

An Assessment of Cognition in Healthy
Individuals to Inform the Assessment of
Cognition in Transient Ischemic Attack

Patients

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June 2017

Research submitted in partial fulfilment of the requirements for the degree of
Doctor in Clinical Psychology (DClinPsy), Royal Holloway, University of London.

Abstract

It is known that people can suffer from cognitive impairments following a TIA. Yet, currently, the methods for measuring this impairment are not very accurate or feasible. Whilst there is a gold standard battery to test for cognitive impairment, there are no up-to-date cohesive UK norms. Furthermore, current screening tools, it has been shown, have ceiling effects, and they are not sensitive in detecting mild cognitive impairments seen in a TIA profile.

This study aims to explore whether a brief battery (BICAMS), which is used in MS could be an improvement on current tools. The sensitivity and specificity of the BICAMS were compared with a gold standard measure of cognitive impairment in TIA (NINDS-VCI; Hachinski et al., 2006). Furthermore, the study develops cohesive UK norms for the full NINDS-VCI battery to determine whether these would provide different outcomes to the available norm sources.

Sixty-seven healthy UK participants were recruited to complete a 90-minute battery of tests – the MoCA, MMSE, BICAMS and NINDS-VCI 60-minute battery and a measure of estimated IQ, fatigue, anxiety and depression. Different norm sources were compared for the NINDS-VCI battery (published and current study). The numbers of participants falling below the expected level on the NINDS-VCI battery were compared with those identified by the three different screening tools. Finally, regression analyses were conducted to show which clinical and demographic factors contributed to performance on the NINDS-VCI and BICAMS.

The study found that different numbers of participants fell below the expected levels on the NINDS-VCI battery, depending on which norm sources were used, with a trend towards more participants being identified with published norms. Years of

education was a significant predictor of NINDS-VCI scores and age was a significant unique contributor to BICAMS scores. BICAMS significantly correlated with NINDS-VCI performance and was found to be more sensitive and specific than the MoCA or MMSE.

Relevant and up-to date cohesive norms are important to evaluate performance accurately on the NINDS-VCI –VCI 60-minute battery. BICAMS shows promise as a suitable screening tool to measure mild cognitive impairment after a TIA. Further research should focus on comparing TIA participants with UK matched controls.

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This introduction reviews the literature pertaining to the current study. It begins by describing the National Institute of Neurological Disorders and Stroke-Canadian Stroke and Vascular Cognitive Impairment Harmonisation Standards 60-minute neuropsychological test battery, and the importance of neuropsychological testing in TIA and mild stroke. It examines the importance of providing up-to-date normative data for comparison with clinical groups, before exploring the prevalence, risk factors and neuropsychological profile of TIA and mild stroke. Furthermore, the current challenges in detecting cognitive impairment and the available screening tools are considered. The rationale and outline of the study are also provided.

1.1 Recommended Neuropsychological Testing in Stroke and TIA

1.1.1 Overview

This section details the current recommendations for neuropsychological testing in Vascular Cognitive Impairment (VCI). It describes what research has been carried out using this battery and the available normative data. It refers to the importance of cohesive and current norms for understanding neuropsychological testing.

1.1.2 The National Institute of Neurological Disorders and Stroke-Canadian Stroke and Vascular Cognitive Impairment Harmonisation Standards (NINDS-VCI).

In 2006, The National Institute of Neurological Disorders and Stroke (NINDS) and Canadian Stroke Network (CSN) together developed a set of data elements that they recommended for use in all future studies of VCI (Hachinski et al., 2006). The aim was to achieve a more comprehensive understanding of VCI. Recommendations for examining cognition were developed. This included a 60-minute, 30-minute and 5-minute neuropsychological test battery. The 60-minute battery is the gold standard

assessment battery, the 30-minute battery is a subset of key tests within the 60-minute battery and the 5-minute battery is the Montreal Cognitive Assessment (MoCA). The 60-minute battery aims to cover deficits across all cognitive domains, with particular emphasis on measuring executive function, information processing speed and working memory, which are considered to be key cognitive deficits in VCI. The working group highlighted the importance of ensuring tests were sensitive to a range of abilities. The protocol includes the following tests: Trail Making Test (Parts A and B) (TMT; Reitan, 1955), Boston Naming Test (BNT; Mack, Freed, Williams, & Henderson, 1992), Rey-Osterrieth Complex Figure Copy (ROCFT; Fastenau, Denburg, & Hufford, 1999), Hopkins Verbal Learning Test-Revised (HVLTR; Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt, 1991), Letter Fluency (Controlled Oral Word Association Test) (COWAT; Benton, Hamsher, & Sivan, 1994) and Category (animals) Fluency (Issacs & Kennie, 1973).

The battery was chosen by expert opinion based on current knowledge on VCI and its related cognitive deficits. Since its development, the battery has been utilised in a number of countries, including France (Godefroy et al., 2011), Canada (Mandzia et al., 2016), the United States (Han, Anderson, Jones, Hermann, & Sattin, 2014; Wang et al., 2016), Korea (Yu et al., 2013), Taiwan (Lin et al., 2016), Hong Kong (Wong et al., 2012), Singapore (Xu et al., 2016) and China (Chen et al., 2015). National databases have been devised and are now in place to collect the outcomes of studies using the battery (Stroke Standards - NINDS Common Data Elements). Furthermore, the battery has been used in research to show that performance on each of the cognitive domains is associated with volumetric brain changes (Wang et al., 2015; Wong et al., 2015). The battery also discriminates between different diagnoses, such as mild cognitive impairment and dementia in memory clinics (Xu et al., 2016).

In the United States the battery has been incorporated into stroke patient care demonstrating good clinical feasibility, and providing an efficient method for the provision of focused neuropsychological assessment (Han et al., 2014).

Many of the studies using the battery have focused on TIA and mild stroke. Their findings have highlighted the prevalence of cognitive impairment in TIA, described the neuropsychological profile of deficits and tested potential screening tools, to examine if they can accurately detect impairments to the same degree as the 60-minute NINDS-VCI battery. Currently, no guidelines exist for the assessment or treatment of cognitive impairment in TIA in the UK (NICE, 2008). Only recently has it been acknowledged that cognitive deficits are present and persist past the acute phase of the TIA. As research develops, the case will be made for further assessment and treatment for cognitive deficits in this clinical group.

Furthermore, understanding of VCI, particularly in TIA, appears to be a growing area of research internationally. There is currently a large multi-centre national trial taking place in France to validate a French version of the NINDS-VCI, although the results are not yet available (ClinicalTrials.gov ID: NCT01339195). The value of developing a neuropsychological test battery to use internationally is that research can develop a clearer picture of the cognitive deficits at the acute phase, sub-acute phase and the chronic phase of stroke and TIA. The systematic application of assessment will improve the ability to evaluate the risk of cardiovascular procedures and safety effectiveness of preventative therapies (Lansky et al., 2017). This will increase knowledge of the disease and, in turn, inform treatment.

1.1.3 Current Norms and the Importance of Cohesive Norms

Despite the NINDS-VCI test battery being validated in a number of countries, and the recognition of its importance in advancing knowledge of VCI, no validation of the battery has taken place in a UK population. Notable UK investigations of TIA cognition have relied on several historical normative datasets from manuals and other sources, spanning several decades and from other countries (Pendlebury, Mariz, Bull, Mehta, & Rothwell, 2012, 2013). The normative comparisons that are currently in use to evaluate performance on the NINDS-VCI in the UK span from 1982 to 1999 (Benedict et al., 1998; Fastenau et al., 1999; Ivnik, Malec, Smith, Tangalos, & Petersen, 1996; Smith, 1982). These norms are also from different parts of the United States (Minnesota, Baltimore, Indiana and Los Angeles), which calls into question their relevance to a UK population. These are derived from a range of standardisation sources recommended by Hackinski et al. (2006) (cf. Crossley, D'Arcy, & Rawson, 1997; Goodglass et al., 2001; Gorp, Satz, & Mitrushina, 1990; Heaton, 2004; Ivnik et al., 1996; Kozora & Cullum, 1995; Ruff, Light, Parker, & Levin, 1996; Selnes et al., 1991; Tombaugh & Hubley, 1997; Wechsler, 1997).

Recency has been argued as the most important factor when considering which normative data to use. This is due to the Flynn effect: mean average scores are likely to change by three to nine points per decade. The Flynn Effect, furthermore, has additional sources of complexity when different tests are used to create a battery. This is because different tests within the battery are normed in different decades. Batteries that provide co-normed subtests in a variety of neuropsychological domains are thought to provide a clear advantage over test combinations (Strauss, Sherman, & Spreen, 2006). Therefore, the lack of current and cohesive datasets for cognitive evaluation in TIA not only weakens experimental investigations of prevalence and

outcome, but also means that individual clinical assessments of cognition lack current, cohesive norms.

Whilst some of the studies have relied on published norms to compare experimental data (Mandzia et al., 2016; Pendlebury et al., 2012), others have used a current comparison of participants from the same population. For example, Chen et al. (2015) compared 50 mild stroke participants with 50 stroke free participants. Group comparisons were then made through t-tests by using a summary z-score for each cognitive domain and comparing z-scores between the two groups. The same approach has been used to validate the battery in Hong Kong (Wong et al., 2012) and Taiwan (Lin et al., 2016).

Traditional norming relies on discrete norms, which provide sets of descriptives for a specific age band. Norms can sometimes be based on rather arbitrary age bands. This can mean that a person's performance can vary depending on which age band he or she falls into. For example, Zachary and Gorsuch (1985) noted that a person's IQ score on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) could increase up to six points by ageing a single day when the raw test scores pass from comparison with the 25–34 to the 35–44 year age group. Furthermore, large samples are required to ensure reliability. Generally 20 to 30 participants are required per stratification band, which means that over 300 participants would be required for five age and education bands, before any other variables are considered (Testa, Winicki, Pearlson, Gordon, & Schretlen, 2009).

Conversely, continuous norms can be calculated using a regression model. Regression-based norms (RBN) can be extremely useful in providing information that is tailored to the individual's attributes, such as age, gender, IQ, educational level and socioeconomic status. The demographic factors can be used in a multiple regression

to predict test performance based on the participant's demographic characteristics. RBN also makes it possible to account for non-linear effects such as age. Compared with traditional norming, regression-based norming requires a smaller sample to obtain equally precise norms, as they depend primarily on the assumptions of multiple regression being met (Bechger, Hemker, & Maris, 2009). The statistical advances in creating norms that account for a wider variety of clinical and demographic factors would facilitate the interpretation of outcomes on the NINDS-VCI 60-minute battery in a UK population.

1.1.4 Summary

The NINDS and CSN have recommended a 60-minute gold standard test battery, which is being used internationally to advance knowledge of VCI. The battery has proved particularly useful in developing knowledge of mild stroke and TIA. However, recent UK studies have used normative data from the United States dating back to the early 1980s to diagnose cognitive impairments. This is likely to be inaccurate and cause misclassification and faulty identification of cognitive impairment. A normative data set using regression-based norms on UK participants across all tests of the NINDS-VCI battery will further enhance our understanding of cognitive impairment in TIA and stroke.

1.2 TIA and Mild Stroke Synopsis

1.2.1 Overview

This section describes the current prevalence of TIA and mild stroke, as well as the prevalence of VCI, before discussing the impact on daily life. It also considers how

cognitive testing could facilitate our understanding and targeted treatment of people who experience difficulties after a TIA or mild stroke.

1.2.2 Epidemiology of TIA

A TIA is commonly known as a mini stroke. Physical symptoms include weakness of the face, arm or leg that is particularly one sided, diplopia (double vision), monocular visual loss, dysarthria (unclear articulation of speech), aphasia and loss of balance or co-ordination. Cognitive signs include disorientation and problems with comprehension and verbalisation. Physical symptoms are known to resolve usually within an hour. It is estimated that 54,000 TIAs occur every year in the UK (Giles & Rothwell, 2007), with an incidence rate of 0.66 in 1000 (0.45 in 1000 for men and 0.89 in 1000 for women).

A stroke is defined as rapidly developing clinical symptoms and or signs of focal and at times global loss of brain function, with symptoms lasting more than 24-hours or leading to death, with no apparent cause other than that of vascular origin (Hatano 1976). There are two competing definitions of TIA. Depending on which one is used, this can change the prevalence rates of both stroke and TIA significantly. The original definition is of “an acute loss of focal brain or monocular function, with symptoms lasting less than 24-hours, which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease” (Hatano, 1976). This definition does not require the use of imaging for diagnosis and is based on observation of clinical symptoms. An alternative and more recent definition has been proposed: “a transient episode of neurologic dysfunction caused by focal brain, spinal chord or retinal ischemia, without acute infarction” (Albers et al., 2002; Easton et al.,

2009). Advances in neuroimaging, particularly diffusion-weight MRI, show that 30–50% of those classically defined as having a TIA have small acute lesions (Brazzelli et al., 2014; Easton et al., 2009; Moreau, Jeerakathil, & Coutts, 2012). Using the later definition would mean that these patients are diagnosed with a stroke rather than a TIA. This has implications for access to assessment and treatment for stroke that is not currently available for TIA. Generally, in clinical practice, brain imaging, which is sensitive to identifying such small changes, is not routinely available and diagnosis is instead usually based on clinical history (NICE, 2008). This means that the first definition, which is time-based is usually favoured and used in clinical practice. This results in a higher rate of TIA diagnosis and a lower rate of stroke diagnosis.

There is a lack of clarity and considerable overlap in the literature between definitions of TIA, minor stroke and stroke, with at least six different definitions of minor stroke (Fischer et al., 2010). Studies often include and report findings for more than one group, and they may lack clear guidance on the definitions used to classify participants. However, the cognitive profile seen in a TIA mirrors the profile in a stroke: the same deficits are present, although in a stroke, they are likely to be more severe and across more than one domain (Sachdev et al., 2004). The cognitive profiles of stroke and TIA are known to be vascular in nature and match the VCI profile (Nyenhuis & Gorelick, 2007; Sachdev et al., 2004). This means that despite the overlap in studies reporting TIA and stroke together, they still can provide valuable information about VCI in TIA. Therefore, it is considered more appropriate to include stroke and TIA as part of a continuum of VCI rather than separate entities. This review of the literature explores both minor stroke and TIA studies.

Studies examining the factors that are likely to increase the occurrence of a TIA have been carried out. A recent study by Ström, Tavosian, and Appelros (2016) compared characteristics of TIA patients with the general population and found that the former were more likely to have diabetes, atrial fibrillation and to smoke. It was less likely for the TIA population to be taking blood pressure medication, suggesting a higher proportion of untreated hypertension, which may be a contributing factor. This confirms previous studies' findings (Dennis, Bamford, Sandercock, & Warlow, 1989; Whisnant et al., 1999), that diabetes and current smoking increased the odds ratio for TIA by 1.5 each and atrial fibrillation by a factor of 5.

The focus of treatment after a TIA is to reduce the risk of stroke and further TIAs. The risk of stroke following TIA is high: 5% at two days, 8% at seven days, 7–12% at 30 days (Lavallée & Amarenco, 2014). This emphasises the importance of immediate medical treatment. The EXPRESS study indicated that early intervention in TIA could reduce the 90-day risk of recurrent stroke by 80% (Rothwell, Algra, & Amarenco, 2011). Various risk stratification formulas have been developed and validated to help target those most at risk of a further vascular event. The ABCD² is the current risk stratification formula recommended in the guidelines of the National Institute of Clinical Excellence (NICE, 2008). The ABCD² score is a risk assessment tool designed to improve the prediction of short-term stroke risk after a transient ischemic attack (TIA). The score is optimized to predict the risk of stroke within 2 days after a TIA, but also predicts stroke risk within 90 days. The ABCD² score is calculated by summing up points for five independent factors: age, blood pressure, clinical features (unilateral weakness and or speech impairment), duration and diabetes. There have been several attempts to enhance this risk stratification process by adding imaging results (Giles et al., 2011) or etiological considerations, though it is recognised that

this would require an extensive diagnosis work up (Wolf, Held, & Hennerici, 2014). However, accurate cognitive screening has the potential to enhance the risk stratification process and predict more reliably who is most at risk of further vascular events. For example, a study with elderly participants showed scores on the MMSE to be a better predictor of stroke than Framingham Vascular Risk Scores (Sabayan, Gussekloo, Ruijter, Westendorp, & Craen, 2013). Cognitive status is likely to be a useful predictor or an additional source of information for understanding future risk of vascular events. Identifying accurate screening tools that are cost and time effective could add to our understanding and prevent further vascular events and vascular dementia (VaD).

1.2.3 Prevalence of Cognitive Impairments after TIA

Rates of cognitive impairment in TIA vary across studies. A recent systematic review found rates of mild cognitive impairment between 29 and 68%, with severe cognitive impairment (impairment in two or more domains) in 8–22% of patients (van Rooij, Kessels, Richard, De Leeuw, & van Dijk, 2016). Another systematic review in 2014 found rates of cognitive impairment between 17 and 54% (Moran et al., 2014).

Studies have examined the profile of cognitive impairments following a TIA. Van Rooij et al. (2014) tested 114 participants aged 45–65, without history of stroke or dementia to 81 controls, three months after TIA. They used CT and MRI imaging to establish the presence of infarction or white matter disease. They found that over one third of the participants experienced cognitive impairment in at least one domain. The most commonly impaired cognitive domains were working memory, information processing and attention. They found global memory was most likely to remain intact.

Subjective complaints were higher in the TIA participants than controls. Imaging studies showed that 59% had brain infarcts, and these participants were much more likely to experience cognitive impairment.

Similarly, Pendlebury et al. (2012) tested 91 participants with TIA or minor stroke one year later on a full neuropsychological battery of tests. They found that 42% experienced cognitive impairment, with the majority being in visuospatial, executive and attentional tasks. Memory and language were more likely to be preserved.

Sachdev et al. (2004) compared 170 participants with mild stroke or TIA to 96 aged matched controls on a detailed neuropsychological battery. They showed that nearly 60% experienced cognitive impairment in one or more domains. Impairment in abstraction, mental flexibility, information processing speed and working memory were the most common deficits.

These studies support the theory that the cognitive impairment seen in TIA has a vascular profile, characterised by attention, information processing and executive function deficits, with relatively intact memory function. However, studies do vary in terms of the specific cognitive domains that are impaired and the percentage of people identified with cognitive impairments. This is likely to be due to different measurement tools and definitions.

The use of a screening tool to identify impairments would be valuable, followed by a full neuropsychological battery to conceptualise the precise profile of TIA related cognitive impairment.

1.2.4 The Impact of Cognitive Impairments after TIA on Daily Life

Separating the impact of cognitive deficits on daily life from other factors is a challenge, as depression, anxiety and fatigue are also known to correlate with quality of life following TIA (Coutts et al., 2012; Moran et al., 2014). Many people continue to self-report negative consequences of TIA many years later. In a qualitative study, participants reported experiencing physical, practical and psychological consequences following a TIA (Croot et al., 2014).

A study by Coutts et al. (2012) found that 90 days after a TIA, 15% of participants were classified as disabled, according to the modified Rankin Scale (mRS), with a score of ≥ 2 . The authors suggest that disability could be due to cognitive impairment, although this cannot be determined through the mRS measure. A similar level of disability was found in another self-report study, which did include a measure of cognitive functioning. At 90 days, 12% of participants were classified as disabled. They reported impairments in social roles and activities, applied cognition, including executive function, and general cognition, including memory, attention and decision-making (Sangha et al., 2015).

Kjörk, Blomstrand, Carlsson, Lundgren-Nilsson and Gustafsson (2015) found that self-reported problems persist at nine months and may also increase. Thirty-two percent of a TIA cohort still reported problems in daily life nine months later. Communication problems increased from 16% at three months to 33% at nine months. This gives further evidence of long-term self-reported difficulties after a TIA.

People working outside the home are more likely to report difficulties (Muus, Petzold, & Ringsberg, 2010). One hundred and five participants with mild stroke or TIA completed the Stroke Specific Quality of Life Scale: 13% with a TIA reported a decrease in quality of life one year later. Those reporting a decrease in quality of life

were more likely to be in employment. This change, it has been proposed, results from the higher cognitive demands placed on them at work; such subtle difficulties may go undetected in other, less cognitively-demanding settings. The study also found that being male was more likely to predict a reduction in quality of life one year later. This contradicts the findings of another recent longitudinal cohort study of 619 first ever stroke and TIA participants, aged between 18 and 50 years old. They noted that 14 years later, 1 out of 10 individuals are still dependent in daily life, with a two to threefold higher risk of a poor outcome in women. The authors proposed that this may be due to less social support for young women than men after stroke (Franzén-Dahlin & Laska, 2012).

Quality of life appears to be negatively affected for a significant number of people following a TIA. Some studies have found this to be linked to cognitive impairment, although no direct correlational studies have been conducted. Studies are mainly self-report, which may bias findings. However, there are clear negative effects on daily life after experiencing a TIA. Assessment of cognition following a TIA would identify those most likely to have difficulties in returning to their day-to-day activities. Being able to provide cognitive rehabilitation and further support for this population would likely increase quality of life and wellbeing following mild stroke and TIA.

