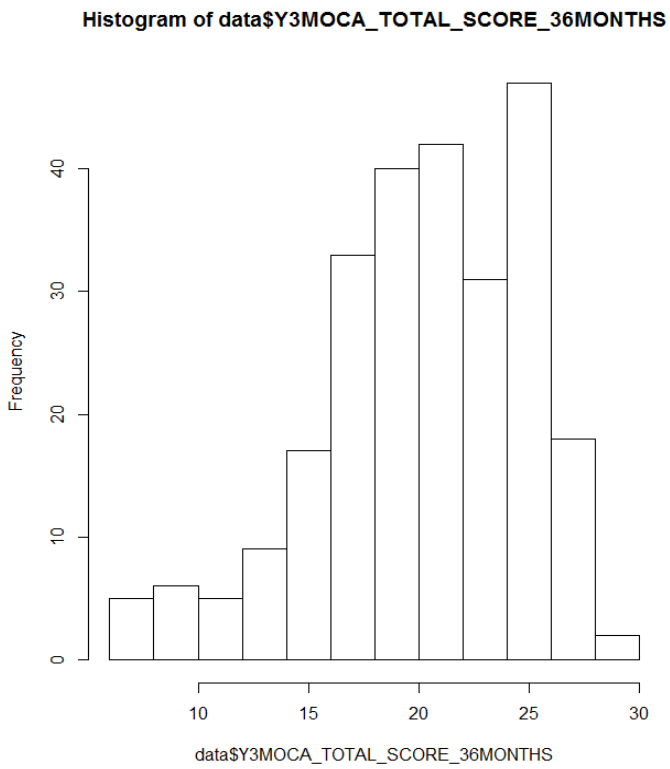
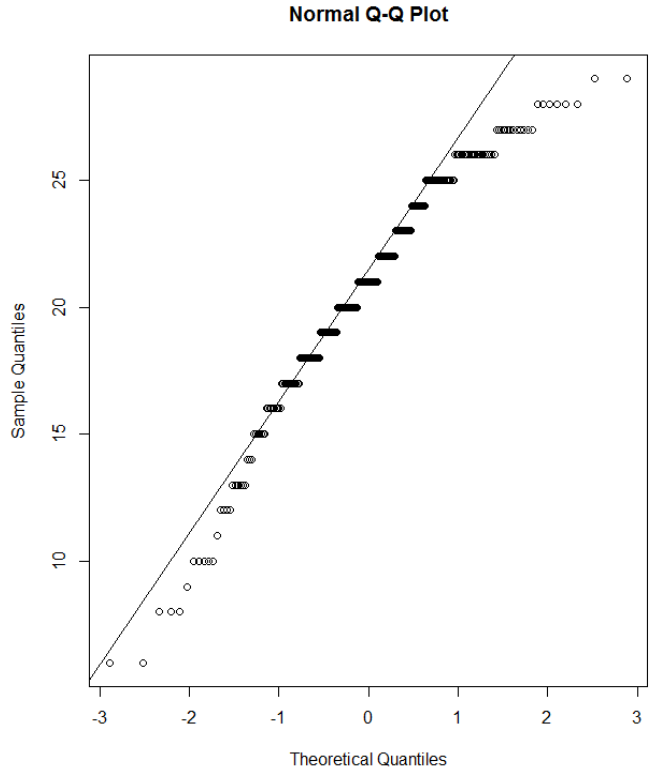
Appendix M: Histogram of MoCA Distribution





Appendix N: Results for Study 2. MoCA Univariate linear regression (using continuous MOCA total scores).

