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Title	The Quick Mild Cognitive Impairment (Qmci) screen: developing a new screening test for mild cognitive impairment and dementia
Authors	O'Caoimh, Rónán
Publication date	2015
Original Citation	O'Caoimh, R. 2015. The Quick Mild Cognitive Impairment (Qmci) screen: developing a new screening test for mild cognitive impairment and dementia. PhD Thesis, University College Cork.
Type of publication	Doctoral thesis
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The Quick Mild Cognitive Impairment (Q*mci*) Screen

Developing a New Screening Test for Mild Cognitive Impairment and Dementia

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This thesis is being submitted in fulfilment of the requirements of a: Doctor of Philosophy (Medicine and Health)

To University College Cork

April 2015

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List of Ethical Approvals

1. Initial Ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals for the study to be conducted in Memory Clinics and GP practices, 23rd March 2012.....269

2. Ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals for the extension of the external validation of the Q*mci* to include additional study sites, 21st November 2013.....270

3. Ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals for the validation of the Quick Memory Check, 2nd July 2012.....271

4. Ethical approval from the Clinical Research Ethics Committee of the Cork Teaching Hospitals for the extension of the validation of the Quick Memory Check into community settings (bridge clubs) and its change of name, 5th January 2015.....272

Index of Abbreviations

ABCS 135: AB Cognitive Screen 135
AD: Alzheimer's dementa
ADAS-cog: Alzheimer`s Disease Assessment Scale-cognitive section
ADL: Activities of Daily Living
aMCI: amnestic Mild Cognitive Impairment
AUC: Area Under the Curve
BI: Barthel Index
CDR: Clinical Dementia Rating scale
CI: Confidence Interval
6CIT: 6-Item Cognitive Impairment Test
DARAD: Doxycycline and Rifampicin for Alzheimer's Disease trial
DR: Delayed Recall
ECG: Electrocardiograph
FTD: Frontotemporal Dementia
GAT: Geriatric Assessment Tool
GP: General Practitioner
GPCOG: General Practitioner Assessment of Cognition
IQR: Interquartile Range
IQCODE: The Informant Questionnaire on Cognitive Decline in the Elderly
IRR: Inter-Rater Reliability
LBD: Lewy Body Dementia
LM: Logical Memory
MCI: Mild Cognitive Impairment
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
NC: Normal Controls
NPV Negative predictive value
PD: Parkinson's disease
PDD: Parkinson's disease Dementia
PPV Positive predictive value
Q*adl*: Quick Activities of Daily Living screen
QMC: Quick Memory Check
Q*mci*: Quick Mild Cognitive Impairment screen
ROC: Receiver Operating Characteristics curves
SADAS-Cog: Standardised Alzheimer`s Disease Assessment Scale-Cognitive section
SD: Standard Deviation
SMC: Subjective Memory Complaints
SMMSE: Standardised Mini-Mental State Examination
UPDRS: Unified Parkinson's Disease Rating Scale
VaD: Vascular Dementia
VF: Verbal Fluency

Acknowledgements

I would like to thank my supervisors Professor William Molloy and Dr Suzanne Timmons for their insight and expert advice over the last three years. Prof Molloy is the copyright holder of the ABCS 135 and developer of the ABCS 100, which we re-christened the Quick Mild Cognitive Impairment (Q*mci*) screen. I thank him for graciously sharing the copyright of the Q*mci* and Quick Memory Check (QMC) with me and guiding me through the process of developing the many screening instruments we have developed together.

I also wish to thank all the nurses in the Assessment and Treatment Centre (memory clinic) in St Finbarrs for their assistence in rating patients, particularly Mary J Foley and Mary Hickey. Without their help and patience in administering some of the cognitive screens, as blinded independent raters, this project would not have been possible. Thanks to Mary J for her support and wisdom over the last four years. The Cork Alzheimer Café would never have survived and thrived as it has without her.

Thanks also go to my friends and colleagues, past and present, in the Centre for Gerontology and Rehabiliation, University College Cork, especially Yang, Ciara, Niamh, Steve, Yvonne, Nicola and Liz, all conquerors of their own PhDs, who have inspired and encouraged me. Particular thanks go to Yang. I acknowledge his assistence in teaching me the secrets of SPSS and many of the statistical methods employed in this PhD. He assisted in the data preparation of the three Canadian databases, included in this PhD, but which formed the basis of his own. I also acknowledge statistical support and advice from Prof Gordon Guyatt and Anton Svendrovski of McMaster University, Canada.