1.2.5 Treatment of TIA in UK NHS

Dementia affects 5–7% of people over the age of 60. Cerebrovascular disease, such as TIA, have been shown to increase significantly the likelihood of experiencing VaD, with the risk increasing for those who experience multiple vascular events (Gorelick et al., 2011; Gorelick, Counts, & Nyenhuis, 2016). Therefore, treatment following a

TIA focuses on medications to reduce the risk factors that are known to increase the possibility of another TIA or other vascular event. Medication is used to reduce hypertension, hyperlipidaemia and atrial fibrillation. A surgical intervention, Carotid Endarterectomy, is used to unblock the main blood vessels that supply the neck and head when there is a narrowing of the carotid artery.

Although medication and surgery are shown to prevent further vascular events, neither has a significant impact on VCI (Pettigrew, Thomas, Howard, Veltkamp, & Toole, 2000; Ritter & Pillai, 2015). VCI following a TIA is known to have an impact on quality of life (Coutts et al., 2012; Moran et al., 2014). Nevertheless, NICE guidelines currently do not include cognitive testing or rehabilitation as part of the treatment. Cognitive testing could be a valuable addition to treatment to understand those who are experiencing cognitive impairments after a TIA. This would allow treatment resources to be directed towards those who are more impaired from a TIA, thus focusing on improving their quality of life. Clinicians would also be provided with valuable information about those who may be more at risk of future vascular events to help target medical and surgical treatments.

1.2.6 The Case for Cognitive Screening

Studies have shown that cognitive impairment at the acute phase can predict long-term cognitive impairment and prognosis. For example, Dong et al. (2012) found that scores on a cognitive screen in the acute stage predict outcomes one year later. This finding has been corroborated by Kliper et al. (2015), who correlated neuropsychological test scores and neuroimaging results across the acute phase, six and 12 months, and found that tests in the acute phase predicted outcomes on cognitive testing at a 12-month follow-up. Studies have also shown that cognitive

impairment in the acute phase can predict risk of stroke and VaD (Dong et al., 2013; Pettigrew et al., 2000). This highlights the important role of assessing for cognitive impairment following TIA, in order to target treatment for those most at risk of further vascular events and cognitive impairments.

However, it is acknowledged that a 60-minute gold standard battery is unlikely to be feasible in TIA clinics, due to limitations on resources. However, a screening tool could be used to identify those who are experiencing cognitive impairments. This would then mean that only those who have been identified as experiencing cognitive deficits undergo a full 60-minute assessment. The screening process is popular in other parts of the health system and has been used effectively in multiple sclerosis (MS) (Dusankova, Kalincik, Havrdova, & Benedict, 2012; O'Connell, Tuokko, Graves, & Kadlec, 2004). Screening tools usually require minimal training and can be delivered by a range of healthcare professionals negating the need for expensive specialists to assess each patient. Screening for cognitive impairment is likely to be a time efficient way to highlight those most in need of treatment and further intervention. Although screening tools, such as the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA), have been proposed and utilised in TIA and mild stroke, they have been shown to have ceiling effects that inhibit the detection of subtle cognitive impairments, which are likely to be seen following a TIA. Further exploration of tools that can improve on the MMSE and the MoCA are necessary.

1.2.7 Summary

TIA is a common vascular event; there are known risk factors that increase the likelihood of experiencing a TIA, including diabetes, atrial fibrillation and smoking.

Cognitive deficits after a TIA are also prevalent and appear to impact peoples everyday life years later. Yet, currently, there is no screening for cognitive impairment following a TIA and thus no treatment available. If cognitive testing was introduced, this could help identify those most at risk of experiencing such negative impacts on their daily life, and those most likely to go on to have further vascular events and possible VaD. Identifying those most at risk would help target treatment and prevention strategies more effectively and thus reduce the impact on peoples quality of life and reduce the prevalence of VaD.

1.3 The Neuropsychological Profile of TIA and Mild Stroke

1.3.1 Overview

This section describes the current research findings on cognition across different functional areas including processing speed, executive function, language, learning and memory and visuospatial abilities.

1.3.2 Processing Speed

Information processing speed is a measure of how quickly information can be taken in and, subsequently, made sense of. TIA and stroke studies have shown slowed information processing speed to be impaired compared with controls. Participants with TIA and stroke produce significantly slower response times than matched controls on a number of well-known tests of information processing speed, including TMT-A (Chan et al., 2014; Mandzia et al., 2016; Sachdev et al., 2004; Sörös, Harnadek, Blake, Hachinski, & Chan, 2015), Symbol Digit Modalities Test (SDMT) (Chan et al., 2014; Pendlebury et al., 2012; Sachdev et al., 2004), WAIS Symbol Digit Coding (Chen et al., 2015; Mandzia et al., 2016), Reaction time tasks (Bakker et al.,

2003; Gerritsen, Berg, Deelman, Visser-Keizer, & Jong, 2003) and Stroop and Concept Shifting Tasks (Rasquin et al., 2004). Furthermore, stroke studies have found that the more complex the decision to be made, the slower the speed of processing compared with controls (Gerritsen et al., 2003). A recent study in a Chinese population looked at WAIS Symbol Digit coding as a screening measure of VCI in a mild stroke cohort and identified a sensitivity of 75% and specificity of 61% (Lin et al., 2016). Dong et al., 2014 also found the SDMT to be equivalent to the MoCA and MMSE in detecting mild cognitive impairment, although it was not sensitive to detecting those with amnesic cognitive impairment, which was 10% in their study.

Stroke studies have also shown processing speed to have a mediating relationship with other cognitive domains (Su, Wuang, Lin, & Su, 2015). Processing speed mediated the impairments across other cognitive domains. Therefore, processing speed is the cognitive function that is affected in terms of severity and prevalence, and also underlies post stroke cognitive dysfunction.

Tham et al. (2002) tested 252 stroke and TIA participants using the SDMT and Digit Cancellation and found scores predicted cognitive decline one year later. Furthermore, a stroke study also found processing speed to be a significant independent predictor of disability and health related quality of life five years after stroke. The contribution of processing speed was a better predictor than age, depression and stroke severity (Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010). This was supported by another study, which found that processing speed independently predicted dependency after stroke and TIA (Narasimhalu et al., 2011).

Processing speed appears to be a key cognitive deficit demonstrated across multiple studies of stroke and TIA. Research has shown that processing speed mediates the relationship between other cognitive domains and is predictive of quality

of life and dependency. Therefore, a measure of information processing speed would be extremely useful in a brief cognitive test to indicate whether cognitive impairment may be present in TIA patients.

1.3.3 Learning and Memory

Memory deficits have typically been associated with dementia and Alzheimer's, rather than the CVD pathology in TIA (Gorelick et al., 2016). However, the ability to learn and recall new information has been shown to be reduced in some people with TIA. A large population based study found that 7% of people who had experienced a TIA also experienced a memory impairment (Takahashi et al., 2009). Verbal word learning list tasks such as the California Verbal Learning Test (CVLT-II) and Hopkins Verbal Learning Test Revised (HVLT-R) have shown significant differences between TIA participants and controls (Chen et al., 2015; Levine et al., 2015; Pendlebury et al., 2012; Wong et al., 2015). A recent study found that 20% of a TIA cohort were impaired on memory domain as measured by CVLT-II and Rey Memory Trial (Mandzia et al., 2016).

However, other studies have differing results; for example, van Rooij et al. (2014) compared TIA participants with controls and identified no significant difference in rates of episodic memory impairment compared with controls. Sachdev et al. (2004) also found impairments in all other domains except verbal memory. According to Pendlebury et al. (2013), TIA participants were less likely to have impairment in memory than other cognitive domains. However, those who did have an impairment in memory, also had an impairment in another cognitive domain, and this group showed more impaired long-term outcomes compared with those who were

only impaired in one domain. This suggests that memory could be a key indicator of more severe impairment and cognitive impairments in the long term.

Tests of visual learning and memory including delayed recall of the ROCFT, Visual Reproduction in Wechsler Memory Scale (WMS) (Chen et al., 2015; Sachdev et al., 2004) and Recognition Memory Test and Doors and People Test (Chan et al., 2014), have been shown to be impaired in TIA participants (Chen et al., 2015; Sachdev et al., 2004), whilst other studies have shown visual memory to remain intact (Pendlebury et al., 2012).

Tham et al. (2002) found scores on both verbal memory and visual memory predicted those most likely to deteriorate in cognition, compared with those who were more likely to improve or remain stable. Neuroimaging studies have correlated early changes in the hippocampus with memory impairment, which continues to be present up to 10 years after TIA and stroke (Kliper et al., 2015; Schaapsmeeders et al., 2015).

The mixed profile demonstrated across studies may be linked to the heterogeneous profile of participants and study design. Tests may not be sensitive to the mild deficits seen in a TIA cohort (Gorelick et al., 2016). Certainly, tests of memory in current screening tools such as the MoCA and MMSE involve the participant remembering three words. This is often unchallenging and errors are usually due to attention or encoding problems, rather than deficits in learning and memory specifically.

In summary, not all studies have shown that impairments in memory occur in a mild stroke or TIA population. These findings may be due to a number of reasons linked to the research design or selection of participants. However, some studies have revealed that impairments in verbal and visual memory tasks are predictive of future outcomes and indicate more severe impairments in cognition. This highlights the need

for further exploration of memory in TIA and mild stroke patients to determine whether a sensitive measure of memory could be useful in identifying those most at risk of further cognitive impairment, vascular events or VaD.

1.3.4 Executive Function

Executive functions are a heterogeneous group of skills required for effective planning and execution of goal-orientated behaviour. Executive functions include working memory, abstraction, reasoning, verbal fluency and cognitive flexibility (Takahashi et al., 2007). Even mild impairments in executive function may impact an individual's ability to plan, initiate and execute behaviours involved in activities of daily living such as managing medication and finances.

The broader literature on VCI shows that executive function is one of the key impairments present even in the very early stages of CVD (Nyenhuis & Gorelick, 2007; Sachdev et al., 2004). Yet, the profile is still variable across different studies and across different aspects of executive functioning. For example, Sörös et al. (2015) found that 57% of their sample were impaired in their executive functioning abilities as measured by TMT. Over one third of participants were classified as impaired on TMT-A and 40% were classified as impaired on TMT-B. Lower, but still significant, rates of impairment in executive functioning have been reported in other studies using TMT. Pendlebury et al. (2012) found impairments of 16% and 7%, respectively, for Parts A and B of the TMT, whilst Sachdev et al. (2004) identified a significant difference in TMT B compared with controls, but did not find a significant difference in TMT-A. Chen et al. (2015) also noted significant differences compared with controls on TMT, although they found a larger effect for TMT-A than TMT-B.

Verbal fluency tests have also shown differing results; significant differences have been found across studies of TIA and stroke patients compared with controls on semantic naming tasks (Bakker et al., 2003; Chen et al., 2015; Sachdev et al., 2004). Furthermore, Pendlebury et al. (2012) highlighted minor impairments compared with controls on animal and letter fluency tests (2% each). Van Rooij et al. (2014) reported 10% of the sample was impaired on either verbal fluency or the Stroop Interference Task compared with controls.

Impairments have been reported in executive functioning across studies. Yet, impairments seen in the executive functioning domain may be attributable to slowed information processing speed as both the TMT and tests of fluency are timed tasks that require the participant to be able to process information quickly to perform well.

1.3.5 Language

Language can be conceptualised as expressive and receptive language functions. Disruptions to language skills are associated with grey matter atrophy, which is not usually seen in TIA patients, but is evident on the severe end of VCI continuum. Gorelick et al. (2016) highlighted that the current test of language function in the NINDS-VCI battery may not be as sensitive in this population as the test for executive function and memory, and so may not show deficits even if they are present. The current suggested test is the BNT (Franzén-Dahlin & Laska, 2012). Participants are presented with line drawings of common objects and animals and asked to name them. The argument is that using similar naming tasks in screening tools may not identify language deficits in this cohort. This, moreover, may artificially inflate their overall scores, as naming is likely to be insensitive to the level of change found in TIA patients' cognitive abilities.

Nonetheless, impairment in language has been identified in some studies. Pendlebury et al. (2012) found that 2% of the TIA cohort were impaired on the BNT. Chen et al. (2015) also revealed a significant difference in scores on the BNT between mild stroke participants and controls. However, most studies have not found impairments in the language domain (Mandzia et al., 2016; Sachdev et al., 2004). Generally, across studies, rate of impairments appears to be low and may be due to variations in inclusion criteria or the insensitivity of language tools used.

1.3.6 Visuospatial Deficits

Visuospatial construction encompasses recognition of visual stimuli and accurate perception of their characteristics. Deficits in visuospatial skills have been found in studies using the ROCFT (Chen et al., 2015; Pendlebury et al., 2012), the Block Design Task (Sachdev et al. 2004) and clock drawing task (Sörös et al., 2015). A recent study found that clock drawing and cube drawing significantly detected cognitive impairment in a stroke and TIA sample (Mai, Sposato, Rothwell, Hachinski, & Pendlebury, 2016). Furthermore, Tham et al. (2002) found WMS-R and Block Design Test to predict patients who were more likely to decline in cognitive functioning over a one-year period compared with those who were more likely to remain stable or improve. A visuospatial test may be a useful component to include in a screening test, which is more sensitive to mild impairments.

1.3.7 Summary

Research into the cognitive domains in TIA has shown a mixture of findings. Impairments have been seen across all cognitive domains, although not all studies concur with regards to which areas the deficits are observed in, other than executive functioning and information processing speed. This may be due to the heterogeneity

of studies and the different ways in which impairment is measured. However, it is also possible that impairments in TIA are global rather than focal. It is hypothesised that certain brain areas are central to the impairments caused by vascular disease and other brain areas that when disrupted overlay on the central dysfunction (Cumming, Marshall, & Lazar, 2013; Sachdev et al., 2004; Su et al., 2015), causing global deficits. Therefore, a test of cognition that can account for small changes in performance across skills that recruit multiple domains may be more helpful than assessing numerous individual cognitive domains at a low level.

1.4 Challenges in Detecting Cognitive Impairment in TIA

1.4.1 Overview

This section describes some of the challenges in understanding cognitive impairments, as well as the factors that influence cognitive testing, including mood, fatigue and anxiety.

1.4.2 Heterogeneity of Studies

No meta-analysis has been possible across TIA studies due to heterogeneity. The difference between studies occurs at each stage of the research process.

1.4.2.1 Inclusion Criteria

The age of participants included across studies varies. For example, van Rooij et al. (2014) included participants under the age of 65, whilst all those in the group of Pendlebury et al. (2013) were over the age of 60. The use of older participants is likely to influence cognitive functioning due to other age-related white matter changes (Ferro & Madureira, 2002). Not all studies have excluded existing dementia or

previous stroke, which is also likely to impact rates of impairment and skew prevalence rates of cognitive impairment.

Participants also have different diagnoses. Studies often combine mild stroke and TIA to report findings, which may mean that cognitive impairments are inflated compared with studies where only TIA participants are included. For example, a study by Shopin et al. (2013) compared stroke with TIA patients across global cognitive function, memory, visuospatial, verbal and attention and found that stroke patients had significantly more impairments across all domains than TIA patients. Time-based and tissue-based definitions have been used varyingly across studies; this is also likely to lead to different reported rates of impairment.

Few studies test participants immediately after their TIA. There is usually a delay of three months to one year. Participants within a study may have been tested at differing times since their TIA. Rates of impairment are known to be higher immediately after a TIA (Salvadori et al., 2013), which needs to be accounted for in comparisons.

1.4.2.2 Measuring Cognition

Screening tools are widely used in this cohort to measure cognition. Suggested cut-offs vary between the studies, and this can often vary depending on the testing period (acute, sub-acute, chronic). The MMSE has been widely criticised as a screening tool for VCI, yet, it continues to be used as an outcome tool. This is likely to have implications for research findings and future directions for research (Webb et al., 2014).

1.4.2.3 Defining Impairment

Some studies have collected data on matched controls to compare outcomes of TIA participants. Impairment on a test or within a domain is generally established by using t-test to determine whether there is a significant difference between the groups on scores. Other studies have relied on published normative data sets.

Furthermore, there is no clear consensus on the definition of cognitive impairment. There are at least 18 different definitions and terms in use (Pendlebury, Wadling, Silver, Mehta, & Rothwell, 2011). Whilst the Peterson criteria class single domain impairment as mild cognitive impairment, other methods require at least two cognitive domains, and in some cases one of those domains is required to be memory, such as in the NINDS-AIREN criteria (Petersen et al., 2001). Pendlebury et al. (2011) found that in a TIA cohort with cognitive impairment, less than half had a specific memory impairment, suggesting that using the NINDS-AIREN criteria (Román et al., 1993) will significantly underestimate rates of cognitive impairment. Classification of impairment can range from one standard deviation (SD) below the mean (Mandzia et al., 2016) to two SD below the mean (Bakker et al., 2003). Using one SD point as a cut off for cognitive impairment may lead to false positives (van Rooij et al., 2014), whilst two SD cut-off points may lead to less detection of subtle changes. Furthermore, some studies require one test to be below the expected norm before classifying the domain as impaired, whilst others specify that at least half of the tests within that domain must fall below the norm for a classification of impairment. Studies may also take an average z-score from the domain to establish how far it falls below the mean.

Ensuring that clinicians and researchers are agreed on a shared understanding of what constitutes cognitive impairment is a key factor that needs to be agreed upon to address the variation within the research findings.

1.4.3 Factors Impacting Cognitive Testing after a TIA

1.4.3.1 Depression and Anxiety

A recent review of the literature on stroke and TIA has shown that depression is an important comorbidity, with a combined prevalence rate of between 11 and 63%. Furthermore, studies have found that 50% of patients who were depressed at three weeks post-event remained so at one year. People with depression are more likely to have longer hospital stays and higher rates of functional disability. They are also less likely to be discharged home. There is a three times greater mortality risk for depressed patients even after accounting for the severity of the stroke or TIA and after accounting for demographics factors (Swartz et al., 2016). Recently, a study identified that TIA patients with depression are more likely to have impaired processing speed (Mandzia et al., 2016). It is suggested that the high rates of depression may be due to preserved insight in this population, and undetected structural changes in white matter, which could potentially influence symptoms of depression (Pendlebury, 2009). Pendlebury et al. (2011) found that cognitive impairment following TIA was associated with a trend towards a higher score on the Geriatric Depression Scale (GDS). This finding is supported by a recent longitudinal study, which showed that scores on the GDS at the time of TIA and stroke, and six months later, significantly predict cognitive impairment two years later. Together these findings suggest depression and its relationship to cognitive impairment is an important factor to consider after TIA.

Anxiety symptoms are also known to increase after a TIA or stroke, with around a 20–30% prevalence rate (Barker-Collo, 2007; Broomfield, Quinn, Abdul-Rahim, Walters, & Evans, 2014; Leppävuori, Pohjasvaara, Vataja, Kaste, & Erkinjuntti, 2003). However, anxiety does not have the same predictive value on recurrent cerebrovascular events that depression has (Yu et al., 2015), or the same impact on cognitive impairment, but it significantly interacts with depression to influence its severity and course (Shimoda & Robinson, 1998).

1.4.3.2 Fatigue

Fatigue is multi-dimensional and comprises physical, emotional and cognitive elements. It is estimated that one third of patients experience and report fatigue after a TIA (Coutts et al., 2012; Moran et al., 2014), with studies reporting significant rates of fatigue up to 12 months later (Kjörk et al., 2015; Moran et al., 2014). A recent study found that TIA patients had a 43% increase in risk of experiencing fatigue compared with controls (Turner, Calvert, Feltham, Ryan, & Marshall, 2016). Studies on stroke have associated fatigue with reduced quality of life and increased mortality. It would be expected that TIA has a similar sequelae. Although studies have established that cognitive impairment and fatigue are both common after a TIA, there has been no investigation of the relationship between fatigue and cognitive performance in this group. This would be valuable to ensure fatigue is considered when carrying out cognitive testing.

1.4.4 Summary

Studies on cognition in TIA have been difficult to compare and draw conclusion from due to their heterogeneity across many aspects of the research process.

Furthermore, depression, anxiety and fatigue appear to have higher prevalence rates among people who have experienced a TIA or mild stroke. This may be due to structural changes in the brain or the impact of a TIA or stroke on their quality of life. There is a suggestion that such clinical factors have further independent effect on cognition. It is important to measure their effect on cognitive testing and whether they are responsible for further reductions in cognitive functioning.

1.5 Evaluation of Current Screening Tools

The two most commonly used screening tools are the MoCA and MMSE. However, a significant amount of cognitive dysfunction is still undetected in stroke settings (Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009).

The MMSE (Folstein, Robins, & Helzer, 1983) is a 30-point tool consisting of 11 items assessing various cognitive functions including attention, orientation, memory, registration, recall, calculation, language and ability to draw a complex polygon. It takes between five and seven minute to administer. Cut-offs vary depending on the clinical setting in which the test is being administered and whether the test is used to screen for dementia or mild cognitive impairment. The conventional cut-off for screening for dementia is 24, although lower cut offs have been suggested (Creavin et al., 2016).