Variable	Categories	Estimate	Std. Error	z-value	*p*-value
Intercept		28.5735	1.4123	20.2319	6.06E-55
Age at event		-0.1162	0.0204	-5.6988	3.32E-08
Intercept		23.2424	0.7781	29.8724	6.20E-85
Age group (ref = < 50 year olds)	51-64	-1.2597	0.9746	-1.2925	0.1974
	65-74	-2.6095	0.9264	-2.8168	0.0052
	75+	-4.3574	0.9138	-4.7685	3.14E-06
Intercept		20.6033	0.4279	48.1543	5.08E-130
Gender	Male	0.1467	0.5882	0.2494	0.8032
Intercept		20.7101	0.3271	63.3075	5.74E-158
Ethnicity (ref = European)	Non-European	-0.1501	0.7417	-0.2024	0.8397
Intercept		21.2166	0.3718	57.0653	3.15E-147
Marital status (ref = Married, civil union or defacto)	Separated/divorced/ widowed	-1.3766	0.5960	-2.3095	0.0217
Intercept	Intercept	23.4600	0.6368	36.8401	4.20E-104
Employment status (ref = Employed)	Employment status (Unemployed/Retired)	-3.4503	0.7096	-4.8627	2.03E-06
Intercept		20.9959	0.3484	60.2701	7.31E-153
Time since stroke		-0.0867	0.0523	-1.6586	0.0984
Intercept		18.9565	0.5526	34.3020	2.50E-96
Education level (ref = Did not complete school)	Completed school	1.3768	0.8477	1.6242	0.1056
	Post-school qualification	2.7177	0.6819	3.9852	0.0001

Intercept		18.9565	0.5550	34.1562	3.79E-96
Education level (ref = Did not complete school)	Completed school/Post-school qualification	2.3440	0.6513	3.5991	0.0004
Intercept		20.6901	0.3225	64.1519	2.39E-159
Recurrent stroke	Yes	-0.0538	0.7795	-0.0690	0.9450
Intercept	Intercept	20.5089	0.3121	65.7216	1.89E-161
Stroke type (ref = ISC)	ICH	-0.1089	1.2456	-0.0874	0.9304
	SAH	2.5466	1.1442	2.2257	0.0269
Intercept		20.5089	0.3131	65.5107	1.55E-161
Stroke type (ref = ISC)	HS	1.3396	0.8737	1.5333	0.1264
Intercept		20.8919	0.5425	38.5077	8.52E-108
Stroke subtype (ref = LACI)	PACI	-1.2893	0.7574	-1.7024	0.0899
	POCI	0.3980	0.7810	0.5095	0.6108
	TACI	0.5248	0.9484	0.5533	0.5805
Intercept		20.3534	0.4331	46.9982	2.66E-127
Hemisphere of lesion (ref = Left)	Right	0.2228	0.6099	0.3654	0.7151
	Both/Brainstem	2.5161	1.0646	2.3634	0.0189
Intercept		20.5368	0.4037	50.8746	7.02E-135
Stroke vascular territory (ref = MCA)	PCA	-0.1768	0.7786	-0.2270	0.8206
	PICA	0.1489	0.8923	0.1669	0.8676
	ACA	1.1299	0.8824	1.2806	0.2015
Intercept		20.9353	0.3989	52.4779	2.47E-138
Location of lesion (ref = Subcortical)	Cortical	-0.8292	0.7031	-1.1794	0.2394
	Unknown	-0.2045	0.7646	-0.2674	0.7893

***** *A value of $p<0.01$ represents statistical significance*

Age at event was significantly associated with reducing MoCA scores (i.e. the older you were at time of stroke, the poorer the cognitive functioning), *p*-value = 3.32×10^{-8}. MoCA scores were lower in those who were unemployed or retired compared to those who were employed (effect = -3.45, *p*-value = 2.03×10^{-6}). MoCA scores were higher amongst those who had completed a post-school qualification (compared to those who did not complete school) effect = 2.71, *p*-value = 0.0001.