I would like to acknowledge occupational therapist Sheena Cadoo for assisting in screening patients in general practice along with all the GPs in Mallow Primary Healthcare Centre and Elmwood Medical Centre. I also wish to acknowledge three medical students Patrick Coughlan, Brian Daly and Nurzakiah Mohd Zaki who assisted me in rating and assessing normal controls in St Finbarrs memory clinic, St Finbarrs rehabilitation unit and in bridge and retirement clubs in Cork, respectively. Patrick worked on the QMC as part of his final year project, assisting me with the initial data collection. He also helped obtain ethical approval for its validation. I would particularly like to thank Brian, who completed his final year project in the department on screening for cognitive impairment in a rehabilitation unit, for his assistance in obtaining permission from Dr Nasreddine to use the Montreal Cognitive Assessment in this project and extending ethical approval to include St Finbarrs rehabilitation unit.

Last but not least, I wish to express my deepest gratitude to my friends and family. Thanks to my friends, Donogh & Claire, Emmet, Donal, Arup, Mort & Kelly, Anto and Davros who have tolerated my laptop travelling everywhere with me (weddings, stags and even Iran!) for the last three years. Thanks to my family for their love and support. My Mother, Gemma, always encouraged me to persist and achieve more than I ever thought possible. Even as she has battled the very disease that I have researched I have found strength in her dignity and love. My best friends, my sister Gemma and my girlfriend Estera, have put up with me and my laptop! I could not have done any of this without their support.

Declaration

I declare that the work submitted by way of this thesis is my work and has not been submitted elsewhere. All publications arising from this PhD are cited. All sources of material not arising from my observation have been clearly indicated in the main text where appropriate. Specifically, this thesis includes the use of some data collected prior to this PhD from research centres in Canada. These data, taken from an outpatient database (The GAT) and a randomised controlled trial (The DARAD trial), were collected by my supervisor, Prof William Molloy. Secondary analysis of these data were conducted by myself with the assistance of two statisticians: Dr Yang Gao and Mr Anton Svendrovski after consultation with Prof Gordon Guyatt of McMaster University, Canada. This specifically relates to Chapters 3-5 and 8. The external validation of the Q*mci*, summarised briefly in Chapter 14, was performed by researchers in the Netherlands and Australia under my direction. I provided the research protocol, assisted in the back-translation (Dutch version), analysis and write up of these data for publication. I had the assistance of several medical students, named in the acknowledgments section above. They contributed to the collection of normal controls in the memory clinic, data from which is included in the analysis of Chapters 7 and 13. I also received assistance from occupational therapist Sheena Cadoo with screening patients in general practice.

Dr Rónán O'Caoimh



Date 10/04/2015

Dedication

This work is dedicated to the three women in my life: my mother Gemma, my sister Gemma and my girlfriend Estera.

Abstract

Introduction: Differentiating mild cognitive impairment (MCI) from subjective memory complaints (SMC) and normal controls (NC) is challenging. Few short instruments have sufficient sensitivity and specificity for use in busy clinic settings. This thesis explores the development, psychometric evaluation and validation of a new short (3–5 min) cognitive screening instrument, designed to screen for MCI and early dementia, called the Quick Mild Cognitive Impairment (Q*mci*) screen. Derived from the ABCS 135, the Q*mci* is composed of six subtests: orientation, registration, clock drawing, delayed recall, verbal fluency and logical memory (LM). Specific aims included assessing 1) content validity (Q*mci* subtests), 2) concurrent validity against other short screens: ABCS 135, Standardised Mini-Mental State Examination (SMMSE), Montreal Cognitive Assessment (MoCA), 6-item Cognitive Impairment Test (6CIT) and General Practitioner Assessment of Cognition (GPCOG), 3) construct validity against detailed global and neuropsychological tests (ADAS-cog and Clinical Dementia Rating-CDR scale) and 4) refining the Q*mci* into a 'home'-carer administered "Quick Memory Check-QMC", with a view to showing the characteristics of an ideal short cognitive screen.

Methods: Data from three Canadian databases were analysed to validate the Q*mci*, explore its subtests, assess its accuracy in different types of cognitive impairment, develop cut-off scores and compare its responsiveness, reliability and internal consistency. Once "ready", the Q*mci* was externally validated in different settings (memory clinic, movement disorder clinic, general practice, rehabilitation unit) in Ireland in a prospective data collection. Translation and external validation in other languages was also begun.

Results: The Q*mci* was more accurate than the ABCS 135, 6CIT, GPCOG, SMMSE and had similar sensitivity but greater specificity than the MoCA in differentiating MCI from SMC or NC. Using maximal accuracy, a cut-off of <60/100 yielded a sensitivity of 89% and specificity of 86% (AUC 0.95), using Youden's Index a cut-off of <62/100 gave a sensitivity of 87% and specificity of 88%. LM was the most accurate subtest for detecting MCI across settings. Cut-off scores adjusted for age and education were produced. The Q*mci* correlated with global functional measures (Lawton-Brody ADL scale and CDR) and the gold standard cognitive measure used in clinical trials, the Standardised ADAS-cog. The Q*mci* had excellent inter-rater and test-retest reliability in clinic and general practice. A shortened Q*mci*, administered by caregivers (QMC), was both acceptable to carers and had comparable accuracy to a battery of short cognitive screens.