A recent systematic review concluded that the MMSE is only appropriate to measure vascular dementia and not milder levels of cognitive impairment (Burton & Tyson, 2015a). The MMSE has been criticised for its insensitivity to the cognitive domains that are most affected in cerebrovascular disease. For example, one third of the possible points on the MMSE are allocated to correct orientation for time and place. It is unlikely that people with mild cognitive impairments following a TIA will

be unable to score maximum points in this domain. Similarly, naming is unlikely to be impaired in this group. It has been shown that the MMSE is not as accurate in estimating cognitive abilities as other measures (Blackburn, Bafadhel, Randall, & Harkness, 2013). There are mixed findings on its predictive validity and criterion validity, studies have generally shown the MMSE to have low sensitivity (Van Heugten, Walton, & Hentschel, 2015). However, it is still a significant predictor of impairment and future stroke following TIA (Dong et al., 2013).

Another more recently developed screening tool is the MoCA (Nasreddine et al., 2005). The MoCA was designed to be more sensitive to mild cognitive impairment than the MMSE as it contains a measure of executive functioning. The MoCA is of a similar design to the MMSE in that it is a 30-point test split into six different domains: short-term memory, visuospatial abilities, executive function, attention, concentration and working memory, language and orientation.

There is generally a lack of consensus on the optimal cut-off for cognitive impairment in stroke and TIA. A cut-off of <26 out of 30 for mild cognitive impairment was derived from a memory clinic population (Nasreddine et al., 2005), although this may not be appropriate for detecting impairment in cerebrovascular disease. Suggested cut-offs have also varied depending on whether testing is carried out in the acute phase, sub acute phase or chronic phase. In studies that have looked at the optimum sensitivity and specificity in the acute phase, normality ranges from 19 to 22 (Dong et al., 2012; Godefroy et al., 2011; Salvadori et al., 2013; Wong et al., 2013), whereas in the sub acute or chronic phase cut-offs for normality range from 20 to 27 (Cumming et al., 2013; Pendlebury, 2013; Wong et al., 2009; Wong et al., 2012; Wu et al., 2007). Previous UK studies looking at impairment in TIA have recommended the following cut-offs for the MMSE and MoCA: scores below 20 on

the MoCA are classed as significant impairment, 20–24 scores as mild cognitive impairment and scores of 25 and above as no impairment. MMSE scores below 23 are classed as significant impairment, 24–26 scores are mild cognitive impairment and scores of 25 and above are no impairment (Pendlebury, Cuthbertson, Welch, Mehta, & Rothwell, 2010; Pendlebury et al., 2012; Webb et al., 2014).

A recent review examined 16 different instruments used for cognitive screening in the acute phase after a stroke. The MoCA proved to be the best current tool. Numerous studies have shown that the MoCA is more sensitive than the MMSE in detecting cognitive impairment (Damian et al., 2011; Pendlebury et al., 2012; Popović, Šerić, & Demarin, 2007).

However, there are still concerns over the MoCA, particularly the ceiling effects; six points are allocated to correct orientation and three to naming of pictures. It is known that most people who have a TIA return to their employment, meaning that test of orientation and naming are unlikely to detect the mild deficits likely to cause problems in everyday functioning for TIA patients with mild cognitive impairments. Furthermore, the MoCA's high sensitivity tends to be associated with low specificity (Godefroy et al., 2011). Pendlebury et al. (2011) compared the MoCA and Addenbrookes Cognitive Assessment Revised (ACE-R), which includes the MMSE, with the NINDS-VCI 60-minute battery. They found that the MoCA and ACE-R were both better at detecting mild cognitive impairment than the MMSE alone, but that both the MoCA and ACE-R were not as sensitive to single domain impairments. This was hypothesised as due to the lack of timed tasks needed to measure information processing speed, and supported by the Chan et al. (2014) study. They compared a mild stroke cohort on the MoCA to a full neuropsychological battery and found that over three quarters of participants who scored 'intact' on the

MoCA scored as impaired on a full neuropsychological battery, of which one third were impaired in one domain and two thirds impaired in two or more domains. The majority of impairments were seen in information processing speed and non-verbal memory, suggesting the MoCA did not accurately detect these deficits. They also found that more than half of the group scored the maximum points on the MoCA for attention, yet were impaired on the full neuropsychological battery for this domain. Similarly, one third who scored in the memory and visuospatial domain were impaired on the full battery. This suggests that the MoCA is not finely calibrated to detect milder impairments and thus is likely to underreport impairments. Therefore, an improved screening tool would be useful, which has adequate sensitivity for the detection of cognitive impairment associated with vascular aetiologies.

Both tests take the approach of covering multiple domains, but providing a very basic or easy test for each to assess for impairment within a domain. An alternative suggestion for a brief screening would be to use tests that have less of a ceiling effect and cover a wider range of ability. This allows for improved variability and a more accurate measure of global cognitive function than a one-minute test of one domain where the participant is highly likely to reach the ceiling score.

A measure designed in this way could incorporate tests of cognitive function that are known to require a high cognitive load across multiple domains. This means that the test could still give an indication of impaired domains even at a screening level.

1.5.1 Summary

The MoCA and the MMSE are the most widely used screening tools for mild cognitive impairment, but both still fail to detect impairments, both take the approach

of simplified screening across multiple cognitive domains, which often means that TIA participants reach the ceiling of the test.

1.6 Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS)

The literature suggests that there is a need for a brief monitoring instrument due to the MoCA and MMSE ceiling effects. The tool would be used during time-limited, routine appointments by a range of health professionals. It would need to be sensitive to subtle neurological deficits. Moreover, the measure would require sufficient psychometric properties to allow accurate cognitive evaluations. Cognitive screening tools should have 80% sensitivity and specificity (Lincoln, Nicholl, Flannaghan, Leonard, & Gucht, 2003). A monitoring instrument needs to be used that can test multiple areas of functioning across different anatomical brain regions and networks. A 15-minute brief test that covers the full range of ability has been designed in multiple sclerosis (Brief International Cognitive Assessment for multiple sclerosis (BICAMS; Langdon et al., 2012). BICAMS includes the SDMT (Smith, 1982), Trials 1–5 of the CVLT-II (Delis, Kaplan, & Kramer, 1987) and Trials 1–3 of the Brief Visuo-Spatial Memory Test-Revised (BVMT-R; Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996). An international panel of experts chose these three tests, whose psychometric properties, clinical utility and external validity were considered before inclusion in the measurement tool. BICAMS assesses information processing speed, verbal memory and visual memory. These are distributed central nervous system processes, which require multiple cognitive skills. Determining them may more accurately measure the structural and functional integrity of the brain. Other brief cognitive assessments, such as the MoCA and the MMSE, attempt to measure a

range of focal deficits, but cover a smaller spread of ability, whereas BICAMS assesses only information processing speed and memory across a wide range of performance levels. Furthermore, studies have shown SDMT to be as good at detecting cognitive impairment as the MoCA and the MMSE, although insensitive to amnesic impairments (Dong et al., 2014; Lin et al., 2016). The addition of a verbal and visuospatial test of memory would detect amnesic impairments and impairments in visuospatial abilities, which are also shown to be prevalent in this population (Chen et al., 2015; Pendlebury et al., 2012; Sachdev et al., 2004; Sörös et al., 2015). Furthermore, tests of information processing speed, verbal and visual memory have been shown to predict cognitive decline (Tham et al., 2002).

BICAMS is well validated in MS, demonstrating good correlations with MRI parameters (Langdon et al., 2012). Several validation studies have shown that it is as sensitive to cognitive impairment as the recommended 90-minute gold-standard MS battery of tests (Dusankova et al., 2012; Eshaghi et al., 2012; O’Connell et al., 2004; Spedo et al., 2015; Strober et al., 2009).

BICAMS does not provide a full assessment, but would need to provide sufficient information to help clinicians identify areas of difficulty. A cognitive screening identifies people who would benefit from a more in-depth cognitive assessment. Once cognitive deficits are understood people can receive appropriate support.

1.7 Summary and Synthesis

This introduction has described the current developments in standardising a 60-minute battery that is used internationally to advance our understanding of VCI, particularly in mild stroke and TIA. The importance of current and cohesive norms, which are

underdeveloped for this battery in the UK, has been highlighted. Following this, the TIA diagnosis, risk factors, prevalence of cognitive impairment and description of gaps in current treatment were examined. Furthermore, evidence from the literature of deficits in executive function and information processing speed and other areas of cognition was discussed. The current screening tools to assess cognition and their limitations were considered, besides the challenges of neuropsychological testing. Finally, BICAMS was proposed as an alternative brief cognitive test. This may be useful in identifying the cognitive impairment in TIA. Following these assertions, the research questions and hypotheses of this study are set out below.

1.8 Study Aim and Hypotheses

The study aims to:

- Compare established cut-offs for the MoCA, MMSE and BICAMS in a UK population-based sample.
- Understand the impact of fatigue and depression on each of the screening tools in a UK population-based sample.
- Calculate cut-off for the NINDS-VCI using a UK population-based sample.
- Calculate new cut-off for detecting cognitive impairment using the MMSE and the MoCA using cut-offs established from the NINDS-VCI battery.
- Compare how established norms for the NINDS-VCI compare with norms established from a UK sample.

Hypothesis 1

Published norms for the NINDS-VCI battery will provide significantly different cut-offs compared with the cut-offs established from a current healthy UK sample.

Hypothesis 2

BICAMS will be more sensitive than the MoCA and MMSE at detecting participants who fall below the expected level on the NINDS-VCI battery.

Hypothesis 3

BICAMS will be able to identify correctly participants who fall below the expected level on the NINDS-VCI.

2 Pilot Study Method

A pilot study of 94 healthy participants utilised a 30-minute brief battery of the MMSE, MoCA, BICAMS, Hospital Anxiety and Depression Scale (HADS) and Fatigue Severity Scale (FSS). The purpose of the pilot study was to look at the relationship between BICAMS and other measures that are currently used for assessing cognition in TIA, such as the MMSE and MoCA. The pilot study allowed us to consider how feasible and acceptable administration was of the screening tests and whether the information gathered was adequate to answer the research questions or whether more information or additional testing was required to answer the research question.

2.1 Ethical Considerations

The study was reviewed by Royal Holloway, University of London Ethics Committee and was suitable for self-certification (Appendix 1). All participants gave written informed consent. Potential ethical issues were considered and addressed.

2.1.1 Informed Consent

Although cognitive deficits in the general population are uncommon, it is important to consider informed consent. The BPS professional practice guidelines were considered and adhered to. Clear leaflets were used explaining the study and participant involvement (Appendix 2).

2.1.2 Confidentiality and Storage of Data

Test data and demographic information were anonymised. The anonymous data were kept in a locked drawer on university premises. The data has now been archived at Royal Holloway, University of London.

2.1.3 Distress and Fatigue of Participants

It was considered that participants may become distressed if they felt they were not performing well, or they became fatigued from the battery of tests. Therefore, all participants were informed that they could stop the test and withdraw consent at any time. They were offered breaks throughout if they wished to take them.

2.2 Participants

A sample of healthy male and female adults across different ages participated in the study. Data from 94 participants were used: 53 female, 37 male and four unknown. The mean age of the group was 48.64 years (with a range of 22–69 years). This age range was chosen as without neuroimaging, it was felt necessary to exclude participants above the age of 69 so as to minimise any confounding concomitant age related white matter changes which were not linked to VCI and TIA. Furthermore, people aged 22-69 are more likely to be in employment, they are likely to experience a more chronic and severe VCI pathway over a more prolonged period of time, and this is more likely to affect their quality of life in terms of the family, social and economic burden.

2.2.1 Data Collection and Recruitment

Recruitment was completed between May 2016 and July 2016. Three masters students, who had received training in the administration of the tests, recruited and tested participants. The testing was scored by the researcher and re-scored by the researcher's supervisor and a PhD student to ensure accuracy and consistency. All of the analyses were carried out by the researcher.

Participants volunteered to take part and were not compensated for their participation. They were all recruited opportunistically through friends and family of

the students. All participants who expressed an interest in the study were sent an information sheet (Appendix 3). Participants were given 24 hours to consider the information and were encouraged to ask any questions they had about the study via email or telephone. Written consent was obtained at the start of the appointment.

2.2.2 Inclusion Criteria

All participants were 18 years or above, fluent in English, able to read and give their informed consent for participation in the study.

2.2.3 Exclusion Criteria

Participants were excluded if they had a prior diagnosis of dementia, the experience of a major psychiatric disorder, current or prior history of alcohol and drug abuse, prior neurological disease, which can influence cognitive function, or a history of head injury.

2.3 Measures

2.3.1 Demographic Information

Information regarding gender and age were collected from participants.

2.3.2 Questionnaires

Participants were asked to complete a brief questionnaire on their levels of fatigue as well as a brief screening measure for depression and anxiety. Each of these will be described in turn.

2.3.2.1 *Fatigue Severity Scale (FSS; Krupp, LaRocca, Muir-Nash & Steinberg, 1989)*

This self-report measure is used to provide a subjective measure of levels of fatigue. The questionnaire consists of nine questions relating to everyday life. Participants are asked to circle the number that represents how they feel about the statement, ranging from 1, strongly disagree with the statement, to 7, strongly agree (Appendix 4). The total score can be averaged to obtain a mean score of 1–7 for each participant. The psychometric properties of this scale have been validated in a stroke cohort with a Cronbach's alpha of 0.86 for reliability (Lerdal & Kottorp, 2011).

2.3.2.2 *The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983)*

The Hospital Anxiety and Depression Scale is a brief self-report measure of anxiety and depression. There are 14 items in total, half relating to anxiety and half to depression (Appendix 5). For both subscales, raw scores of between 8 and 10 identify mild cases, 11–15 moderate cases and 16 or above severe cases. Besides good homogeneity and test-retest reliability of the total scale and subscales, the dimensional structure and reliability of the HADS has been found to be stable across medical settings and age groups (Spinhoven et al., 1997). In a review of 747 papers that had used the HADS, Bjelland, Dahl, Haug, and Neckelmann (2002) found that Cronbach's alpha for HADS-Anxiety varied from .68 to .93 (mean .83) and for HADS-Depression from .67 to .90 (mean .82). They also noted sensitivity and specificity for both HADS-Anxiety and HADS-Depression of approximately .80. Crawford, Henry, Crombie, and Taylor (2001) provided normative data for the HADS and found that demographic variables have only a modest influence on test scores. There is evidence

that the HADS has the same properties whether it is used with the general population, in general practice or with psychiatric patients (Bjelland et al. 2002), making it an appropriate screening instrument for the current study. The measure has been validated in a stroke cohort (Burton & Tyson, 2015b; Spurgeon, James, & Sackley, 2015).

2.3.3 Neuropsychological Tests

2.3.3.1 *Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS; Langdon et al., 2012)*

The Oral Symbol Digits Modalities Test (SDMT; Smith, 1982) assesses processing speed. It requires approximately five minutes to complete. Participants are given a sheet of paper, which at the top has a printed key pairing each abstract symbol with a number of 1–9. Eight rows containing symbols on the top with a small blank square at the bottom are presented on the rest of the page. The examinee has a trial of the first 10 squares, before being given 90 seconds to complete as many of the squares as possible by verbally stating the number associated with each symbol (Appendix 11). The oral SDMT has good test-retest reliability ($r = .98$) (Morrow et al., 2010). It has significant correlations with other processing speed tests such as the Wechsler Digit-Symbol coding subtest ($r = .91$) (Morgan & Wheelock, 1992).

California Verbal Learning Test-II (Trials 1-5) (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) measures new learning and verbal memory using a multiple trial-list-learning task (Appendix 12). The first five learning trials have been shown to be the most sensitive measure of new learning and verbal memory (Benedict et al., 2012). The CVLT-II has demonstrated good test-retest reliability ($r = .82$) and good internal consistency (.87-.89) (Delis et al., 2000). To administer the CVLT-II, the

examiner reads out a list of 16 words in 18–20 seconds. Participants are asked to recall as many words as possible in any order. The examiner records the responses and continues to re-read the list of words for five trials. The sixteen words are made up of four semantic categories. In this study the original form was used (Delis et al., 2000). The total number of correct items recalled across all five trials was used as a measure of verbal memory and new learning. The CVLT-II has good test-retest reliability for healthy controls (Delis et al., 1987; Woods, Delis, Scott, Kramer, & Holdnack, 2006)

Brief Visuospatial Memory Test-Revised (Trials1-3) (BVMT-R; Benedict et al., 1996) measures visual learning and memory using a multiple trial list-learning paradigm. For administration, participants are given an A4 sheet of paper with six figures on the page. They have 10 seconds to look at the page before it is removed and they are asked to draw as many figures as they can recall and in their correct location on the page (Appendix 13). The BICAMS consists of three trials of the BVMT-R. Participants receive one point for the accuracy of the figure and one point for the accuracy of the location on the page. Therefore, there is potentially 12 marks to be given. The BVMT-R has excellent test-retest reliability of .80 (Benedict, 1996). Internal consistency ranges from .96 to .97 for the three learning trials (Benedict et al., 1996). Performance on the BVMT-R has been found to correlate with other measures of verbal memory and recall such as the Visual Reproduction subtest of the Wechsler Memory Scale–Revised (WMS-R; Wechsler, 1987) and the Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995). The BVMT-R has excellent internal consistency on all measures (Benedict, 1997).

Norms for the BICAMS were based on a healthy UK sample of 68 participants with a mean age of 44 (SD 10 years, range 27–60), of which 37 were female and 31

were male, with an average of 16 years of education (SD 2.8) and average estimated IQ of 111 (SD 8.8) (Orchard, 2013).

2.3.3.2 *Montreal Cognitive Assessment (MOCA; Nasreddine et al., 2005)*

The MoCA is designed to measure global cognitive function and detect mild cognitive impairment. It is scored out of 30 and takes 10 minutes to administer. It measures short-term memory, visuospatial abilities, executive function, attention, concentration and working memory, language and orientation (Appendix 14). The original validation study found a cut-off of <26 out of 30 for mild cognitive impairment, although this was derived from a memory clinic population (Nasserredine et al., 2005). It has also been identified as suitable for detecting impairment in cerebrovascular disease. UK studies on impairment in TIA have recommended the following cut-offs: scores below 20 on the MoCA are classed as significant impairment, scores between 20 and 24 are classed as mild cognitive impairment and scores of 25 and above are no impairment (Pendlebury et al., 2010, 2012; Webb et al., 2014). Internal consistency has been assessed using Cronbach's alpha and is above .90 for the measure (Freitas, Simões, Marôco, Alves, & Santana, 2012).

2.3.3.3 *Mini-Mental State Examination (MMSE; Folstein et al., 1983)*

The MMSE is an 11-item measure that covers five areas of function, namely, orientation, registration, attention and calculation, recall, language and copying (visuoconstructional abilities). The maximum possible total score is 30 points (Appendix 15). It is designed to measure mental impairment in the elderly, and it takes 5 to 10 minutes to administer. The conventional cut-off for detecting dementia is 24. In a recent meta-analysis by the Cochrane review, a cut-off point of 24 yielded a sensitivity of .85 and specificity of .90 for the detection of dementia in people over 65

in the community and in primary care populations. UK studies of impairment in TIA have recommended the following cut-offs: scores below 23 are classed as significant impairment, scores between 24 and 26 are mild cognitive impairment and scores of 25 and above are no impairment (Pendlebury et al., 2010, 2012; Webb et al., 2014). Internal consistency, assessed using Cronbach's alpha, is .62 (Tombaugh & McIntyre, 1992).

2.4 Procedure

Participants were asked to complete the standardised questionnaire to screen for depression and anxiety. This was followed by a questionnaire on fatigue, the MOCA, MMSE and BICAMS. Participants were not advised about their performance on the tests. The assessment took 30 to 40 minutes to complete. The majority of assessments took place in people's homes or their workplace.

2.5 Terminology

It was necessary to use diagnostic terminology relating to cognitive impairment and depression and anxiety when referring to references and cut-offs utilised by other authors who had used clinical samples. For the sake of clarity, the same definitional terms were applied. However, as the current study utilises healthy controls and a full and detailed clinical interview has not been carried out, it was not possible to determine if participants were in fact cognitively impaired or experiencing clinical depression or anxiety, for this reason, the term 'falling below expected levels' was used in place of 'cognitive impairment' when not referring to another author's work and operational definitions.

2.6 Statistical Analysis

2.6.1 FSS

Frequencies for different levels of fatigue were calculated using the following categories outlined by Krupp et al. (1989): sub-clinical fatigue ($FSS < 4$), borderline fatigue ($4 < FSS \leq 5$) and fatigued ($FSS > 5$).

2.6.2 HADS

Standard cut-offs for the differing severity levels of depression and anxiety were used to establish the frequencies of each. Cut-off scores for depression and anxiety were applied: normal (0-7), mild (8-10), moderate (11-14) and severe (15-21) (Zigmond & Snaith, 1983).

2.6.3 BICAMS

Dusankova et al. (2012) suggested that if one or more BICAMS tests have a z-score of more than 1.5SD below the mean, BICAMS performance should be considered impaired. z-scores were derived using the norms from a UK normative sample as described in Orchard (2013).

2.6.4 MoCA and MMSE

Webb et al. (2015) established the cut-off for the MoCA and MMSE: a score of < 20 on the MoCA was classed as 'significant impairment', scores between 20 and 24 were 'mild impairment' and ≥ 25 was 'no impairment'. A score of < 23 on the MMSE was classed as 'significant impairment,' scores between 24 and 26 were 'mild impairment' and ≥ 27 was no impairment. No educational adjustment was made on either test.