Appendix O: Results for Study 2. MoCA Multivariate linear regression (using the continuous MoCA total scores)

Variable	**Category**	**Estimate**	**Std. Error**	**z-value**	***p*-value**
Intercept		26.1367	1.5047	17.3706	1.35E-44
Age at event		-0.0925	0.0232	-3.9926	0.0001
Employment status (ref = employed)	Unemployed/Retired	-1.3657	0.8013	-1.7043	0.0896
Education level (ref = Did not complete school)	Completed school	1.1806	0.7938	1.4874	0.1382
	Post-school qualification	2.3108	0.6428	3.5947	0.0004
Hemisphere of lesion (ref = Left)	Right	0.5547	0.5669	0.9785	0.3288
	Brainstem	2.0054	1.0114	1.9827	0.0485

Using a forwards selection procedure to fit a multivariate linear regression model, only age, education level and hemisphere of lesion were significantly associated with MoCA total scores. Employment status was retained in the model as it met the 10% threshold for being associated with the MoCA total scores.

Appendix P: Copyright Agreement

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Appendix Q: Sensitivity and specificity analysis comparing the MoCA to the CNS-VS

Global		CNS		
		Poor	*Good*	*Total*
MOCA	*Poor*	15 (A)	22 (B)	119
	Good	7 (C)	42 (D)	111
	Total	34	112	

Sensitivity = A/(A+C) Specificity = D/(B+D)

Executive		CNS		
		Poor	*Good*	*Total*
MOCA	*Poor*	16 (A)	39 (B)	149
	Good	3 (C)	35 (D)	80
	Total	35	121	

Sensitivity = A/(A+C) Specificity = D/(B+D)

Visuospatial		CNS		
		Poor	*Good*	*Total*
MOCA	*Poor*	14 (A)	31 (B)	122
	Good	6 (C)	41 (D)	107
	Total	30	126	

Sensitivity = A/(A+C) Specificity = D/(B+D)

Memory		CNS		
		Poor	*Good*	*Total*
MOCA	*Poor*	16 (A)	50 (B)	158
	Good	4 (C)	21 (D)	71
	Total	36	118	

Sensitivity = A/(A+C) Specificity = D/(B+D)

Appendix R: License Agreement Figure Chapter Two

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Appendix S: Univariate Analysis of MoCA and Ethnicity

Univariate Analysis of Variance

Between-Subjects Factors

		Value Label	N
ETHNICITYREG	1	Asian/Other	31
	2	Maori	12
	3	Pacific	7
	4	European	206

Descriptive Statistics

Dependent Variable: Y3MOCA_TOTAL_SCORE_36MONTHS

ETHNICITYREG	Mean	Std. Deviation	N
Asian/Other	21.87	4.890	31
Maori	18.92	4.680	12
Pacific	17.57	5.623	7
European	20.71	4.605	206
Total	20.68	4.705	256

Parameter Estimates

Dependent Variable: Y3MOCA_TOTAL_SCORE_36MONTHS

Parameter	B	Std. Error	t	Sig.	95% Confidence Interval		Partial Eta Squared
					Lower Bound	Upper Bound	
Intercept	20.714	.325	63.659	.000	20.073	21.354	.941
[ETHNICITYREG=1]	1.157	.900	1.286	.199	-.614	2.929	.007
[ETHNICITYREG=2]	-1.797	1.387	-1.296	.196	-4.528	.934	.007
[ETHNICITYREG=3]	-3.142	1.795	-1.751	.081	-6.677	.393	.012
[ETHNICITYREG=4]	0[a]	.	.	.	.	.	.

a. This parameter is set to zero because it is redundant.