2.6.5 Relationships between Variables

Pearson's correlations were used to establish the relationship between the cognitive tests (MoCA, MMSE, BICAMS) and clinical and demographic factors (fatigue, depression, anxiety, age and gender).

2.7 Section Summary

This section presented the ethical approval process, and the participants included and excluded from the study. The measures and procedure for administration were described. This was followed by an outline of the planned statistical analyses. The following results section describes the statistical analyses and findings.

3 Pilot Study Results

3.1 Data Screening

Quantitative analysis of the data was carried out using IBM SPSS version 21.0 for Macintosh (IBM Corp., 2012). Data were screened for missing values, accuracy and normality prior to analyses. Descriptive statistics, histograms and box plots for each variable were calculated.

3.1.1 Missing Data

Group means were assigned to one total MoCA score (out of 30), a total HADS depression score (out of 21) and a total trial 2 score for one BVMT-R (out of 12). Age and fatigue data were unavailable for 33 participants.

3.1.2 Outliers

One outlier was identified (defined as data points falling more than three standard deviations from the mean). A CVLT-II score was found to be more than three standard deviations below the mean. As this was the participant's sole outlying score, it was assumed to be a true representation. As recommended by Tabachnick and Fidell (2012), the statistical impact of the outliers was reduced by replacing the outlying score with the value of the next lowest in the population, plus one unit of measurement. This was repeated at the other end of the distribution.

3.1.3 Normality

Distribution was assessed to establish whether the data met the assumption of normally distributed data for parametric analysis. As suggested by Tabachnick and Fidell (2012), a z-score cut-off of between -2.58 and 2.58 for both Skew and Kurtosis was used to determine normality of distribution for each variable. HADS anxiety, age,

BICAMS and MoCA scores were all within the limits of normality $z=2.57$. Fatigue was significantly positively skewed ($z = 3.20, p<0.1$). A square root transformation was carried out on fatigue scores, which resulted in them being normally distributed ($z= .837, p>0.1$). HADS depression scores were significantly positively skewed ($z=3.23, p<0.1$). A square root transformation was carried out on HADS depression scores, which resulted in them being normally distributed ($z= -1.57, p>0.1$). MMSE was significantly negatively skewed ($z=-3.02, p<0.1$). MMSE scores were squared, which resulted in them being normally distributed ($z=-2.51, p>0.1$).

3.2 Demographic and Clinical Characteristics

Descriptives of demographic and clinical variables were calculated for each of the demographic and clinical variables of interest. These included gender, age, fatigue, anxiety and depression. Table 1 displays the means, standard deviations and range for each of the demographic and clinical variables.

Table 1. Demographic and Clinical Characteristics of the Pilot Group (N=94).

	Mean (SD)	Range
Age in years	48.64* (12.46)	22-69
FSS	3.78* (2.11)	1.29-9
HADS-Anxiety	5.96 (3.92)	0-18
HADS-Depression	3.69 (2.59)	0-12

*n=61

3.2.1 Gender

The ratio of male to female participants was 37:53, with gender information not available for four participants.

3.2.2 Fatigue

The Fatigue Severity Score (FSS; Krupp et al., 1989) was employed to measure fatigue and the following categories, as outlined by Krupp et al. (1989), were applied: FSS < 4 (*sub-clinical fatigue*), $4 < \text{FSS} \leq 5$ (*borderline fatigue*) and FSS > 5 (*fatigued*). Fatigue data were not available for 33 participants. Table 2 shows the classification frequency across participants. In total, 40% of participants were identified as experiencing a level of fatigue.

Table 2. Classifications and Scores on the Fatigue Severity Rating Scale (FSS)

	Number in Classification (%)
Sub-clinical fatigue (FSS <4)	37 (60%)
Borderline fatigue (4 < FSS ≤5)	14 (24%)
Fatigued (FSS > 5)	10 (16%)

3.2.3 Anxiety and Depression

Depression and anxiety were measured using the self-report Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The standard HADS classification and cut-off scores for depression and anxiety were applied: normal (0–7), *mild* (8–10), *moderate* (11–14) and *severe* (15–21). In total, 9% of participants were identified as experiencing a level of depression and 34% were classified as experiencing a level of anxiety.

Table 3. Classification and Scores on the Hospital Anxiety and Depression Scale (HADS) for Pilot Data (n=94).

	Number in Classification (%)
Sub-clinical depression (Scores 0–7)	85 (91%)
Mild depression (Scores 8–10)	7 (7%)
Moderate depression (Scores 11–14)	2 (2%)
Severe depression (Scores 15–21)	0 (0%)
Sub-clinical anxiety (Scores 0–7)	60 (64%)
Mild anxiety (Scores 8–10)	19 (20%)
Moderate anxiety (Scores 11–14)	13 (14%)
Severe anxiety (Scores 15–21)	2 (2%)

3.3 Screening Tools

The MoCA, MMSE and BICAMs were carried out. The mean, SD and range for each sub-domain on each screening test are outlined in Table 4. Clinical cut-offs for the MoCA and MMSE were derived from established sources in the TIA literature (Webb et al., 2014). Scores below 20 on the MoCA were classed as significant impairment, scores between 20 and 24 were mild cognitive impairment and scores of 25 and above were no impairment. In MMSE, scores below 23 were classed as significant impairment, scores between 24 and 26 were mild cognitive impairment and scores of 25 and above were no impairment. In BICAMS, the established consensus is 1.5SD below the mean on one or more tests (Dusankova et al., 2012; O'Connell et al., 2004; Orchard, 2013). Norms derived from a UK population were used for BICAMS (Orchard, 2013).

Table 4. Means, Standard Deviations (SD) and Ranges for Sub-Domains of Each Neuropsychological Measure in the Pilot Group (N=94).

	M (SD)	Range
MoCA	25.66 (2.44)	18-30
Short-Term Memory	3.72 (0.56)	0-5
Visuospatial Abilities	3.04 (0.66)	1-4
Executive Function	3.72 (0.56)	1-4
Attention, Concentration & Working Memory	5.58 (0.70)	3-6
Language	4.94 (0.29)	3-5
Orientation	5.95 (0.23)	5-6
MMSE	28.25 (1.49)	24-30
Orientation	7.89 (0.34)	6-8

Registration	3.00 (0)	3-3
Attention and Calculation	4.65 (0.80)	1-5
Recall	1.81 (1.24)	0-3
Language	7.89 (0.27)	6-8
Visuospatial Abilities	0.96 (0.20)	0-1
BICAMS	111.05 (20.59)	86-110
BVMT-R Total Learning	20.54 (7.38)	2-36
CVLT-II Total Learning	45.73 (9.90)	26-68
SDMT	53.04 (11.22)	25-85

3.4 Number of Participants Falling Below Established Cut-Offs

Frequencies of participants falling below the expected level on the MoCA, MMSE and BICAMS are provided in Table 5. Overall, 32% of participants fell below expected levels on the MoCA, 10% on MMSE and 69% on BICAMS. BICAMS classified the highest number of participants as falling below the expected level.

Twelve participants were impaired across all three BICAMS measures. Seventeen people were impaired across BVMT-R and CVLT-II, four people on SDMT and CVLT-II and five people on BVMT-R and SDMT. BICAMS identified 29 (97%) of the 30 participants in the impaired range on the MoCA and nine (100%) participants in the impaired range of the MMSE. The MoCA also identified all nine participants of the impaired range on the MMSE.

Table 5. Participants Falling Below Established Cut-Off Scores on the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE) and Brief International Cognitive Assessment Measure (BICAMS) in the Pilot Group (N=94).

	MoCA	MMSE	BICAMS
	Number in Classification		
	(%)		
Significant Impairment	1	0	65
	(1%)	(0%)	(69%)
Mild Impairment	29	9	
	(31%)	(10%)	
No Impairment	64	85	
	(68%)	(90%)	

3.5 Relationships Between Variables

Pearson’s correlation was used to establish the relationship between the cognitive tests and fatigue, depression, anxiety and age and gender. Results are shown in Table 6.

Table 6. Summaries of Correlations between Neuropsychological Measures and Fatigue, Anxiety and Depression for Pilot Group (N=94).

	BICAMS z-score	MMSE	MoCA	FSS (n=61)	Depression	Anxiety
MMSE	.41**					
MoCA	.50**	.45**				
FSS (n=61)	.02	-.08	-.08			
Depression	.00	-.06	-.03	.40**		
Anxiety	.09	.06	.09	.31*	.40**	
Age (n=61)	-.55**	-.37**	-.32**	-.09	-.22	-.36**
Gender (n=90)	.09	.09	.03	-.09	-.11	.08

* $p < .05$, ** $p < .01$

3.6 Summary of Pilot Data

Thirty-two percent of participants fell in the impaired range on the MoCA, 10% on MMSE and 69% on BICAMS. Despite the high number of participants scoring in the clinical range for fatigue (40%) and anxiety (34%), no significant correlations were found between fatigue, depression or anxiety in any of the screening tests. Gender was not significantly correlated with any of the screening tests. However, age was significantly negatively correlated with all three screening tests.

In summary, BICAMS seems to be a potential candidate for a suitable screening tool for mild cognitive impairment.

4 Pilot Study Discussion

The pilot study was carried out to look at the feasibility of the BICAMS and to draw comparisons between the measures. The results showed that BICAMS was highly correlated with the MoCA and the MMSE. This suggested that BICAMS could be a useful tool, which could potentially improve the sensitivity and specificity to detect cognitive impairment in TIA participants.

There were no significant correlations between any of the screening measures and fatigue, depression or anxiety, despite the high number of participants scoring in the clinical range within these demographic variables. There was a significant negative correlation with age, suggesting that performance on the tests declines with age. Currently, none of the tools account for variance in age and how this may affect performance. This may be because the MoCA and MMSE have been mainly utilised in elderly populations rather than across the whole age range.

4.1 Interpretation

4.1.1 BICAMS is Positively Correlated with the MoCA and MMSE

This would suggest that all three tools measure cognition. Further exploration of the tools is required to determine how closely each compares with a full battery of neuropsychological tests and whether other clinical or demographic variables may be partially correlated with the measures.

4.1.2 Age is Significantly Negatively Correlated with BICAMS, MoCA and MMSE

This finding is in line with other studies showing that age is a significant predictor of neuropsychological testing scores (Reitan & Wolfson, 1995). Generally, research has focused on exploring the use of the MoCA and MMSE in an older population. This

pilot study has highlighted that if screening tools are to be used across a broader age range, it is important to account for age effects. It is likely that some tests within each of the screening tools are likely to be affected by age in varying degrees. For example, tests of information processing speed, such as the SDMT in the BICAMS and verbal fluency tasks in the MoCA and MMSE, may be more highly influenced by age than the orientation tasks in the MoCA and MMSE.

4.1.3 Gender is not Significantly Correlated with BICAMS, MoCA or MMSE

Studies of neuropsychological testing have generally shown that gender is not significantly correlated with neuropsychological test performance. It is important to consider other cultural factors, which may sometimes account for differences in performance; for example, ensuring that years of education do not differ between male and female participants.

4.2 Strengths and Limitations

4.2.1 Clinical and Demographic Information

A relative strength of the study is the collection of further clinical information on depression, anxiety and fatigue. It is interesting to note that these clinical factors do not correlate with the screening measures despite relatively high numbers of participants in the clinical range. Future studies should continue to collate information on clinical factors such as anxiety, depression and fatigue to see how rates differ in a TIA population and if these clinical factors are correlated with screening tools in a TIA population. This may provide more information on how anxiety, fatigue and depression are experienced within the TIA population and if this is different to anxiety, depression and fatigue in the general population.

No information on years of education was collected from participants, meaning that no adjustment was made on any of the screening tools for participants with lower than average educational experience. Neither BICAMS nor the MMSE adjust scores for years of education. However, the MoCA awards one additional point for less than 12 years of education. This was not possible to conduct in the pilot study. Future studies should ensure accurate information on years of education to explore how this demographic factor relates each of the cognitive tests.

4.2.2 Level of Impairment in a Non-Clinical Sample

A high proportion of participants were classified in the impaired range on all three screening tools. The highest numbers were identified by the BICAMS, followed by the MoCA and then the MMSE. Such findings are not uncommon with control studies (Binder, Iverson, & Brooks, 2009; Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008) and highlight the importance of considering test scores in the wider context of the participant's wellbeing.

4.2.3 Rigour of Marking Procedure

A relative strength of the pilot study was the rigour of the marking procedure, in which all tests were scored and then ratified by a second marker. This ensured a high level of consistency across participants within the pilot group.

4.2.4 Normative Data

The age of participants in this sample fell outside the age range in which BICAMS normative data have been collected. Furthermore, as no information on years of education or IQ was provided in this sample, it is difficult to know if the normative data for BICAMS accurately reflect the sample of participants in this study. Future

studies should consider collecting further demographic information to aid with matching the group to a similar normative sample data set.

4.3 Clinical and Research Implications

To understand more why the measures are correlated, it would be helpful to compare the screening tools with a larger battery of neuropsychological tests that fully explore multiple domains of cognitive functioning. Future studies should continue to collect information on clinical factors such as depression, anxiety and fatigue and consider collecting supplementary information on demographic factors such as years of education and IQ, in order to understand the population further. Investigation into if an age-adjusted score is necessary should also be explored.

5 NINDS-VCI Group Method

5.1 Ethical Considerations

Ethical considerations for both the pilot and NINDS-VCI group can be found in Section 2.1.

5.2 Participants

A sample of healthy male and female adults across different ages and different educational backgrounds participated in the study. Data from 67 participants were used in the 90-minute test group. This comprised 44 female and 23 males. The mean age of the group was 43.86 (range 18–67). Mean years of education was 16.24 (range 10–24).

5.3 Data Collection and Recruitment

Recruitment was completed between August 2016 and February 2017. The researcher recruited and tested participants for the 90-minute battery, and a psychology graduate trained in the administration of the test battery recruited and tested a further nine participants. The testing was scored by the researcher and re-scored by the research supervisor and a PhD student to ensure accuracy and consistency. The researcher carried out all analyses.

Participants volunteered to take part and were not compensated for their participation. They were all recruited opportunistically in London, the Midlands and Surrey. Posters were distributed in a London hospital to recruit participants. All participants who expressed an interest in the study were sent an information sheet (Appendix 3). Participants were given 24 hours to consider the information and were

encouraged to ask any questions they had about the study via email or a telephone call. Written consent was obtained at the start of the appointment.

5.3.1 Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for both the pilot study and main study are given in sections 2.2.2 and 2.2.3.

5.3.2 Individuals Excluded

Of the potential participants expressing an interest, 69 took part and 67 were included in the analysis. Reasons for exclusion were history of head injury or epilepsy (n=1) and withdrawal before the end of testing (n=1).

5.3.3 Sample Size

Regression analysis was planned to investigate which factors contributed to a significant amount of the variance in NINDS-VCI and BICAMS scores. An a priori power analysis was carried out to see how many participants were needed to have a power of .80 at a 0.5 level. This is to ensure that the prediction equation has generalisability. It was calculated that a total of 40 participants were required to complete the neuropsychological battery to ensure adequate power for a large effect size. This was calculated using G*power 3.1.3 (Faul, Erdfelder, Lang, & Buchner, 2007), with a traditional p-value of .05 and power value of .80 (Cohen, 1992).

5.3.4 Retrospective Power Analysis

A post hoc power analysis was conducted using the software package G*Power (Faul, Erdfelder, Lang, & Buchner, 2007). The sample size of 67 was used for the statistical power analyses and a four predictor variable equation was used as a baseline. The recommended effect sizes used for this analysis were as follows: small ($f^2 = .02$),

medium ($f^2 = .15$) and large ($f^2 = .35$) (Cohen 1992). The alpha level used for this analysis was $p < .05$. The post hoc analyses revealed the statistical power of this study was .948 for detecting an effect. Thus, there was more than adequate power (i.e., power * .80) at the moderate to large effect size level.

5.4 Measures

The tests administered to both the pilot group and 90-minute test battery group are discussed in section 2.3.

5.4.1 Neuropsychological Tests

5.4.1.1 National Institute for Neurological Disorders and Stroke Test Battery for Stroke- (NINDS-VCI; Hachinski et al., 2006)

Participants in the 90-minute test battery group all completed the NINDS-VCI tests. The battery is used in stroke and TIA research, with an administration time of 60 minutes. The battery is drawn from seven different neuropsychological assessments, which are discussed below. The normative data selected for each test are also described. Cronbach's alpha of the cognitive tests within NINDS-VCI is 0.87; intra-rater reliability as measured by ICC (95% CI) was 0.90 (0.66-0.97) (Chen et al., 2015).

The Trail Making Test (Part A and B) (TMT; Ivnik et al., 1996; Reitan, 1955) is a measure of attention, speed and mental flexibility. In Part A, participants are asked to connect the numbers in ascending order with a pencil, while they are timed. The numbers run from 1–25 and scattered across an A4 page. In Part B, participants are asked to alternate between connecting numbers and letters in ascending order (e.g., *I, A, 2, B, 3, C...*) to *I3* and *L* (Appendix 6). Part B requires the use of divided

attention and set shifting. Studies have shown age to be a significant contributor to scores, with education making a moderate contribution and gender making a non-significant contribution (Mitrushina, Boone, Razani, & D'Elia, 2005). Reliability is high, although this may not be reliable across populations and time intervals (Strauss et al., 2006). Inter-rater reliability has been reported as .94 for Part A and for Part B (Fals-Stewart, 1992). The test has been shown to be sensitive to cerebrovascular dementia (Barr, Benedict, Tune, & Brandt, 1992).

The norms suggested by Hachinski et al. (2006) were provided by Selnes et al. (1991) for 733 males ranging from 25 to 54 years of age, with a mean age of 37 years (SD: 7.6) and a mean of 16 years (SD: 2.3) of education. The majority (92%) of the sample were white non-Hispanic, 4% white Hispanic, 2% black non-Hispanic and the remaining few belonged to the other racial categories.

Boston Naming Test (15-item version) (BNT; Mack et al., 1992) assesses visual naming, language and lexical retrieval. Participants are presented with 15 black and white line drawings of everyday objects and asked to name each one (Appendix 7). Reliability co-efficients vary from .49 to .84 (Schefft, Testa, Dulay, Privitera, & Yeh, 2003). The BNT correlates highly with other language measures, such as the Visual Naming Test of Multilingual Aphasia Examination ($r = .76$ to $.86$). A study has shown that the BNT is able to detect differences between controls and those with white matter infarcts in the brainstem (van Zandvoort, de Haan, van Gijn, & Kappelle, 2003).

The norms suggested by Hachinski et al. (2006) were provided by Fastenau et al. (1999) based on a sample of 108 healthy individuals, aged 57 to 85 years ($M 72.2$, $SD 7.0$), in the United States. The sample was predominantly Caucasian (95%) and

well educated (97% had at least 12 years of education). Data were stratified by three age-adjusted categories.

Rey-Osterrieth Complex Figure Copy (RCFT; Fastenau, Denburg, & Hufford, 1999) measures organisational and visuo-perceptual skills. Participants were first shown a complex geometric figure and asked to draw the same figure. Immediately after the copy trial, they were instructed to draw the design from memory. After a 30-minute delay, they were asked to draw the figure from memory again (Appendix 8). Both split-half and coefficient alpha reliabilities were greater than .60 (Strauss et al., 2006). The reliability and validity of the RCFT has been described by Meyers and Meyers (1995). Range from .93 to .99 indicates excellent inter-rater reliability. Pearson correlations were .75 for the immediate trial and .88 for the delayed. The RCFT also has good construct validity and correlates with other tests. The convergent and discriminant validity shows that it is a measure of visuospatial constructional ability and visuospatial memory.

The norms suggested by Hachinski et al. (2006) were provided by Fastenau et al. (1999), who conducted tests involving 211 healthy American adults. Ages ranged from 30 to 85 years (M 62.9, SD 14.2), education ranged from 12 to 25 years (M 14.9, SD 2.6), 55% were women and 45% were male, and over 95% were Caucasian.

Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict et al., 1998; Brandt, 1991) measures strategic learning and episodic memory indices. A list of 12 words from three semantic categories is read out to the examinee. There are three learning trials, a delayed recall trial and a recognition trial of 24 words, 12 target and 12 non-target words, six of which are drawn from the same semantic category. Form 1 was used in the current research study (Appendix 9). Reliability coefficients for the

four primary HVLT-R variables are .74 for Total Recall, .66 for Delayed Recall and .40 for the recognition trial (Benedict & Zgaljardic, 1998).

The norms suggested by Hachinski et al. (2006) were provided by Benedict et al. (1998), in their study of 541 American subjects. The average age of the sample population was 48.1 years (*SD* 17.3), with a range from 17 to 88 years. The education level ranged from 5 to 20 years, with a mean of 13.8 (*SD* 2.3). There were 200 (37%) men in the sample and 341 (63%) women.

Letter (*Controlled Oral Word Association Test*) Fluency (COWAT; Benton et al., 1994) is a measure of phonemic fluency and evaluates the spontaneous production of words. The participant is asked to produce as many words as he or she can in 60 seconds beginning with a particular letter. Three separate trials are given with three different letters. The letters C, F, L were used in this research. Internal reliability is reported to be high ($r=0.83$) (Ruff, Light, Parker, & Levin, 1996). Inter-rater reliability is also high (.99) (Laukka, Jones, Small, Fratiglioni, & Bäckman, 2004)

The norms suggested by Hachinski et al. (2006) were provided by Ruff et al. (1996), in their study of 360 volunteers aged between 16 and 70. All participants were native English speakers and resided in California and Michigan. Four education groups and three age groups were provided.