Appendix T: Univariate logistic regression NAB attention domain

	Estimate	**Std Error**	**z-value**	***p*-value**
Intercept	1.565964	1.611498	0.971744	0.331178
Age at event	0.020351	0.025921	0.78513	0.432378
Intercept	2.397895	0.738549	3.246766	0.001167
2. 51-64	0.167054	0.951015	0.175659	0.860562
3. 65-74	0.737599	1.033051	0.714001	0.475227
4. 75+	0.969401	1.256955	0.771229	0.440571
Intercept	4.110874	1.007909	4.078617	4.53E-05
M	-1.7393	1.082622	-1.60656	0.108151
Intercept	2.917771	0.419119	6.961671	3.36E-12
2. Non-European	-0.39204	0.845967	-0.46342	0.64306
Intercept	2.933857	0.458932	6.392796	1.63E-10
2. Never married/Not specified/Separated/divorced/widowed	-0.2948	0.753498	-0.39124	0.695619
Intercept	2.374906	0.522739	4.543198	5.54E-06
Unemployed/Retired/Unspecified	0.771399	0.730759	1.055614	0.291145
Intercept	-6.8929	5.230909	-1.31772	0.187596
Time since stroke	3.055784	1.670294	1.829488	0.067326

	Estimate	Std Error	z-value	*p*-value
Intercept	20.56607	3619.197	0.005682	0.995466
2. Completed school	9.20E-11	4974.11	1.85E-14	1
3. Post-school qualification	-18.2388	3619.197	-0.00504	0.995979
Intercept	19.56607	2195.154	0.008913	0.992888
2. Completed school/Post-school qualification	-16.9542	2195.154	-0.00772	0.993838
Intercept	2.745438	0.389912	7.041171	1.91E-12
Y	0.550399	1.090444	0.504748	0.613736
Intercept	2.656757	0.365748	7.263891	3.76E-13
2.ICH	16.90931	3802.118	0.004447	0.996452
3.SAH	16.90931	2874.131	0.005883	0.995306
Intercept	2.656757	0.365748	7.263891	3.76E-13
2.HS	16.90931	2292.763	0.007375	0.994116
Intercept	2.140066	0.528594	4.0486	5.15E-05
2.PACI	17.426	1639.972	0.010626	0.991522
3.POCI	0.855666	0.89689	0.954037	0.340065
4.TACI/Uncertain/Unknown	0.111226	0.912164	0.121936	0.90295
Intercept	2.639057	0.517547	5.09916	3.41E-07
2.Right	0.421213	0.785321	0.536358	0.591711
3.Both/Brainstem/Uncertain	0.133531	1.153399	0.115772	0.907833

	Estimate	Std Error	z-value	*p*-value
Intercept	2.639057	0.46291	5.701015	1.19E-08
2.PCA	-0.19671	0.870496	-0.22597	0.821221
3.PICA	16.92701	2404.67	0.007039	0.994384
4.ACA/AICA/SCA/Unknown	0.496437	1.121501	0.442654	0.658016
Intercept	3.120895	0.589841	5.291081	1.22E-07
2.Cortical	-0.20312	0.935358	-0.21716	0.828082
3.Unknown	-0.78552	0.844691	-0.92995	0.352397

Appendix U: Univariate logistic regression NAB executive function domain

	Estimate	**Std Error**	**z-value**	***p*-value**
Intercept	0.833731	1.223645	0.68135	0.49565
Age at event	0.021015	0.01961	1.071621	0.28389
Intercept	2.397895	0.738549	3.246766	0.001167
2. 51-64	-1.23474	0.822621	-1.50099	0.133358
3. 65-74	0.71562	1.033284	0.692568	0.488581
4. 75+	0.969401	1.256955	0.771229	0.440571
Intercept	2.061423	0.401289	5.137006	2.79E-07
Male vs. Female	0.149595	0.547454	0.273256	0.784657
Intercept	2.06978	0.294333	7.032106	2.03E-12
2. Non-European	0.455949	0.7916	0.575984	0.564626
Intercept	1.969441	0.308158	6.391013	1.65E-10
2. Never married/Not specified/Separated/divorced/widowed	0.669617	0.672385	0.995883	0.319307
Intercept	1.308333	0.356409	3.67088	0.000242
Unemployed/Retired/Unspecified	1.593089	0.581378	2.740194	0.00614
Intercept	-5.11965	4.109576	-1.24578	0.212844
Time since stroke	2.267729	1.295756	1.750121	0.080097