Category (animals) Fluency (Issacs & Kennie, 1973) is a measure of semantic fluency and also evaluates the spontaneous production of words. It requires participants to list as many animals as possible within the 60-second time limit. Baldo, Shimamura, Delis, Kramer and Kaplan (2001) reported that the test re-test reliability is good to high, and the test has good correlations with other verbal fluency tests, such as COWAT (FAS) ($r = .52$ ($p < .01$)) (Tombaugh, Kozak, & Rees, 1999).

The norms suggested by Hachinski et al. (2006) were provided by Selnes et al. (1991), in their study of 733 males ranging from 25 to 54 years of age, with a mean age of 37 years (SD: 7.6), and a mean of 16 years (SD: 2.3) of education. The majority (92%) of the sample were white non-Hispanic, 4% white Hispanic, 2% black non-Hispanic and the remaining few belonged to the other racial categories.

WAIS-IV Digit-Symbol Coding Test: Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV, Wechsler, 2008) (Appendix 10). The WAIS-IV is a comprehensive test battery with excellent psychometric properties. A large standardisation sample of 2200 individuals means that normative data are available for individuals up to the age of 90. The digit symbol-coding subtest provides a measure of information processing speed on non-verbal visual information. The average split-half reliability is excellent (.93) with a test-retest stability of .87. The reliability and validity of the WAIS-IV has been demonstrated in a wide range of clinical populations (Wechsler et al., 2008).

The norms suggested by Hachinski et al. (2006) were provided by Wechsler et al. (2008), in their study of 2200 people across 13 age groups. The nine younger groups consisted of 200 participants, and 100 subjects represented each of the four older groups. The normative population was proportional to US census data in 2005, in terms of gender, race and ethnicity, with equal numbers of males and females in the younger groups, and the older groups containing more women.

5.4.1.2 Intellectual Functioning

Test of Premorbid Intellectual Functioning (TOP-F; Wechsler, 2011) was used as a measure of intellectual functioning (Appendix 16). Word reading is relatively preserved even after the loss of cognitive functioning. Participants read aloud 70

irregular words. The TOP-F is highly correlated with the WAIS-IV (Wechsler, 2008) ($r = .72$), with high internal consistency and good test-retest reliability (Alpha .96 to .99 and .89 to .95) (Wechsler, 2011).

5.5 Procedure

Sixty-seven healthy controls took part in the study, which included the NINDS-VCI, MMSE, MoCA, BICAMS and HADS and FSS and TOP-F, to determine how performance on the gold standard NINDS-VCI battery compares with performance on shorter batteries (MMSE, MoCA, BICAMS).

5.5.1.1 Administration of the Measures

Participants were asked to complete the HADS and the FSS. A battery of tests was then administered to assess premorbid intelligence, speed of information processing, executive functioning, language and visuospatial and memory functioning. Administering the tests across participants in two different orders counterbalanced test order. These are outlined in the table below.

Table 7. Order of Test Delivery.

Odd Participant Number	Even Participant Number
MOCA	NINDS-VCI
MMSE	TOP-F
BICAMS: SDMT, BVMT & CVLT-II	MOCA
NINDS-VCI	MMSE
TOP-F	BICAMS: SDMT, BVMT & CVLT-II

Participants were not advised about their performance on the tests. The assessment took 60 to 90 minutes to complete. The majority of assessments took place in people's homes or their workplace.

5.6 Safety

A protocol that followed the Guidance from the National Health Service Lone Worker Policy (NHS Security Management, 2005) was established in order to ensure the researcher's safety when undertaking testing, particularly in participants' homes. Only participants personally known to the researcher were seen at home.

5.7 Statistical Analysis

Section 2.6 provides details on the descriptive analysis for the FSS, HADS, BICAMS, MoCA and MMSE, and correlational analyses that apply to both the pilot study and the 90-minute test battery group.

5.7.1 z-Scores

z-scores were derived for each participant on each of the cognitive measures. The first was calculated by using the group mean and standard deviation. The second z-score was calculated using the means and standard deviations from normative data sources recommended by Hachinski et al. (2006). Z-scores were then used to see which participants fell below the expected levels, using different criteria.

5.7.2 Defining Impairment

The modified Peterson criteria were used to identify participants who were falling below expected levels and whether the impairment was across multiple domains or within memory domains. The following four categories were used: amnesic single domain impairment, amnesic multiple domain impairment, non-amnesic single

domain impairment, non-amnesic multiple domain impairment (Peterson et al., 2001). Frequencies were calculated for each of the four categories at 1SD, 1.5SD and 2SD. For the MCI-single test definition, participants were divided into those with and without memory impairment on the HVLT-R immediate or delayed recall. Participants with impairment on the HVLT-R were then classified as MCI amnesic single-domain (no other tests abnormal) or amnesic multiple-domain (≥ 1 other test abnormal). Participants without impairment on the HVLT-R were classified as non-amnesic single domain if they were impaired on a single non-memory test, or non-amnesic multiple-domain if more than one non-memory test was impaired. For the MCI-multiple tests definition, participants were divided into those with and without memory impairment on the HVLT-R immediate and delayed recall. Participants with impairment on the HVLT-R were then classified as amnesic single-domain (no other domain abnormal), or amnesic multiple domain if a non-memory domain was also impaired. Participants without impairment on the HVLT-R were classified as non-amnesic single domain if they were impaired in one non-memory domain, or non-amnesic multiple-domain if more than one non-memory domain was impaired.

5.7.3 Norm sources

Norms were chosen on recency and the demographic factors, which matched the participants of the current study as closely as possible. Norms stratified by age from Welschler et al. (2008) were used for the WAIS Digit Symbol Coding. Norms stratified by gender and education from Ruff et al. (1996) were used for COWAT. Norms stratified by age from Selnes et al. (1991) were used for semantic fluency and TMT. Norms stratified by age from Mack et al. (1992) were used for the BNT. Norms

stratified by age from Fastenau et al. (1999) were used for the Rey-Osterrieth. Norms stratified by age from Benedict et al. (1998) were used for the HVL-T-R.

5.7.4 Test of Proportions

Numbers of participants falling below the expected level on each cognitive test were totaled using both published and current norms. Total numbers of participants falling 1.5SD below the expected level, using both norming sources, were then compared using a McNemar chi-squared analysis. This determined if the proportion of participants falling below the expected levels differed between the two methods of norming.

5.7.5 Regression

Regression analyses were performed to explore the relationship of demographic factors (gender, age², years of education and estimated IQ) to NINDS-VCI scores. Similarly, a regression was carried out to explore the relationship of demographic factors to BICAMS performance. Age was squared before the analysis to account for non-linear age effects as suggested by Parmenter, Testa, Schretlen, Weinstock-Guttman and Benedict (2010).

5.7.6 Sensitivity and Specificity

Cases were identified as falling below expected levels on the NINDS-VCI; these were then compared with the number of cases identified as falling below expected levels on the BICAMS. The accuracy, sensitivity and specificity of BICAMS were calculated in comparison with the NINDS-VCI. McNemar's test of proportions was utilised to explore if the proportion of participants identified differed between NINDS-VCI and BICAMS. Suitable cut-offs for the MoCA and MMSE were explored to see which

cut-off point was the most sensitive and specific at identifying those who fell below the expected level on the NINDS-VCI battery.

5.8 Section Summary

This section presented the ethical approval process, and discussed which participants were included and excluded from the study. The measures and procedure for administration were considered. This was followed by an outline of the planned statistical analyses. The results section below describes the statistical analyses and the findings.

6 Results 90-Minute Neuropsychological Test Battery Group

6.1 Data Screening

Data were screened for missing values, accuracy and normality prior to analyses using descriptive statistics, histograms and box plots for each variable.

6.1.1 Missing Data

Where one participant's age was missing, a group mean was assigned.

6.1.2 Outliers

Three outliers were identified (defined as data points falling more than three standard deviations from the mean). A TMT-B score was found to be more than three standard deviations above the mean. A Rey copy (RCFT) score and BNT score were also found to lie more than three standard deviations below the mean. All scores were from individual participants, and these were their only outlying scores; it was felt that all participants should remain in the data set. As recommended in Tabachnick and Fidell (2012), the statistical impact of the outliers was reduced in both cases by replacing the outlying score with the value of the next highest or lowest in the population plus one unit of measurement. This was repeated at the other end of the distribution.

6.1.3 Normality

Distribution was assessed to establish whether the data met the assumption of normally distributed data for parametric analysis. As suggested by Tabachnick and Fidell (2012), a z-score cut-off of between -2.58 and 2.58 for both Skew and Kurtosis

was used to determine normality of distribution for each variable. Age, years of education, Estimated IQ and all BICAMS measures were within normal limits.

The Rey immediate recall test was significantly negatively skewed $z=-4.62$, $p<0.1$. TMT-B scores were significantly positively skewed $z=5.35$, $p<0.1$. BNT scores were significantly negatively skewed $z=6.85$, $p<0.1$. MoCA and MMSE scores were significantly negatively skewed -2.68 and -2.82 , respectively.

Based on the recommendations of Tabachnick and Fidell (2012) for positively skewed data, the TMT-B raw scores were transformed using the $\text{LOG}_{10}(X)$ function. This produced normally distributed data for the TMT-B score $Z=1.69$, $p>0.1$. Following the recommendation of Tabachnick and Fidell (2012), moderately negatively skewed data scores on the MoCA and MMSE were squared. This produced normally distributed scores for the MoCA $z=2.18$, $p<0.1$ and within the limits of normally distributed data for MMSE -2.69 . Following the recommendation of Tabachnick and Fidell (2012) for severely negatively skewed data, inverse reciprocal transformations were used to transform the substantially negatively skewed data for the Rey immediate recall test and BNT $1/(k-X)$ function. This produced normally distributed scores for the Rey immediate recall $z=2.01$, $p<0.1$. However, the BNT remained skewed.

6.2 Demographic and Clinical Characteristics

Table 8 summarises participant demographic and clinical information. Measures of depression, anxiety and fatigue were also completed.

6.2.1 Gender and Age and Years of Education

The ratio of male to female participants was 23:44. Participants' ages ranged from 18 to 67 (M 43.86, SD 15.51). They had spent a mean of 16.24 years in education (SD 2.73, range 10-24).

Table 8. Demographic and Clinical Characteristics of the 90-minute battery (N=67).

	Mean (SD)	Range
Age in years	43.86 (15.51)	18-67
Years in Education	16.24 (2.73)	10-24
IQ (TOPF)	113.91 (8.83)	97-133
FSS	3.22 (1.13)	1.22-6.44
HADS-Anxiety	5.51 (3.14)	0-13
HADS-Depression	2.67 (2.18)	0-9

6.2.2 Estimated IQ

The Test of Premorbid Functioning (TOP-F; Wechsler, 2011) gave estimated IQs ranging from 97 to 133.0 (M 113.91, SD 8.83). Twenty-four participants fell in the average range (90–110), 27 in the high average range (111–120), 11 in the superior range (121–129) and five in the very superior range (130–150).

6.2.3 Fatigue

The Fatigue Severity Score (FSS; Krupp et al., 1989) was employed to measure fatigue and the following categories, as outlined by Krupp et al. (1989), were applied: $FSS < 4$ (*sub-clinical fatigue*), $4 < FSS \leq 5$ (*borderline fatigue*) and $FSS > 5$ (*fatigued*).

Table 9. Classification and Scores on the Fatigue Severity Scale (FSS) for 90-minute Battery (N=67).

	Number in Classification (%)
Sub-clinical fatigue ($FSS < 4$)	43 (64%)
Borderline fatigue ($4 < FSS \leq 5$)	22 (33%)
Fatigued ($FSS > 5$)	2 (3%)

6.2.4 Anxiety and Depression

Depression and anxiety were measured using the self-report Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983). The standard HADS

classification and cut-off scores for depression and anxiety were applied: normal (0–7), *mild* (8–10), *moderate* (11–14) and *severe* (15–21). Table 10 shows the number of participants in each group, who self-reported on the Hospital Anxiety and Depression scale.

Table 10. Classification and Scores on the Hospital Anxiety and Depression Scale (HADS) for 90-minute Battery (N=67).

	Number in classification
	(%)
Sub-clinical depression	65
(Scores 0-7)	(97%)
Mild depression	2
(Scores 8-10)	(3%)
Moderate depression	0
(Scores 11-14)	(0%)
Severe depression	0
(Scores 15-21)	(0%)
Sub-clinical anxiety	48
(Scores 0-7)	(72%)
Mild anxiety	14
(Scores 8-10)	(21%)
Moderate anxiety	5
(Scores 11-14)	(7%)
Severe anxiety	0
(Scores 15-21)	(0%)

6.3 Descriptives for Neuropsychological Measures

Table 11 shows the means and SD for each of the neuropsychological measures within the 90-minute battery, which included the MoCA, MMSE, BICAMS and NINDS-VCI measures. As participants were administered the test in a counterbalanced order, t-tests were carried out to see if there had been significant

interference between the two verbal memory tests (CVLT-II and HVLTR) and the two trails tests (MoCA and TMT-B), both t-tests showed no significant difference in scores between the two orders of test delivery on either the TMT-B ($t(65) = -1.67$, $p > .05$) or the HVLTR delayed recall trial ($t(65) = .592$, $p > .05$).

Table 11. Means and Standard Deviations for all Neuropsychological Tests within the 90-Minute battery (N=67).

	Mean	(SD)
MoCA	27.78	(1.56)
MMSE	29.07	(1.08)
BVMT-R Total Learning	23.63	(6.00)
CVLT-II Total Learning	52.15	(9.16)
SDMT	55.72	(8.55)
WAIS-IV Digit Symbol Coding	72.28	(12.50)
COWAT	45.61	(14.58)
Semantic Fluency	22.51	(5.48)
TMT A	23.40	(5.65)
TMT B	44.18	(16.00)
Rey Copy	35.57	(1.98)
BNT	15.21	(1.59)
HVLTR Immediate Recall	25.15	(4.51)
HVLTR Delayed Recall	8.66	(2.57)
RCFT Delayed Recall	20.69	(6.66)

The age of participants in this study was outside the age range for the normative UK data for the BICAMS battery. Mean scores on the BICAMS tests were compared with the full sample and an age-matched sample (Table 12). The means for the NINDS-VCI battery were closer to the current UK normative data sample when participants who did not match the age range were removed from the analysis. The lower means on BICAMS measures in this study shows how sensitive the BICAMS measures are to age effects, as the data shows that when participants are removed that are not within the age bracket of the normative data sample the means move closer together. However, the means in this study are still lower than the previous normative data collected in BICAMS. There is no known information on the frequency distribution of participants within the different age bands across the normative data populations. It may be that the current study has a high frequency of participants at the older end of this scale than the Orchard study, which is likely to be responsible for the current norms, even when matched for age still not being consistent with the Orchard study.

Table 12. Comparison of Means on BICAMS Across Different Healthy UK Control Samples.

	Orchard et al. (2013) means	90-minute battery full sample means	90-minute battery age- matched sample means
BVMT-R Total Learning	27.59	23.63	24.83
CVLT-II Total Learning	55.87	52.15	54.29
SDMT	62.16	55.72	56.88

6.4 Number of Participants Falling Below Established Cut-Offs on the MoCA, MMSE and BICAMS

Established cut-off scores for the MoCA, MMSE and BICAMS were applied (Orchard, 2013; Webb et al., 2014). Table 13 displays the frequency of participants falling within each range. Scores below 20 on the MoCA were classed as significant impairment, scores between 20 and 24 were mild cognitive impairment and scores of 25 and above were no impairment. In MMSE, scores below 23 were classed as significant impairment, scores between 24 and 26 were mild cognitive impairment and scores of 25 and above were no impairment. In BICAMS, the established consensus is 1.5SD below the mean on one or more tests (Dusankova et al., 2012; O’Connell et al., 2004; Orchard, 2013). Norms derived from a UK population were used for BICAMS (Orchard, 2013).

Table 13. Participants Falling Below the Established Cut-Off Scores on the MoCA, MMSE and BICAMS (N=67).

	MoCA	MMSE	BICAMS
	Number in Classification		
	(%)		
Significant Impairment	0	0	33
	(0%)	(0%)	(49%)
Mild Impairment	2	0	
	(3%)	(0%)	
No Impairment	65	67	34
	(97%)	(100%)	(51%)

No participants fell in the significantly impaired range on either the MMSE or the MoCA. BICAMS, and NINDS-VCI identified the two participants of the mildly impaired range on the MoCA.

6.5 NINDS-VCI Battery

Using similar procedures to that of earlier studies (Chen et al., 2015; Pendlebury et al., 2012; van Rooij et al., 2014), a z-score was calculated for each participant on each sub-test across the NINDS-VCI batteries. The z-score was derived for the mean and SD of the group on each neuropsychological test. TMT scores were *-1 as established by Chen et al. (2015). The modified Peterson criterion was then applied at the test level and at a domain level to compare the frequencies of those falling below the expected level. Table 14 shows the frequency of participants falling below the

expected level with different definitions of impairment used, as outlined in Pendlebury et al. (2013).

Table 14. Classification of Different Participants Using Different Impairment Criteria

	Modified			Modified Peterson		
	Peterson Criteria-			Criteria-multiple tests		
	single test definition			definition		
	1SD	1.5SD	2SD	1SD	1.5SD	2SD
Total Impaired	51	35	16	20	13	10
	(76%)	(52%)	(24%)	(29%)	(19%)	(15%)
Single Domain Impairment	18	23	13	12	11	3
Amnestic	4	4	2	0	0	0
Non-amnestic	16	19	11	12	11	9
Multiple Domain Impairment	30	6	3	8	2	1
Amnestic	18	0	0	6	0	0
Non-amnestic	12	6	3	2	2	1

Z-scores were also derived from the most suitable published norms available for each of the tests. These scores were compared with z-scores derived from the mean of the group. Participants were identified as falling below the expected level when they scored 1.5SD below the mean on one or more tests. Table shows the number of participants falling below the cut-off for each test.

Table 15. Frequency of Participants Scoring more than 1.5 SD Below the Mean Across all Neuropsychological Measure of the 90-Minute Battery from Published Norms and Means and Norms of the Current from the Current Group.

	Participants 1.5SD below the mean on published norms	Participants 1.5SD below the mean on current study norms
WAIS-IV Digit Symbol Coding	0	3
COWAT	6	4
Sematic Fluency	10	7
TMT A	7	6
TMT B	3	4
BNT	6	6
Rey Copy	0	6
HVLT-R immediate recall	25	6
HVLT-R delayed recall	25	4
RCFT- delayed recall	2	5

Using published norms, a total of 45 participants were identified as falling below the expected level on one or more test. Using the group mean, 35 participants were identified as falling below the expected level in one or more test. A McNemar test was carried out to see if published norms identified a different proportion of participants to the group mean; the test was approaching significance $p=.052$.

When considering domains made up of multiple tests (executive function and memory), scores derived using the mean of the group showed that no participants scored below the expected level on a test of executive function or on a test of memory. This is compared with 1 and 22 participants, respectively, on published

norms. When z-scores were summed and averaged out across all tests, no participants fell less than 1.5 SD below the mean on either the published norms or the mean of group.

6.6 Relationships to other Variables

6.6.1 Correlations

Bivariate correlations were carried out to evaluate the relationship between cognitive tests including NINDS-VCI z-score, BICAMS z-score, MoCA and MMSE to fatigue, depression and anxiety. These are displayed in Table 16.

Table 16. Summary of Correlations between Neuropsychological Measures and Clinical and Demographic Factors in the 90-Minute Battery (N=67).

	NINDS- VCI	BICAMS	MMSE	MoCA	FSS	Depression	Anxiety
BICAMS	.358**						
MMSE	.056	.398**					
MoCA	.039	.217	.408**				
FSS	-.279*	-.153	-.118	-.064			
Depression	-.282	-.090	.127	.090	.537**		
Anxiety	-.170	.153	.114	.016	.341**	.582**	
Gender	-.042	.060	.080	.140	-.011	-.081	.148

*correlation is significant at the $p < .05$,

** correlation is significant at the $p < .01$

Strong positive correlations were found between NINDS-VCI and BICAMS, BICAMS and MMSE, MoCA and MMSE, fatigue and HADS depression and HADS depression and anxiety scores ($p < .01$). Weaker but still significant correlations were found between fatigue and NINDS-VCI and HADS depression and NINDS-VCI.

Although fatigue was significantly negatively correlated with NINDS-VCI z-score, when HADS anxiety and HADS depression were held constant, the correlation was no longer significant ($p = .211$). There was a strong positive correlation between NINDS-VCI and BICAMS, but the correlation was not significant between MoCA and NINDS-VCI or MMSE and NINDS-VCI, which suggests that MoCA and MMSE do not capture the full normal range of scores that BICAMS and NINDS-VCI are capable of.

Correlation with depression, anxiety and fatigue is not expected due to the low numbers of participants falling in the clinical range in the group.