	Estimate	Std Error	z-value	*p*-value
Intercept	2.397895	0.738549	3.246766	0.001167
2. Completed school	0.860201	1.258183	0.683685	0.494174
3. Post-school qualification	-0.539	0.801108	-0.67281	0.501066
Intercept	2.397895	0.738549	3.246766	0.001167
2. Completed school/Post-school qualification	-0.32812	0.795038	-0.4127	0.679823
Intercept	2.149822	0.305012	7.048317	1.81E-12
Y	-0.02956	0.682889	-0.04328	0.965474
Intercept	2.206441	0.304151	7.254434	4.03E-13
2.ICH	15.35963	1398.721	0.010981	0.991238
3.SAH	-0.90716	0.718853	-1.26195	0.206966
Intercept	2.206441	0.304123	7.255086	4.01E-13
2.HS	-0.36061	0.691705	-0.52134	0.602129
Intercept	1.88707	0.479899	3.932223	8.42E-05
2.PACI	1.108663	0.869036	1.275739	0.202048
3.POCI	0.11441	0.676262	0.169181	0.865655
4.TACI/Uncertain/Unknown	-0.09531	0.786887	-0.12112	0.903594
Intercept	2.379546	0.46746	5.090378	3.57E-07
2.Right	-0.23111	0.614851	-0.37588	0.707004
3.Both/Brainstem/Uncertain	-0.8391	0.789481	-1.06285	0.287849

	Estimate	Std Error	z-value	*p*-value
Intercept	2.427748	0.425878	5.700566	1.19E-08
2.PCA	0.014599	0.851381	0.017147	0.986319
3.PICA	-0.23052	0.858445	-0.26854	0.788287
4.ACA/AICA/SCA/Unknown	-1.09275	0.65879	-1.65872	0.097172
Intercept	1.913649	0.357078	5.359194	8.36E-08
2.Cortical	0.571257	0.69901	0.817238	0.413793
3.Unknown	0.421726	0.702208	0.600571	0.548126

Appendix V: Univariate logistic regression NAB language domain

	Estimate	**Std Error**	**z-value**	***p*-value**
Intercept	28.02787	5.941762	4.717098	2.39E-06
Age at event	-0.35654	0.076924	-4.63504	3.57E-06
Intercept	21.56607	5967.046	0.003614	0.997116
2. 51-64	6.07E-09	7480.088	8.12E-13	1
3. 65-74	-4.10E-10	7308.109	-5.61E-14	1
4. 75+	-22.5777	5967.046	-0.00378	0.996981
Intercept	1.648659	0.345298	4.774595	1.80E-06
M	0.11493	0.465671	0.246805	0.805059
Intercept	1.640528	0.25067	6.544564	5.97E-11
2. Non-European	0.438913	0.661678	0.663333	0.507117
Intercept	1.803594	0.288432	6.253091	4.02E-10
2. Never married/Not specified/Separated/divorced/widowed	-0.27212	0.484995	-0.56107	0.574748
Intercept	19.56607	1568.634	0.012473	0.990048
Unemployed/Retired/Unspecified	-18.3396	1568.634	-0.01169	0.990672
Intercept	-1.57639	3.425376	-0.46021	0.645366
Time since stroke	1.018486	1.06371	0.957485	0.338322