6.7 Development of Regression Based Norms

6.7.1 NINDS-VCI

A standard multiple regression was performed with total NINDS-VCI z-score as the dependent variable, and age², years of education and estimated IQ as independent variables. The data were screened for violation of assumptions prior to analyses.

An analysis of standard residuals was carried out, which showed that the data contained no outliers (Std. Residual Min = -2.532, Std. Residual Max = 1.942).

Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (Gender, Tolerance = 0.825, VIF = 1.212; Years of Education, Tolerance = .407, VIF = 2.459; Estimated IQ, Tolerance = .361, VIF =

2.767; Age², Tolerance= .938, VIF =1.066). The data met the assumption of independent errors (Durbin-Watson value = .515).

The histogram of standardised residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were not completely on the line, but close. The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity.

The multiple regression was performed with total NINDS-VCI z-score as the dependent variable, and gender, age², years of education and estimated IQ as independent variables. These variables accounted for a significant amount of the variance in total NINDS-VCI z-score ($R^2 = .18$; $F(4,62) = 4.59$, $p < .01$).

The partial regression coefficients showed that years of education had a significant unique contribution to NINDS-VCI z-score ($B = -.62$, $\beta = .442$, $t(62) = 2.53$, $p < .05$). However, gender, estimated IQ and age² were not independently associated with NINDS-VCI z-score ($t(62) = 0.31$, $p = .755$), ($t(62) = 0.16$, $p = .87$), ($t(62) = 1.48$, $p = .15$). Therefore, the model showed a significant relationship to the DV, and this was carried by years of education.

As years of education increases by 1SD (2.73), NINDS-VCI z-score will increase by .442. The SD for z-score is 0.38 so this constitutes a change of 0.17 (.442*.38). Therefore, for every 2.7 increase in years of education, an additional 0.17 in NINDS-VCI z-score is found.

6.7.2 BICAMS

A standard multiple regression was performed with total BICAMS z-score as the dependent variable, and age², years of education and estimated IQ as independent variables. The data were screened for violation of assumptions prior to analyses.

An analysis of standard residuals was carried out, which showed that the data contained no outliers (Std. Residual Min = -2.357, Std. Residual Max = 2.105). Tests to see if the data met the assumption of collinearity indicated that multicollinearity was not a concern (Years of Education, Tolerance = .428, VIF = 2.338; Estimated IQ, Tolerance = .427, VIF = 2.343; Age², Tolerance = .938, VIF = 1.066). The data met the assumption of independent errors (Durbin-Watson value = 2.014). The histogram of standardised residuals indicated that the data contained approximately normally distributed errors, as did the normal P-P plot of standardised residuals, which showed points that were not completely on the line, but close. The scatterplot of standardised predicted values showed that the data met the assumptions of homogeneity of variance and linearity.

The multiple regression was performed with total BICAMS z-score as the dependent variable, and age², years of education and estimated IQ as independent variables. These variables accounted for a significant amount of the variance in total BICAMS z-score ($R^2 = .27$; $F(3,63) = 6.138$, $p < .01$).

The partial regression coefficients showed that age² had a significant unique contribution to BICAMS z-score ($B = -.000$, $\beta = -.446$, $t(63) = -4.076$, $p < .001$). However, estimated IQ and years of education were not independently associated with BICAMS z-score ($t(63) = .961$, $p = .340$), ($t(63) = -.066$, $p = .95$). Therefore, the model showed a significant relationship to the DV, and this was carried by age².

As age² increases by 1SD (1,368), BICAMS z-score decreases by .466. The SD for BICAMS z-score is 0.689, so this constitutes a change of 0.321. Therefore, for every 1367.56 increase on age², a 0.321 decrease will be seen in BICAMS z-score.

6.8 Sensitivity and Specificity of BICAMS, MoCA and MMSE

To establish how accurate BICAMS is at detecting participants that fall below the expected level on the NINDS-VCI, accuracy, sensitivity and specificity were calculated. This was done by comparing the number of participants that NINDS-VCI highlighted as falling below the expected level and calculating how many of these were detected by BICAMS.

Using the established international criteria for BICAMS (Orchard, 2013), the measure was 67% accurate with a sensitivity of 66% and a specificity of 69%, and a positive predictive value of 70% and negative predictive value of 65%. Figure 1 shows the relationship between sensitivity and specificity in a ROC curve.

A McNemar test was carried out to see if BICAMS identified a different proportion of participants to the NINDS-VCI; the results were non-significant $p=$. 832.

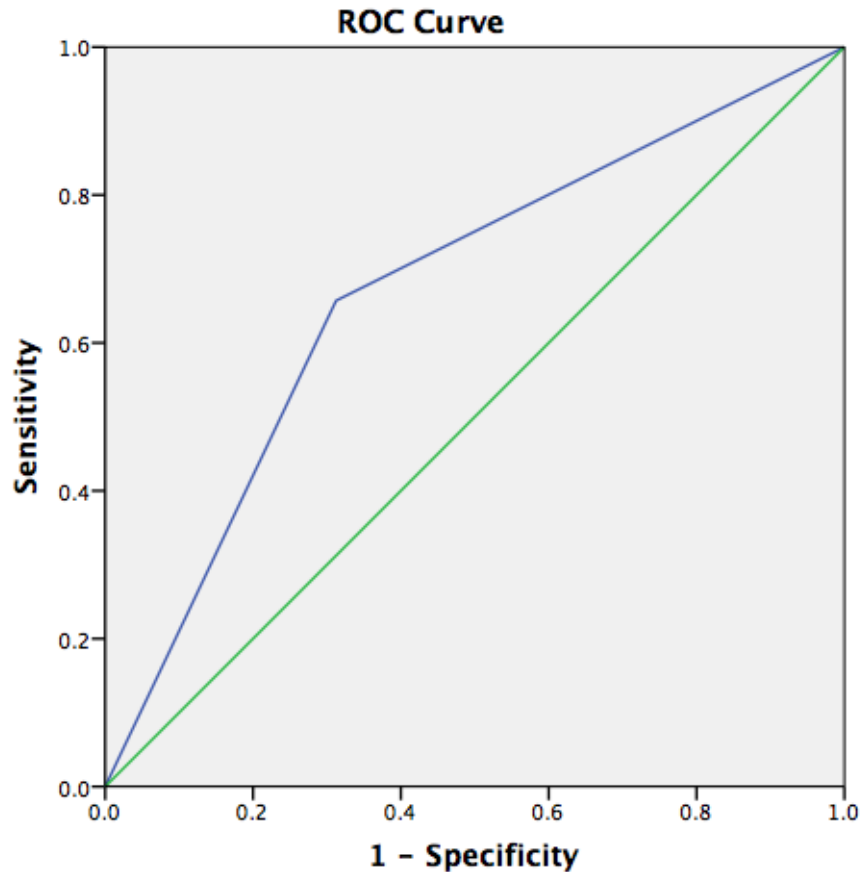


Figure 1. ROC Curve Sensitivity and Specificity of BICAMS compared with NINDS-VCI battery

Further exploration of the sensitivity and specificity of the BICAMS was carried out at the 2SD cut-off for the BICAMS. This yielded a sensitivity of 35% and specificity of 89%. Using a 1 SD cut-off this yielded a sensitivity of 100% and a specificity of 35%. Optimal sensitivities and specificities using the MoCA and MMSE were investigated. MoCA accuracy =59%, optimal cut-off of >29, sensitivity =94%, specificity of 16%, >28, sensitivity =71%, specificity of 44% >27 sensitivity 37% and specificity = 69%. MMSE accuracy =68%, optimal cut-off of >29 sensitivity of 71%, specificity of 68%. As the MMSE is only scored out of 30 and the measure is most sensitive at detecting impairment at 30, the test has reached its ceiling, meaning even

those that score 100% on the test would be identified as in the 'impaired' range using this cut-off. Therefore despite the highest levels of sensitivity and specificity we know that this cut off is not correctly identifying participants that fall in the impaired range. The BICAMS 1.5SD in one or more tests provides the best balance between sensitivity and specificity out of the three measures across the various cut-off points.

Table 17. Sensitivity and Specificity for BICAMS, MoCA and MMSE.

		Sensitivity	Specificity
<u>Test & cut off</u>	BICAMS 1SD cut off	100%	35%
	BICAMS 1.5SD cut off	66%	69%
	BICAMS 2SD cut-off	35%	89%
	MoCA >27	37%	69%
	MoCA >28	71%	44%
	MoCA >29	94%	16%
	MMSE>29	71%	68%

6.9 Summary of Results

6.9.1 Hypothesis 1

Published norms for the NINDS-VCI battery will provide significantly different cut-offs compared with the cut-offs established in a current UK sample. Hypothesis 1 was explored using McNemar chi-squared. Using published norms, a total of 45 participants were identified as falling below the expected level in one or more tests. Using the group mean, 35 participants were identified as falling below the expected level in one or more tests. A McNemar test was carried out to see if published norms identified a different proportion of participants to the group mean; the test was approaching significance $p=.052$.

6.9.2 Hypothesis 2

BICAMS will be more sensitive than the MoCA and MMSE at detecting participants that fall below the expected level on the NINDS-VCI battery. Optimal sensitivities

and specificities using the MoCA and MMSE were investigated. MoCA accuracy =59%, optimal cut-off of >29, sensitivity =94%, specificity of 16%, >28, sensitivity =71%, specificity of 44% >27 sensitivity 37% and specificity = 69%. MMSE accuracy =68%, optimal cut-off of >29 sensitivity of 71% specificity of 68%. This showed the ceiling effects of both tests. BICAMS was 67% accurate with a sensitivity of 66% and a specificity of 69, and a positive predictive value of 70% and negative predictive value of 65%.

6.9.3 Hypothesis 3

BICAMS will be able to identify correctly participants who fall below the expected level in the NINDS-VCI battery. McNemar test of proportions was used to assess how similar the proportion of participants identified by the BICAMS was to those identified by NINDS-VCI. There was a non-significant difference in the proportions identified between the tests ($p=. 832$).

7 Discussion

It is known that people can suffer from cognitive impairments following TIA. Yet currently, ways of measuring impairment are inaccurate. While there is a gold standard battery to test cognition, there are no up-to date cohesive UK norms for the battery. Furthermore, current screening tools have been shown to have ceiling effects and to be insensitive in detecting mild cognitive impairments seen in a TIA profile. The current study aimed to explore whether a brief battery, which is used in MS and focuses on global deficits rather than focal deficits, could be an improvement on available tools. The sensitivity and specificity of BICAMS was compared with a gold standard measure of cognitive impairment in TIA (NINDS-VCI; Hachinski et al., 2006). Furthermore, the study aimed to develop cohesive UK norms for the full NINDS-VCI battery to see if these would provide different outcomes to the current norm sources available. The study addressed the following questions: Will norms from current published sources provide different outcomes compared with a current healthy UK sample? Will BICAMS predict participants that fall below the expected level on a comparable level with the NINDS-VCI?

7.1 Review of the Findings

Hypothesis 1

Published norms for the NINDS-VCI battery will provide significantly different cut-offs compared with the cut-off established from a current healthy UK sample.

This hypothesis is partially supported. Numbers of participants classified as impaired using two different methods of scoring were compared. Norms recommended by

Hachinski et al. (2006), which were from a variety of sources, across different countries and different decades, were compared with a current UK healthy control sample. Rates of impairment classification were compared using chi-squared McNemar test of proportions. When comparing the number of participants identified as falling below the expected level of performance, the published norms identified more participants on the NINDS battery than the group mean method. Forty-five participants were identified as falling below the expected level on published norms, while 35 were identified as falling below the expected level on the group mean norming method.

In 5 of the 10 sub-tests (COWAT, Semantic fluency, TMT A, HVLT-R immediate recall and HVLT-R delayed recall) more participants were identified as falling below the expected level on published norms. This was particularly evident in the HVLT-R tests, where 25 participants were identified by the published norms as falling below the expected levels on both immediate and delayed recall. The group mean identified more participants in four of the measures (WAIS Digit Symbol Coding, TMT-B, RCFT and RCFT delayed recall), although in much smaller numbers. A McNemar test was carried out to see if published norms identified a different proportion of participants to the group mean; the test was approaching significance $p = .052$.

Hypothesis 2

BICAMS will be more sensitive than the MoCA and MMSE at detecting participants who fall below the expected level on the NINDS-VCI battery. This hypothesis was supported. BICAMS was more accurate, sensitive and specific than the MoCA. The MoCA demonstrated good sensitivity, but this was offset by the low specificity.

Although numbers were slightly higher for the MMSE, this was at a cut-off of 30 on the 30-point scale, meaning that the MMSE had reached its ceiling. However, BICAMS did not meet the recommended level of sensitivity and specificity for screening tests (Lincoln et al., 2003), although it should be noted that other widely used tools such as the MoCA and MMSE have also missed this recommendation. It is expected that screening tools will perform less well in non-clinical populations, as the spread of scores is likely to be smaller across healthy participants, and there will be much smaller and subtler deviations from the mean than what would be expected in a clinical sample, in which cognitive impairment is known to be prevalent. Other studies using the MoCA to detect mild cognitive impairments in a healthy population have shown higher rates of sensitivity and specificity than what was found in this study. However, the sample has a higher than average IQ, which may be partly responsible for this finding, as participants would have to score significantly less on a test before falling in the impaired range compared with those of a low average IQ. A recent meta-analysis found an optimum cut-off of 24/25, with a sensitivity of 80% and a specificity of 82% (Ciesielska et al., 2016), although participants were all over the age of 60. However, in studies using TIA populations, the MoCA's high sensitivity has been associated with low specificity (Godefroy et al., 2011). This was in line with findings in this study. A recent meta-analysis of the MMSE in detecting mild cognitive impairments found similar results with an optimum cut-off point of 27/28, yielding a sensitivity of 66% and specificity of 73%. In a study of the MMSE in a TIA population, Pendlebury et al. (2012) also found a ceiling effect for the MMSE and concluded that it is not a suitable tool for screening for single domain cognitive impairment. This is the general consensus in the literature (Burton & Tyson, 2015a).

In studies where BICAMS has been compared with other neuropsychological batteries, similar rates of accuracy sensitivity and specificity have been found. For example, when being compared with the Minimal Assessment of Cognitive Functioning in Multiple Sclerosis (MACFIMS), sensitivity and specificity for experimental and control participants was found to be 85% and 83% respectively (Orchard et al., 2013), whilst in an MS only population sensitivity and specificity were 94% and 86% (Dusankova et al., 2012).

This is the first study to compare directly the MMSE, MoCA and BICAMS in a healthy UK population. BICAMS shows promise as a tool that could be used to detect mild cognitive impairments in samples where deviations from expected performance levels are likely to be subtle. BICAMS performed better than the MMSE and the MoCA in this particular sample. It is likely that using a clinical sample will increase the sensitivity and specificity of all of the measures, and that BICAMS may potentially perform at the desired level of above 80% sensitivity and specificity in a clinical population. As noted by the Cochrane reviews and other systematic reviews of the MMSE and the MoCA (Creavin et al., 2016; Burton & Tyson et al., 2015a) different cut-offs are optimal and different rates of sensitivity and specificity are found depending on whether you are testing in a high or low prevalence setting. As the BICAMS has shown the most promising levels of sensitivity and specificity in a low prevalence setting we would cautiously predict that this would improve in a high prevalence setting such as a TIA clinic.

Hypothesis 3

BICAMS will be able to identify correctly participants who fall below the expected level on the NINDS-VCI. This hypothesis was supported. BICAMS was able to

identify correctly the majority of participants who fell below the expected level on the NINDS-VCII battery. These findings suggest that BICAMS could be a valid and sensitive screening tool for identifying cognitive impairment in a TIA population on a comparable level with the 60-minute NINDS-VCII battery. As BICAMS takes less than 15 minutes to administer, and could be delivered at routine healthcare appointments by a range of health professionals, it could increase our understanding of the rate of cognitive impairment after a TIA. Additionally, BICAMS allows us to assess and monitor those most at risk of poor prognostic outcomes following TIA.

The results support findings in MS that BICAMS identifies cognitive impairment on a comparable level with other large batteries of tests (Dusankova et al., 2012; Parmenter et al., 2010).

7.2 Interpretation

7.2.1 Current available published norm sources provide different rates of impairment compared with a current UK sample

This finding is supported by current knowledge about normative data sets. The Flynn effect postulates that there will be changes in performance on neuropsychological tests over time and over generations. Thus, using normative data sets from over 10 years ago will provide differing results compared with data collected from a current sample. It is widely recognised that the normative data used should match as closely as possible the current population of participants being studied. Key demographic factors have been identified that explain variation in performance such as age, education, IQ and socioeconomic status. The effects of using norms that do not match these key characteristics have not been thoroughly explored and documented for batteries where a diagnosis of cognitive impairment is being made, such as NINDS-

VCI. This study goes some way to explaining the importance of accurate and cohesive norms and how they might influence findings, on an individual clinical and wider research level.

A number of studies have compared older norms with revised norms, and scores have generally been found to increase over time; for example, the average number of words produced in the COWAT has increased by four from 1964 to 1996 (Ruff et al., 1996). It is widely accepted that norms should not be considered stable over time as changing educational and cultural practices, including increased access to a wider range of media sources, influences tests. However, results in this study did not consistently show an increase in performance compared with averages from older tests, suggesting that the Flynn effect is unlikely to be responsible for the differing results. It is noteworthy that the biggest difference between the frequencies was observed in the HVLIT-R with 25 participants being identified as falling below the expected level on immediate and delayed recall tests. Interestingly, verbal memory scores have been shown to be stable over time and not so susceptible to the Flynn effect (Baxendale, 2010).

The data from the present study should be viewed as an initial step in the development of adequate cohesive normative data for the NINDS-VCI battery in a UK sample. However, the utility of this data from a healthy UK population also needs to be considered in light of the limitations outlined below before using them in current clinical and research practice.

7.2.2 BICAMS is more sensitive than the MMSE and the MoCA at detecting participants who fall below the expected level of scores on the NINDS-VCI in a healthy UK population

As of yet, no studies have compared the BICAMS battery with the MoCA or MMSE, as BICAMS is a measure that has been validated only for use in MS. However, rates of sensitivity and specificity for the MoCA and MMSE are similar to what have been found in other studies of TIA. In particular, Godefroy et al. (2011) found that the sensitivity of the MOCA is associated with low specificity and inability to provide adequately across both criteria. In terms of the MMSE, our results confirmed the findings of Pendlebury et al. (2012), that the MMSE has a ceiling effect and was not sensitive at picking up single domain impairments. These previous studies provide support for the current findings, which suggest that the MoCA and MMSE have significant flaws in detecting mild cognitive impairment. BICAMS may be a potential tool to address this. The Pearson's correlation showed that BICAMS was highly correlated with NINDS-VCI battery; this is likely to be because both batteries can assess scores over a wide range of performance levels, rather than the MoCA and the MMSE, which reach their ceiling in detecting subtle deviations from expected levels.

BICAMS measures scores over a wider spread of ability, meaning that it is able to detect subtle changes in performance levels, across key tests that require distributed processes. This appears to give a more sensitive reflection of impairment rather than measuring a range of focal deficits at a low level. A recent study looking at stroke participants supports this, and shows that participants can score full marks within a MoCA specific domain and still be impaired on corresponding neuropsychological assessments that assess the full domain (Chan, Altendorff, Healy, Werring, & Cipolotti, 2017). This is supported by other studies looking at severe

cognitive impairments, where poor correlations with the MoCA sub-domains and their corresponding standard cognitive test have been found (Coleman, Coleman, MacKinley, Pasternak, & Finger, 2017). This suggests that testing participants with a low level, simplified version of a test is a compromise rather than using a test that can assess their full ability. An alternative approach that BICAMS utilises is detecting impairment across global skills rather than testing a range of domains at a low level, which is shown to give an inaccurate account of performance and cognition.

This interpretation is evidently limited to a healthy UK population, and we cannot necessarily infer how BICAMS would perform in detecting cognitive impairments in TIA participants. However, it shows potential as an area that warrants further research and investigation. Screening tools such as the MoCA and MMSE are often used to measure the usefulness of treatment interventions in reducing impairments and the risk of further cardiovascular disease (Pettigrew et al., 2000). Studies have not been able to demonstrate any reversible or stabilising effects on cognition, using medication. This may be due to the insensitivity of screening tools utilised. If it is not viable to use a full battery such as the 60-minute NINDS-VCI, ways to improve on the sensitivity and specificity of screening tools are imperative to ensure that we are accurately identifying and discarding the right treatments for VCI. A more sensitive measure may provide different outcomes.

7.2.3 Years of education explains a significant amount of the variance in test scores in the NINDS-VCI battery and scores should be adjusted accordingly

A multiple regression analysis showed that years of education explained a significant amount of the variance in NINDS-VCI scores. This suggests that scores should be adjusted to account for different educational backgrounds to ensure test scores

accurately account for this. The cognitive reserve hypothesis (Stern, 2012) supports the finding that years of education significantly predicts NINDS-VCI performance; participants of higher educational attainment are likely to perform better on cognitive tests. Therefore, should they experience a decline in their cognition they would have further to descend before being identified as falling below the mean. For this reason, other researchers have noted the need to improve the sensitivity and specificity of tests for individuals who are above average intelligence (Drebing, Van Gorp, Stuck, Mitrushina, & Beck, 1994; Rentz et al., 2004). In accounting for differences in educational attainment, those with high educational achievements will still be detected even when their scores fall within the broader average range. This will allow participants to be identified at an early stage of impairment, rather than waiting for their scores to decline even more significantly before being detected by the battery.