	Estimate	Std Error	z-value	*p*-value
Intercept	1.609438	0.547723	2.938418	0.003299
2. Completed school	-0.12783	0.738549	-0.17309	0.862583
3. Post-school qualification	0.362115	0.635269	0.570018	0.568665
Intercept	1.609438	0.547723	2.938418	0.003299
2. Completed school/Post-school qualification	0.233094	0.610247	0.381967	0.702486
Intercept	1.630272	0.25088	6.49821	8.13E-11
Y	0.489992	0.660489	0.741862	0.458171
Intercept	1.570598	0.239833	6.548706	5.80E-11
2.ICH	15.99547	1398.721	0.011436	0.990876
3.SAH	0.994351	1.065102	0.933573	0.350524
Intercept	1.570598	0.239833	6.548706	5.80E-11
2.HS	1.473924	1.051148	1.402204	0.160854
Intercept	2.890372	0.726459	3.978714	6.93E-05
2.PACI	-1.56124	0.817475	-1.90983	0.056155
3.POCI	-1.72722	0.811783	-2.12769	0.033363
4.TACI/Uncertain/Unknown	0.105361	1.256019	0.083885	0.933148
Intercept	2.197225	0.430296	5.106309	3.29E-07
2.Right	-0.56977	0.542145	-1.05095	0.293281
3.Both/Brainstem/Uncertain	-1.32176	0.684462	-1.93109	0.053472

	Estimate	Std Error	z-value	*p*-value
Intercept	1.871802	0.339683	5.510442	3.58E-08
2.PCA	-0.21357	0.642653	-0.33233	0.739639
3.PICA	-0.77319	0.618102	-1.25091	0.210968
4.ACA/AICA/SCA/Unknown	0.074108	0.70451	0.105191	0.916224
Intercept	1.808289	0.341165	5.300339	1.16E-07
2.Cortical	-0.10354	0.559788	-0.18496	0.853257
3.Unknown	-0.26784	0.564601	-0.47439	0.635218

Appendix W: Univariate logistic regression NAB memory domain

	Estimate	**Std Error**	**z-value**	***p*-value**
Intercept	2.173346	1.769667	1.22811	0.219406
Age at event	0.012629	0.027958	0.45172	0.651471
Intercept	3.135494	1.021508	3.069477	0.002144
2. 51-64	0.578078	1.437997	0.402002	0.687682
3. 65-74	-0.76059	1.14749	-0.66283	0.507441
4. 75+	0.231802	1.441513	0.160804	0.872247
Intercept	2.674149	0.516954	5.172895	2.30E-07
M	0.583948	0.783195	0.745597	0.455911
Intercept	2.908721	0.419235	6.938171	3.97E-12
2. Non-European	0.349376	1.101916	0.317062	0.751197
Intercept	3.455265	0.586395	5.892389	3.81E-09
2. Never married/Not specified/Separated/divorced/widowed	-1.12799	0.786288	-1.43457	0.151409
Intercept	2.374906	0.522739	4.543198	5.54E-06
Unemployed/Retired/Unspecified	1.059081	0.78571	1.347928	0.177681
Intercept	-6.36952	5.513905	-1.15517	0.248019
Time since stroke	2.933635	1.760723	1.666154	0.095683

	Estimate	Std Error	z-value	*p*-value
Intercept	3.135494	1.021508	3.069477	0.002144
2. Completed school	0.122602	1.442893	0.08497	0.932285
3. Post-school qualification	-0.31412	1.120439	-0.28035	0.779209
Intercept	3.135494	1.021303	3.070093	0.00214
2. Completed school/Post-school qualification	-0.22677	1.103994	-0.20541	0.837251
Intercept	3.091042	0.457196	6.760866	1.37E-11
Y	-0.52609	0.864574	-0.6085	0.542856
Intercept	3.144152	0.45675	6.883747	5.83E-12
2.ICH	-1.19824	1.162531	-1.03072	0.302673
3.SAH	-0.5792	1.133818	-0.51084	0.609461
Intercept	3.144152	0.45675	6.883747	5.83E-12
2.HS	-0.84157	0.870988	-0.96622	0.333934
Intercept	2.890372	0.726459	3.978714	6.93E-05
2.PACI	0.105361	1.025993	0.102691	0.918208
3.POCI	0.105361	1.025993	0.102691	0.918208
4.TACI/Uncertain/Unknown	0.105361	1.256019	0.083885	0.933148
Intercept	3.349904	0.719405	4.656494	3.22E-06
2.Right	-0.59306	0.885108	-0.67005	0.502828
3.Both/Brainstem/Uncertain	-0.57732	1.256998	-0.45928	0.646032

	Estimate	Std Error	z-value	*p*-value
Intercept	3.164068	0.589422	5.368089	7.96E-08
2.PCA	16.402	2150.803	0.007626	0.993915
3.PICA	-0.96684	0.950249	-1.01746	0.308933
4.ACA/AICA/SCA/Unknown	-0.76617	0.944919	-0.81083	0.417461
Intercept	3.10608	0.590037	5.264214	1.41E-07
2.Cortical	-0.18831	0.935482	-0.2013	0.840466
3.Unknown	-0.33349	0.937753	-0.35563	0.722119

Appendix X: Univariate logistic regression NAB spatial domain

	Estimate	**Std Error**	**z-value**	***p*-value**
Intercept	1.221267	1.025763	1.190593	0.233813
Age at event	0.003715	0.015811	0.234948	0.814249
Intercept	1.609438	0.547723	2.938418	0.003299
2. 51-64	-0.16252	0.674101	-0.24109	0.809485
3. 65-74	-0.42381	0.64706	-0.65498	0.512478
4. 75+	0.262364	0.767112	0.342016	0.732339
Intercept	2.233592	0.429513	5.200289	1.99E-07
Male vs. Female	-1.18377	0.498766	-2.3734	0.017625
Intercept	1.509354	0.241133	6.259414	3.86E-10
Non-European vs. European	-0.25659	0.521949	-0.4916	0.623
Intercept	1.425009	0.255519	5.576927	2.45E-08
2. Never married/Not specified/Separated/divorced/widowed	0.106467	0.466173	0.228386	0.819346
Intercept	1.440362	0.370711	3.8854	0.000102
Unemployed/Retired/Unspecified	0.025975	0.453655	0.057258	0.954339
Intercept	4.741202	3.143994	1.508019	0.13155
Time since stroke	-1.007	0.957563	-1.05163	0.292968

	Estimate	Std Error	z-value	*p*-value
Intercept	1.609438	0.547723	2.938418	0.003299
2. Completed school	0.139762	0.770375	0.181421	0.856037
3. Post-school qualification	-0.23713	0.60798	-0.39003	0.696515
Intercept	1.609438	0.547723	2.938418	0.003299
2. Completed school/Post-school qualification	-0.15719	0.596735	-0.26341	0.792235
Intercept	1.684339	0.256641	6.563005	5.27E-11
Yes	-0.93712	0.479174	-1.95571	0.050499
Intercept	1.345472	0.224537	5.99222	2.07E-09
2.ICH	-0.24686	0.846808	-0.29152	0.770655
3.SAH	16.2206	1057.334	0.015341	0.98776
Intercept	1.345472	0.224536	5.992222	2.07E-09
2.HS	0.957113	0.77472	1.23543	0.216671
Intercept	0.538997	0.336296	1.602743	0.108991
2.PACI	1.070441	0.533408	2.006798	0.044771
3.POCI	1.252763	0.554563	2.259011	0.023883
4.TACI/Uncertain/Unknown	18.02707	1423.356	0.012665	0.989895
Intercept	1.076139	0.298988	3.599274	0.000319
2.Right	0.921956	0.480979	1.916834	0.055259
3.Both/Brainstem/Uncertain	0.102516	0.645226	0.158883	0.873761

	Estimate	Std Error	z-value	*p*-value
Intercept	1.455287	0.296808	4.90312	9.43E-07
2.PCA	-0.06899	0.581459	-0.11865	0.905549
3.PICA	-0.06899	0.632926	-0.10901	0.913198
4.ACA/AICA/SCA/Unknown	0.154151	0.622973	0.247444	0.804565
Intercept	1.575536	0.317135	4.968028	6.76E-07
2.Cortical	-0.51083	0.484827	-1.05362	0.292055
3.Unknown	0.182322	0.578841	0.314977	0.752779