The next step would be to look at each of the individual tests within the NINDS-VCI and to run multiple regression analyses on each test. It is likely that some tests in the battery will be influenced more heavily by demographic factors than others, and by summing all measures some of this individual variation across tests will be lost. For example, in other studies, estimated IQ has been found to be a significant predictor of TMT-B score, but not TMT-A (Testa et al., 2009).

7.2.4 Age² explains a significant amount of the variance in test scores in BICAMS and scores should be adjusted accordingly

A multiple regression analysis showed that age² accounts for a significant amount of the variance in BICAMS scores. Thus, when using this test on clinical participants, their scores should be adjusted accordingly to account for the effect of demographic information. Age is a factor that has long been known to affect performance on

neuropsychological tests and in particular speed timed tests (Ruff & Parker, 1993), of which BICAMS contains two (SDMT, and BVMT-R). Most normative data sets provide age-banded norms to account for this. The use of the regression-based model to determine this is of benefit because the participant's scores do not dramatically change from one age band to the next, but all scores are adjusted on a sliding scale dependent on age.

It is likely that age will affect tests in BICAMS to varying degrees; the next step would be to examine how each test is impacted by demographic variables, and to provide regression-based norms on an individual test.

7.3 Strengths and Limitations of the Study

7.3.1 Sampling

Information on gender, age², depression, anxiety, fatigue, years and education and estimated IQ were collated in the study. This is a relative strength as these factors were all analysed. In particular, rates of depression, anxiety and a fatigue are likely to be higher in a TIA population (Broomfield et al., 2014; Moran et al., 2013; Yu et al., 2015). Being able to compare the prevalence of anxiety, depression and fatigue in healthy controls with TIA participants will not only help with further stratification of the data, but also aid the understanding of how these clinical factors may change in people who have experienced a TIA, as well as the impact on cognitive testing in a clinical group.

7.3.1.1 Age

The average age of participants was 43.86 years. The mean average age across other studies of TIA have ranged from 61 to 73 years (Giles & Rothwell, 2007). A younger sample was chosen in this study to limit the influence of concomitant cognitive disorders, such as the impact of older age on cognition and other possible disease, which might impact cognition in later life. Furthermore, people who experience a cognitive impairment after TIA earlier in life are likely to experience a greater impact on their working life, productivity and family life. They will also have a longer, more chronic VCI pathway. Therefore, having data available for a younger population is useful in being able to assess the cognitive impairment in this group. This is in keeping with other research studies in the area that have looked specifically at cognitive impairment after TIA in people under the age of 65 (van Rooij et al., 2014) and other studies that have shown that TIA in younger people has the largest effects on quality of life (Franzén-Dahlin & Laska, 2012). Future studies should consider how to widen the age range within the sample, whilst limiting the influence of age-related concomitant cognitive disorders.

7.3.1.2 Gender

Although there is a higher ratio of women to men included in both samples, there were no significant correlations between gender and neuropsychological tests. However, depending on cultural practices, particularly in older participants, there may be significant differences in years of education and gender. As years of education is a significant predictor of scores on the NINDS-VCI further studies should ensure years of education is equally split between male and female participants.

7.3.1.3 Estimated IQ

Similarly, measures of pre-morbid IQ and years of education allowed for improved understanding of the sample. However, this highlighted that the sample was above average in estimated IQ. The spread of scores within the IQ range was also quite limited as all participants were in the average range or above, which may in part explain why estimated IQ was not a significant predictor of BICAMS or NINDS-VCI z-scores. However years of education was more varied within the sample and was shown to be a significant predictor of NINDS-VCI scores. However, researchers have noted the importance of designing sensitive and specific measures for higher cognitively functioning adults, particularly those aged below 69 as their risk of neurological disease is gradually increasing, while work and family responsibilities remain high for many (Drebing et al., 1994).

The TOP-F was used as an estimated measure of pre-morbid IQ. This is usually used with participants who have experienced some level of cognitive decline. Although the TOP-F is highly correlated with WAIS performance, using a full measure of IQ would have been more appropriate in this study. Replicating the study with a full measure of IQ and with participants who span the full range of IQ would be a helpful addition to developing cohesive and current norms for comparison on NINDS-VCI and BICAMS.

7.3.1.4 Sampling methods

It may be that people are more likely to take part in cognition research if they believe that they have cognitive difficulties. Many people who took part in the study also revealed some history of neurological disturbance in their own family. It may be possible that some participants had undetected neurological conditions. Similarly,

other cardiovascular risk factors such as hypertension and diabetes are known to affect cognition (Gorelick et al., 2011). These were not controlled for in the current study. The use of neuroimaging techniques and risk stratification information for participants would be useful in overcoming difficulties, but this was beyond the scope of the current study.

7.3.1.5 Samples size

Sixty-seven participants were recruited to the main study. This is a relatively small sample, although within the recommended sample for the multiple regression analyses (Testa et al., 2009), but well below the recommended level using traditional norming methods, where it is recommended that 50–75 participants per variable are required. Bridges and Holler (2007) suggested that that small sample sizes may lead to overpathologising results. It is interesting to note that within the regression analyses, there were a number of significant correlations (age and IQ), but they did not explain an individual significant proportion of the variance. One possible explanation for this finding is that the study was underpowered. It may be that with a larger sample these correlations could have contributed to a significant amount of the variance individually.

7.3.2 Study Design

7.3.2.1 Test selection

A general strength of the study is that the neuropsychological tests were given in a counterbalanced order to prevent order effects. However, during the administration it was noted that those who received the CVLT–II first, and then received the HVLT-R later, experienced some interference when they completed the delayed recall trial of

the HVLT-R. Nevertheless, when looking at the findings there was no significant difference on the HVLT-R and CVLT-II between odd and even numbered participants. Similarly, it should be noted that a trail making test was repeated in the MoCA and as part of the TMT individual sub-test. This meant that the task was not novel for some participants the first time they approached the task. However, there were no significant differences between odd and even numbered participants scores on the TMT task, showing that previous exposure of the MoCA trail or the TMT task did not interfere with the performance on either test.

7.3.2.2 Assessment conditions

Participants were tested in their homes or at their place of work across both groups. This is different to the usual testing environment, which is usually within a clinical setting such as a hospital or clinic room. Although attempts were made to minimise distractions, there were notably some distractors, which may have influenced performance. TIA participants are likely to be tested in a clinical environment with fewer distractions, which may result in improved performance compared with the control group. However, they are likely to have also experienced a stressful medical event that impacted their ability to concentrate and perform on neuropsychological tests. Furthermore, the time of day participants were tested varied across the group, depending on their availability to complete testing. Level of fatigue at different times of day may influence scores within the group, which may not have been detected in the FSS.

7.3.2.3 Test Administration

Instructions for delivering the MoCA are provided by Nasreddine et al. (2005). A discrepancy in the instructions delivered to participants and the standardised

instructions were discovered post-testing. Both sets of instructions are included in the appendices (Appendix 17 and 18) for comparison. The fact that the instructions differ from the standardised instruction may have made it more difficult to achieve a higher score on the MoCA. However, using available conversion tables which compare how MoCA scores should compare with MMSE scores, we can see that the scores on the MoCA are within the 95% confidence intervals that we would expect based on the MMSE scores (Bergeron et al., 2017). This means that the MoCA scores were not significantly influenced by the deviation from the standardised instructions and highlights the robustness of the MoCA for clinical use.

The pilot group and the control group found different rates of falling below the expected level, with 31% of the pilot group falling within the mild cognitive impairment range on the MoCA. This is compared with 3% of the NINDS-VCI group. There was also a disparity across the MMSE and BICAMS measures in both groups, with more participants in the pilot group scoring below the expected level than in the NINDS-VCI battery. Other studies have also found similarly high rates of scores below the cut-offs with participants from a healthy population when using the MoCA (Binder, Iverson, & Brooks, 2009; Palmer, Boone, Lesser, & Wohl, 1998; Rossetti, Lacritz, Cullum, & Weiner, 2011). One possible explanation for this discrepancy is differences in the test administrators across the pilot group and main study. A trainee clinical psychologist, who was trained in delivering neuropsychological tests, conducted the NINDS-VCI battery, whereas postgraduate students, from another science discipline and with little training, administered the pilot group tests. This would have implications for the use of such screening tools being implemented and used by non-clinical health care professionals. It highlights the importance of experience and training in delivery. As these tools are being developed for delivery by

non-specialist healthcare professionals, it will be important that training is carried out and test administrators are examined on their standardisation and adherence to formal testing procedures across clinical settings and research settings. However, cognitive screening tools have been successfully delivered by a range of healthcare professionals, with sufficient training and supervision (Chodosh et al., 2008). This is an area of research that may warrant further investigation before the implication of screening tools to be used by non-clinical health care professionals with TIA patients.

A further explanation for the discrepancy in findings between NINDS-VCI and the pilot group, may be linked to the latter's demographic factors; age was shown to have a significant negative correlation with scores in the pilot group. However, age data were not available for 33 participants, which may have meant that part of the sample was drawn from a particularly older group of participants, who were more likely to have experienced age-related cognitive decline. Furthermore, years of education in the NINDS-VCI group was shown to explain a significant amount of the variance in the regression model for the NINDS-VCI battery. As such data were not available for the pilot group, we cannot be sure if they are from the same population as the NINDS-VCI group, because they have above average IQ. Neither group was given the educational point for less than 12 years of education. In this way, the effect of years of education could be explored in the analyses. However, there were very few participants within the NINDS-VCI group who would have gained an extra point. As we did not have information on years of education for the pilot group, it may be that more participants warranted an extra point added for lower years of education. This could then have brought scores more in line with a normal healthy UK population.

7.3.3 Statistical Methods

7.3.3.1 *Level of impairment classification*

In this study, participants were classified as falling below the expected level on the NINDS-VCI battery when they scored 1.5SD below the mean on one or more tests. Thirty-five participants fell below the expected level in one or more tests. The criteria included a higher proportion of participants than the more conservative 2SD cut-off in one or more tests, but a lower proportion of participants than the criteria to fall below the expected level in more than one test within a domain, or multiple domain impairment. However, even more participants would have been identified if the criteria of falling 1SD below the expected level in one or more tests was used. Other authors have used other cut-off criteria; for example, Chen et al. (2015) averaged scores across the domain and used a cut-off of 1.5SD below the mean to establish impairment. Using this method, no participants were identified as falling below the expected level (1.5SD on average from the domain) for executive function or memory and when averaging all of the sub-domain scores, no participants scored less than 1.5SD below the mean as an average across all tests. It was harder for participants to ‘fail’ the executive functioning domain as this was averaged across five tests, whereas memory consisted of three tests and language and visuospatial skills one test each. This clearly shows the criteria used impacts on the rate of impairment found and in which domains, and, in turn, influences the sensitivity and specificity of any screening tool being tested. This is a limitation that has been discussed in other studies (Liepelt-Scarfone et al., 2011; Pendlebury, Mariz, et al., 2013), where a fourfold increase can be observed in rates of impairment depending on the definition that is used. It would be a misrepresentation to say that 49% of the sample were impaired, as participants

were from the general population and not reporting any cognitive deficits. This highlights the importance of a thorough clinical interview and accounting for self and family reports of cognition alongside cognitive screening and or testing before making diagnosis of cognitive impairment. Different cut-offs and different ways of calculating impairment should be explored both with BICAMS and the NINDS-VCI, such as averaging scores, which may be more specific and lead to less false positive than the current cut-off criteria, other statistical methods such as the Monte Carlo simulation methods had been explored too (Binder et al., 2009; Palmer et al., 1998). As the number of tests administered increases it is more likely that participants will score below the expected level in one or more tests. The development of base rates which calculate the likelihood of a participant having such discrepant scores could help to ascertain if the scatter of scores is within the normal range.

Future studies with a clinical sample of TIA participants should further explore which criteria is most sensitive to detecting cognitive impairment, whilst limiting the rate of false positives. As VCI is known to be present in the executive functioning domain it would be of interest to see how many TIA participants fall below the expected level when all five tests of executive functioning, within the NINDS-VCI are averaged. The cut-offs chosen will have clear implications for the accuracy, sensitivity and specificity of a screening measure, such as BICAMS. In clinical practice, it will have implications for those who are identified and receive further treatment and rehabilitation.

7.3.3.2 *BICAMS norms*

Norms for the BICAMS were based on a healthy UK sample of 68 participants with a mean age of 44 (SD 10 years), range 27–60, of which 37 were female and 31 were

male, with an average of 16 years of education (SD 2.8), and average estimated IQ of 111 (SD 8.8). The normative data provided higher means on every measure used within BICAMS. Whilst this did quite closely match the group in the current study, when those outside the age range of the norms data were removed, the means of scores on the BICAMS moved closer towards the means of the normative data sample used (See Table 12). This corroborates the findings of age being an important independent predictor of BICAMS score and demonstrates the importance of ensuring the normative data are reflective of the individual being assessed, both in research and clinical practice.

7.4 Clinical Implications of the Study

Deficits in cognition have implications for people's everyday functioning after experiencing a TIA or mild stroke. Activities of daily living, quality of life and relationships are all affected by cognitive decline. This will particularly affect young adults who have a longer and more chronic duration of VCI. The cognitive difficulties associated with TIA and mild stroke are likely to have impact on employment, finances and wellbeing.

It is important that people who have had a TIA and mild stroke have access to appropriate cognitive testing to help them understand the difficulties and access appropriate services and support. BICAMS shows promise as a short assessment battery to assess cognition. It could be a useful instrument in understanding more about the prevalence of cognitive impairment after a TIA, and provide further evidence of the need for cognitive assessment and rehabilitation to be part of the NICE guidelines for this client group. Furthermore, the battery could prove useful in identifying those most at risk of having further cerebrovascular events, and help

clinicians target treatment in time-limited appointments within TIA clinics, which are conducted by various non-psychology healthcare professionals. It could be a useful tool for baseline measures and follow-up to track the course of disease progression.

BICAMS could be used to identify individuals who would benefit from further in-depth cognitive testing. Having reliable, consistent and specific information on the rates of cognitive impairment and how this impacts long-term health outcomes will raise awareness of the importance of cognitive testing in this population. It is hoped that this initiates a change in the NICE guidelines to recommend cognitive testing after a TIA as standard practice.

7.5 Directions for Further Research

This is a small-scale investigation into the utility of BICAMS as a cognitive measure, which may be useful in detecting mild impairments in people who have experienced a TIA, and into the development of UK norms for the 60-minute NINDS-VCI battery.

A clear goal would be to use a larger sample of healthy controls to develop normative data for the NINDS-VCI performance in a UK population across a wider age, estimated IQ and education level. Providing up to date and cohesive norms would help build a firm basis for the development of further research into VCI and TIA, knowing that clinical data are comparable with an appropriate normative and representative sample. National databases already exist for the collation of data and findings; it is important that what we are contributing is an accurate measure of cognitive impairment in TIA populations in the UK. The development of cohesive and relevant norms alongside clear guidance for classifying impairment will further aid longitudinal studies to understand the long-term impact of cognitive impairment and the true predictive value of cognitive testing in the acute stage after a TIA.

Longitudinal studies that use the same scales and criteria for impairment are important to compare precisely and effectively and draw firm conclusions from the findings.

Additionally, future research should test BICAMS with TIA participants to see if it is sensitive at detecting those who fall below the mean on the NINDS-VCI, as it has been in healthy control participants. This may lead to further exploration of whether tests could be substituted or supplemented within BICAMS to be more sensitive to VCI.

Large-scale collaborative studies that employ more sophisticated sampling techniques should be used. The use of brain imaging data to support cognitive testing findings would also be invaluable.

7.6 Conclusion

No studies have provided a normative UK sample for the NINDS-VCI battery. This study investigated whether a UK sample is likely to differ in performance on the NINDS-VCI battery compared with the current variety of norms available. It was found that UK participants did differ in their performance, and thus it was highlighted the importance of using relevant and cohesive norms when testing cognitive impairment in clinical samples.

Furthermore, this study investigated the sensitivity and specificity of BICAMS to detect participants whose scores fall below the expected level on the NINDS-VCI battery. It showed promise as a suitable brief test to detect cognitive impairment in TIA.

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Appendices

Appendix 1- Ethics Details



Ethics Review Details

You have chosen to self certify your project.	
Name:	Langdon, D
Email:	D.Langdon@rhul.ac.uk
Title of research project or grant:	Brief International Cognitive Assessment for TIA (BICAT)
Project type:	Royal Holloway staff research project/grant
Department:	Psychology
Funding Body Category:	No external funder
Funding Body:	
Start date:	01/04/2016
End date:	31/03/2019

Research question summary:

Does the Brief International Cognitive Assessment for MS (BICAMS) constitute a better cognitive assessment for TIA than the currently used assessments (MOCA and MMSE)?

The most widely used assessments of cognition in TIA clinics are the Montreal Cognitive Assessment (MOCA) and Mini Mental State Examination (MMSE). The MOCA is designed to detect mild cognitive impairment, including Alzheimer's disease. The MMSE is a screening test for dementia. Both are constructed to test a range of focal deficits, at a low level ("a set of low hurdles"). They have a marked false negative rate. BICAMS calibrates information processing speed and memory function over the whole range of mental abilities and is therefore a more precise measure of distributed cognitive processes, hypothesised to be a more accurate assessment of the distributed cerebral vascular pathology sustained by TIA patients and hence their cognitive impairment. In order to validate BICAMS for TIA, we will also be including the "gold standard" NINDS battery. In multiple sclerosis, the 15 minute BICAMS has been shown to have equivalent sensitivity to cognitive impairment to the "gold standard" MACFIMS.

Research method summary:

This application is asking for permission to collect normal control data on the battery. Once IRAS ethics permission has come through, I will re-apply for permission to assess NHS patients.

A battery of cognitive tests, taking less than 30 minutes in total, will be administered to healthy control participants. This will comprise the MOCA, the MMSE and BICAMS. There are brief cognitive assessments which have been used in research with thousands of patients across the world.

A proportion of participants will also complete the longer, "gold standard" NINDS battery, which takes another 30 minutes.

NINDS battery -(Hachinski et al., 2006). Testing frontal/executive, attentional, language, visuospatial, and memory domains. It takes approximately 50 to 60 minutes to administer. This comprises:

- a. Trail Test (Parts A and B) (Reitan, 1955; Ivnik, Malec, Smith, Tangalos, & Petersen, 1996)
- b. Boston Naming Test (30-item version)(Franzen, Haut, Rankin, & Keefover, 1995)
- c. Rey-Osterrieth complex Figure copy (Fastenau, Denburg, & Hufford, 1999).
- d. Hopkins Verbal Learning Test- Revised (Brandt, 1991; Benedict, Schretlen, Groninger, & Brandt, 1998)
- e. Letter (Controlled Oral Word Association Test) (Benton, Hamsher, & Sivan, 1994)
- f. Category (animals) fluency (Issacs & Kennie, 1973)

All participants will also complete the

Hospital Anxiety and Depression Scale (HADS), a measure has been validated in a stroke cohort (Spurgeon et al., 2015; Burton and Tyson, 2015);

and the Fatigue Severity Scale (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989), the psychometric properties of this scale have been validated using a stroke cohort (Lerdal & Kottorp, 2011).

Risks to participants

Does your research involve any of the below?

Children (under the age of 16),

No

Participants with cognitive or physical impairment that may render them unable to give informed consent,

No

Participants who may be vulnerable for personal, emotional, psychological or other reasons,

No

Participants who may become vulnerable as a result of the conduct of the study (e.g. because it raises sensitive issues) or as a result of what is revealed in the study (e.g. criminal behaviour, or behaviour which is culturally or socially questionable),

No

Participants in unequal power relations (e.g. groups that you teach or work with, in which participants may feel coerced or unable to withdraw),

No

Participants who are likely to suffer negative consequences if identified (e.g. professional censure, exposure to stigma or abuse, damage to professional or social standing),

No

Details,

Design and Data

Does your study include any of the following?

Will it be necessary for participants to take part in the study without their knowledge and/or informed consent at the time?,

No

Is there a risk that participants may be or become identifiable?,

No

Is pain or discomfort likely to result from the study?,

No

Could the study induce psychological stress or anxiety, or cause harm or negative consequences beyond the risks encountered in normal life?,

No

Does this research require approval from the NHS?,

No

If so what is the NHS Approval number,

Are drugs, placebos or other substances to be administered to the study participants, or will the study involve invasive, intrusive or potentially harmful procedures of any kind?;

No

Will human tissue including blood, saliva, urine, faeces, sperm or eggs be collected or used in the project?;

No

Will the research involve the use of administrative or secure data that requires permission from the appropriate authorities before use?;

No

Will financial inducements (other than reasonable expenses and compensation for time) be offered to participants?;

No

Is there a risk that any of the material, data, or outcomes to be used in this study has been derived from ethically-unsound procedures?;

No

Details,

Risks to the Environment / Society

Will the conduct of the research pose risks to the environment, site, society, or artifacts?;

No

Will the research be undertaken on private or government property without permission?;

No

Will geological or sedimentological samples be removed without permission?;

No

Will cultural or archaeological artifacts be removed without permission?;

No

Details,

Risks to Researchers/Institution

Does your research present any of the following risks to researchers or to the institution?

Is there a possibility that the researcher could be placed in a vulnerable situation either emotionally or physically (e.g. by being alone with vulnerable, or potentially aggressive participants, by entering an unsafe environment, or by working in countries in which there is unrest)?;

No

Is the topic of the research sensitive or controversial such that the researcher could be ethically or legally compromised (e.g. as a result of disclosures made during the research)?;

No

Will the research involve the investigation or observation of illegal practices, or the participation in illegal practices?,

No

Could any aspects of the research mean that the University has failed in its duty to care for researchers, participants, or the environment / society?,

No

Is there any reputational risk concerning the source of your funding?,

No

Is there any other ethical issue that may arise during the conduct of this study that could bring the institution into disrepute?,

No

Details,

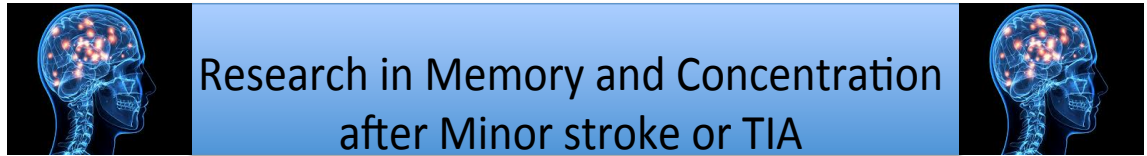
Declaration

By submitting this form, I declare that the questions above have been answered truthfully and to the best of my knowledge and belief, and that I take full responsibility for these responses. I undertake to observe ethical principles throughout the research project and to report any changes that affect the ethics of the project to the University Research Ethics Committee for review.

Certificate produced for user ID, uhjt092

Date:	21/03/2016 15:03
Signed by:	Langdon, D
Digital Signature:	Dawn Langdon
Certificate dated:	3/21/2016 3:45:38 PM
Files uploaded:	

Appendix 2- Information Leaflet



After a minor stroke people experience difficulties with memory and concentration. We need to collect information about healthy people's memory and concentration to work out what has been affected in TIA patients.

If you chose to take part you will be asked to complete various tests, which measure your attention, memory, language, visuo-spatial and problem solving skills. Some use spoken language whilst others pencil and paper. You may find some easy and others more challenging but most people find them enjoyable.

Participation will take about 1 hour and can usually be completed in one session with breaks if you need them.

Please contact me if you would like to take part or for any further information:

Danielle.lambert.2011@live.rhul.ac.uk

Appendix 3 –Information Sheet



Information about the Research

Study Title: Cognition in TIA

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve. **Someone will go through the information sheet with you, discuss the information and answer any questions you have.** Please feel free to talk to others about the study if you wish.

Part 1 tells you the background/purpose of the study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study.

Ask us if anything is not clear.

Important Contacts

Site where the research is taking place:

*Some participant's homes or
Royal Holloway, University of London*

- Dept. of Clinical Psychology, Bowyer Building, Royal Holloway University of London, Egham, Surrey, TW20 0EX, Telephone: 01784 443851
-

Questions about the research can be directed to:

The Chief Investigator: Professor Dawn Langdon

- Dept. of Clinical Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
- Tel: 01784 443 851
- Email: d.langdon@rhul.ac.uk

Complaints procedure:

If you have a concern about any aspect of this study, you should ask to speak to the Chief Investigator mentioned above who will do her best to answer your questions (01784 443 851).

If you remain unhappy and wish to complain formally, you can do this by contacting

Professor Dawn Langdon,

Department of Psychology, Royal Holloway University of London, Egham, Surrey, TW20 0EX
Email: d.langdon@rhul.ac.uk

Part 1

Background to the project

People who have experienced transient ischaemic attacks (TIA's) or minor strokes, may have subsequent difficulties with memory and concentration ("cognition"). We need to collect information about healthy people's memory and concentration to work out what has been affected in TIA patients.

Purpose of the research

The current study aims to validate a measure (BICAMS) which could be used in less specialist centres by a variety of health care professionals as a brief cognitive assessment tool.

Who can take part?

You are eligible to take part if you are between 18 and 60 years old and your first language is English. We will also not be able to include you if you are currently abusing drugs or alcohol or if you have a significant psychiatric condition. You should also not have any medical condition which could affect your cognitive skills. If you are unsure that any of these apply to you, please discuss it with the chief investigator.

Do I have to take part?

Your participation is completely voluntary. We would like you to take part because we believe you can make a significant contribution to the research and healthcare of people with MS.

How do I take part?

If you agree to take part, someone will go through the information sheet with you and you will be asked to sign a consent form. Please bear in mind that you are free to withdraw at any time, without giving a reason.

What will I have to do if I take part?

You will be asked to complete various tests, which measure your attention, memory, language, visuo-spatial and problem solving skills. Some use spoken language whilst others pencil and paper. You may find some easy and others more challenging but most people find them enjoyable.

Where will I have to go and for how long?

The researcher may see participants at Royal Holloway, University of London, or in community settings.

Participation will take about 2 hours and can usually be completed in one session with breaks if you need them.

Part 2

What are the potential benefits of taking part?

Whilst there may be no personal benefits to participating, the information you give could greatly contribute to improvements in the availability of cognitive testing for people with TIA.

Are there possible disadvantages or risks involved in taking part?

It is possible that the tests may cause you to feel fatigued. If this happens you can ask to take a break or we can arrange another time to finish testing.

Will my participation be kept confidential?

We will follow ethical and legal practice to ensure that all information you provide to us, and the results from your tests will be kept strictly confidential. All data will be coded anonymously and stored securely.

The overall results of the study will be made public in a completely anonymous form ensuring that no participants can be identified.

What will happen to my results after the study?

All your information will be stored anonymously. Analysis of the information obtained will be completed on a computer by the chief investigator based at Royal Holloway, University of London.

13.04.16 version 1

The broad findings of the study will be published in a scientific paper or peer reviewed journal and used to compile the chief investigator's Doctoral Thesis. They may also be distributed through voluntary organisations such as the MS Society and presented at appropriate scientific conferences.

If you would like a summary of the study's findings please indicate this on the consent form.

What will happen if I want to withdraw from the study?

You can decide you no longer wish to take part at any point. Results from testing you have completed will be destroyed. This will not affect the standard of care you receive or your legal rights.

Should you give consent and later lose capacity to do so we will include your data in the study unless you indicate otherwise on the consent form.

Who is organising the research?

The study is being organised and undertaken by post graduate students and is sponsored by Royal Holloway University of London.

Ethics permission for this study has been granted by Royal Holloway, University of London.

Appendix 4- Fatigue Severity Scale Questionnaire

This appendix has been removed due to copyright.

Appendix 5- Hospital Anxiety and Depression Scale

Chart I — Hospital Anxiety and Depression Scale

This questionnaire will help your physician know how you are feeling. Read every sentence. Place an "X" on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important. Mark only one answer for each question.

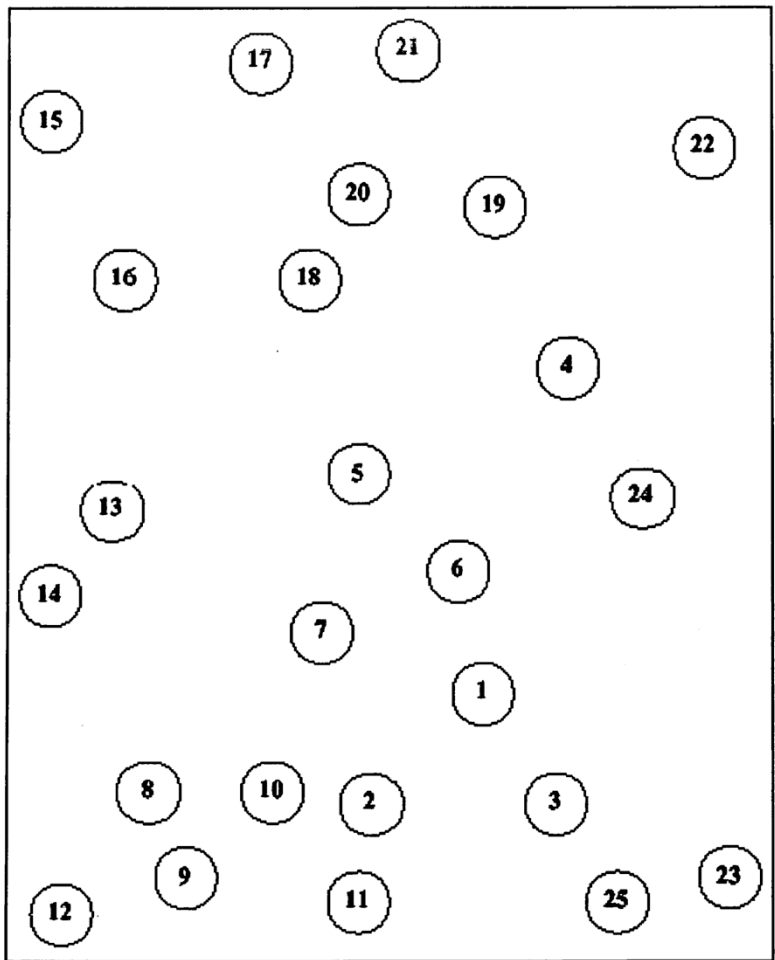
<p>A (1) I feel tense or wound up:</p> <p>3 () Most of the time</p> <p>2 () A lot of times</p> <p>1 () From time to time</p> <p>0 () Not at all</p>	<p>D (8) I feel as I am slowed down:</p> <p>3 () Nearly all the time</p> <p>2 () Very often</p> <p>1 () From time to time</p> <p>0 () Not at all</p>
<p>D (2) I still enjoy the things I used to:</p> <p>0 () Definitely as much</p> <p>1 () Not quite so much</p> <p>2 () Only a little</p> <p>3 () Hardly at all</p>	<p>A (9) I get a sort of frightened feeling like butterflies in the stomach:</p> <p>0 () Not at all</p> <p>1 () From time to time</p> <p>2 () Quite often</p> <p>3 () Very often</p>
<p>A (3) I get a sort of frightened feeling as if something awful is about to happen:</p> <p>3 () Very definitely and quite badly</p> <p>2 () Yes, but not too badly</p> <p>1 () A little, but it doesn't worry me</p> <p>0 () Not at all</p>	<p>D (10) I have lost interest in my appearance:</p> <p>3 () Definitely</p> <p>2 () I don't take so much care as I should</p> <p>1 () I may not take quite as much care</p> <p>0 () I take just as much care as ever</p>
<p>D (4) I can laugh and see the funny side of things:</p> <p>0 () As much as I always could</p> <p>1 () Not quite as much now</p> <p>2 () Definitely not so much now</p> <p>3 () Not at all</p>	<p>A (11) I feel restless, as if I had to be on the move:</p> <p>3 () Very much indeed</p> <p>2 () Quite a lot</p> <p>1 () Not very much</p> <p>0 () Not at all</p>
<p>A (5) Worrying thoughts go through my mind:</p> <p>3 () Most of the time</p> <p>2 () A lot of times</p> <p>1 () From time to time</p> <p>0 () Only occasionally</p>	<p>D (12) I look forward with enjoyment to things:</p> <p>0 () As much as I ever did</p> <p>1 () A little less than I used to</p> <p>2 () Definitely less than I used to</p> <p>3 () Hardly at all</p>
<p>D (6) I feel cheerful:</p> <p>0 () Most of the time</p> <p>1 () Usually</p> <p>2 () Not often</p> <p>3 () Not at all</p>	<p>A (13) I get a sudden feeling of panic:</p> <p>3 () Very often indeed</p> <p>2 () Quite often</p> <p>1 () From time to time</p> <p>0 () Not at all</p>
<p>A (7) I can seat at ease and feel relaxed:</p> <p>0 () Definitely</p> <p>1 () Usually</p> <p>2 () Not often</p> <p>3 () Not at all</p>	<p>D (14) I can enjoy a good TV or radio program or book:</p> <p>0 () Often</p> <p>1 () Sometimes</p> <p>2 () Not often</p> <p>3 () Hardly at all</p>

Appendix 6- Trail Making Test

Trail Making Test Part A

Patient's Name: _____

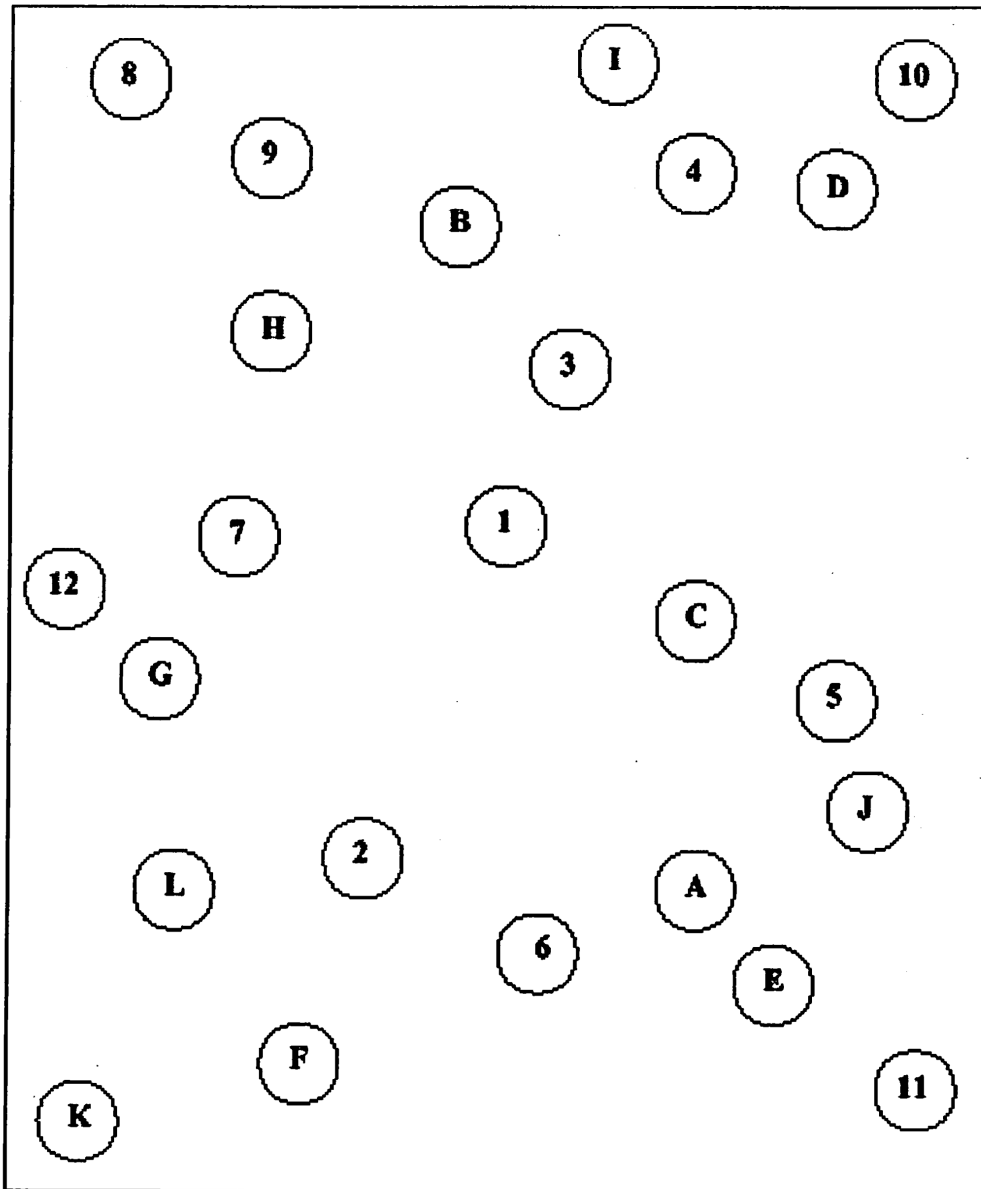
Date: _____



Trail Making Test Part B

Patient's Name: _____

Date: _____



Appendix 7- The Boston Naming Test

This appendix has been removed due to copyright.

Appendix 8- The Rey Ostreith Complex Figure Test

This appendix has been removed due to copyright.

Appendix 9- The Hopkins Verbal Learning Test

This appendix has been removed due to copyright.

Appendix 10- Wechsler Coding Test

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Appendix 11- Symbol Digits Modalities Test (SDMT)

This Appendix has been removed due to copy right.

Appendix 12- California Verbal Learning Test (CVLT)

This Appendix has been removed due to copy right.

**Appendix 13- The Brief Visuospatial Memory Test-Revised
(BVMT-R)**

This Appendix has been removed due to copy right.

Appendix 14- Montreal Cognitive Assessment (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education :
Sex :

Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE		POINTS	
<p style="text-align: center;">[] []</p>	Copy cube	Draw CLOCK (Ten past eleven) (3 points)	[] [] [] Contour Numbers Hands ___/5
NAMING		POINTS	
<p style="text-align: center;">[]</p>	<p style="text-align: center;">[]</p>	<p style="text-align: center;">[]</p>	___/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	No points	
	1st trial 2nd trial		
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	
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[] FBACMNAAJKLBFAKDEAAAJAMOF AAB	
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	
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	
DELAYED RECALL		Has to recall words WITH NO CUE FACE [] VELVET [] CHURCH [] DAISY [] RED []	
Category cue		Points for UNCUED recall only	
Multiple choice cue			
ORIENTATION		[] Date [] Month [] Year [] Day [] Place [] City	
___/6			
© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30		TOTAL ___/30	
Administered by: _____		Add 1 point if ≤ 12 yr edu	

Appendix 15- The Mini-Mental State Examination- MMSE

This Appendix has been removed due to copyright.

Appendix 16-Test of Premorbid Functioning (TOP-F)

This Appendix has been removed due to copy right.

Appendix 14- MoCA Instructions used in the study

MOCA instructions to participant

Visuospatial/executive

Here are some letters and numbers. I want you to join them up like this: 1, A, 2 and so on.

Please copy this cube.

Please draw a clock that says 10 past 11

Naming

Please name these animals.

Memory

I am going to read a list of words, then I want you to say them back to me.

Face, Velvet, Church, Daisy, Red

Now say them back

I am going to say them again

Face, Velvet, Church, Daisy, Red

Now say them back

Record time _____

At time +5 minutes, say

Do you remember that list of words, can you tell me what they were?

Attention

I am going to say some digits, when I have finished I would like you to repeat them

I am going to say some digits, when I have finished I would like you to repeat them backwards

I am going to say some letters, please tap your hand on the table every time I say "A"

Starting at 100, please subtract 7 over and over again.

Language

Please repeat the following sentence.

Please repeat the following sentence.

Please tell me as many words as you can that begin with F (*start timing*)

(*after 60 seconds*) Thanks that's fine.

Abstraction

How are a banana and orange alike? *Fruit*

How are a train and bicycle alike? *Forms of transport*

How are a watch and ruler alike? *They measure things*

Orientation

~~Can you tell me the date, the month, the year, the day, the place we are in, the town we are in~~

Appendix 18- Standardised MoCA instructions.

Montreal Cognitive Assessment (MoCA)

Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."*

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 -A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the **cube**: *"Copy this drawing as accurately as you can, in the space below"*.

Scoring: One point is allocated for a correctly executed drawing.

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)

A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: *"Draw a clock. Put in all the numbers and set the time to 10 past 11"*.

Scoring: One point is allocated for each of the following three criteria:

- Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
- Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
- Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.

A point is not assigned for a given element if any of the above-criteria are not met.

Serial 7s: Administration: The examiner gives the following instruction: “Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.” Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond “92 – 85 – 78 – 71 – 64” where the “92” is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. **Sentence repetition:**

Administration: The examiner gives the following instructions: “I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: **I only know that John is the one to help today.**” Following the response, say: “Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: **The cat always hid under the couch when dogs were in the room.**”

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. **Verbal fluency:**

Administration: The examiner gives the following instruction: “Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop.”

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject’s response in the bottom or side margins.

9. **Abstraction:**

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”. If the subject answers in a concrete manner, then say only one additional time: “Tell me another way in which those items are alike”. If the subject does not give the appropriate response (*fruit*), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification. After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”. Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:

Train-bicycle = means of transportation, means of travelling, you take trips in both;

Ruler-watch = measuring instruments, used to measure.

The following responses are **not** acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

10. **Delayed recall:**

Administration: The examiner gives the following instruction: *“I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.”* Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: Allocate 1 point for each word recalled freely **without any cues**.

Optional:

Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, *“Which of the following words do you think it was, NOSE, FACE, or HAND?”*

Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE: category cue: part of the body

multiple choice: nose, face, hand

VELVET: category cue: type of fabric

multiple choice: denim, cotton, velvet

CHURCH: category cue: type of building

multiple choice: church, school, hospital

DAISY: category cue: type of flower

multiple choice: rose, daisy, tulip

RED: category cue: a colour

multiple choice: red, blue, green

Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. **Orientation:**

Administration: The examiner gives the following instructions: *“Tell me the date today”*. If the subject does not give a complete answer, then prompt accordingly by saying: *“Tell me the [year, month, exact date, and day of the week].”* Then say: *“Now, tell me the name of this place, and which city it is in.”*

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.