Discussion: This thesis presents an exploration of a new and arguably much needed short, yet highly sensitive and specific, cognitive screening instrument for use in clinics and general practice. It also demonstrates the potential of shortening the instrument to allow caregivers score patients at home in an attempt to reduce performance anxiety. This project suggests that the Q*mci* could be substituted for more detailed and longer instruments in a wide variety of settings, as a rapid screening test for cognitive impairment, particularly where the suspicion favours the presence of MCI. Further research will focus on 1) increasing the sample size to confirm superiority over highly sensitive instruments such as the MoCA, 2) validation in other settings with lower prevalence of cognitive impairment, 3) the development of normative data and 4) external validation in other cultures and languages. The Q*mci* may be close to an ideal short cognitive screening instrument though further research is warranted.

Word Count (including all tables): 48,137.

Publications and abstracts arising from the thesis

Publications

O'Caoimh R, Gao Y, McGlade C, Healy L, Gallagher P, Timmons S, Molloy DW. Comparison of the Quick Mild Cognitive Impairment (Q*mci*) screen and the SMMSE in Screening for Mild Cognitive Impairment. *Age and Ageing* 2012 Sep;41(5):624-9.

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Section 1

Chapter 1

Introduction

This thesis documents the work of a three year PhD commenced in 2012 and describes research conducted in the Centre for Gerontology and Rehabilitation (University College Cork), St Finbarr's Hospital and selected general medical practices (Mallow Primary Healthcare Centre, Mallow and Elmwood Medical Centre, Douglas) in Cork City and County, Ireland.

1.1 Overall Objective

The overall objective is to develop, validate, refine and externally validate a new short cognitive screening instrument to differentiate normal cognition from mild cognitive impairment (MCI) and early dementia. The new screen is developed from an existing instrument called the AB Cognitive Screen 135 (ABCS 135) designed by Professor William Molloy; first validated and published in 2005. This new instrument, initially called the ABCS 100 after its predecessor and re-weighted scoring to accommodate a new subtest called logical memory (LM), was re-christened the Quick Mild Cognitive Impairment (Q*mci*) screen consistent with its intended use as a brief cognitive screen to identify MCI.

1.2 Specific Aims

This project aims:

1) To validate the Q*mci* screen by analysing the original derivation data set, collected by Professor William Molloy in Canada between 2004 and 2010. This database,

containing Standardised Mini-Mental State Examination (SMMSE), ABCS 135 and LM scores, allows the Q*mci* to be reconstituted and validated against the SMMSE and ABCS 135.

2) To explore the instruments psychometric properties (reliability, administration times, concurrent validity) and that of its individual cognitive domains (subtests).

3) To analyse data from the original derivation sample and additional reconstituted Q*mci* data from two other data sets, collected by Professor William Molloy, to create usable Q*mci* cut-off scores for normal cognition, mild cognitive impairment, and dementia. To adjust these according to age and level of educational attainment.

4) To examine the concurrent validity of the Q*mci* by correlating it with detailed neuropsychological tests in an clinical trial database.

5) To investigate the diagnostic accuracy of the Q*mci* and its subtests in different dementia subtypes.

6) To externally validate the Q*mci* in an older Irish population in four settings: a) a memory clinic, b) a movement disorder clinic, c) general practice and d) a hospital rehabilitation unit, against a battery of other short cognitive screening instruments including the Montreal Cognitive Assessment (MoCA), the 6-item Cognitive Impairment Test (6CIT) and the General Practitioner Assessment of Cognition (GPCOG). An important step in this involves the training of general practitioners (GP) in the use of the Q*mci* and measuring inter-rater reliability (IRR).

7) To develop a modified, (shorter and reduced) version of the Q*mci*, with reweighted subtests, to increase the tools sensitivity and specificity in differentiating MCI from

normal cognition and dementia. To investigate if this shortened version could be used by caregivers to provide "home" cognitive screening in advance of clinic appointments.

8) To translate and begin the external validation of the Q*mci* with colleagues in other countries. These include Dutch, Italian, German, Turkish, Chinese and Portugese translations and a further English language external validation in Australia.

1.3 Overview of the structure of the thesis

This thesis is divided into 5 sections comprising 15 chapters. This first section explores the objectives of the project and sets out the background behind and rationale for developing a new short screening instrument for MCI and early dementia. The second places emphasis upon the classification of neurocognitive disorders, principles of cognitive screening, characteristics of existing cognitive screening instruments and on the structure and scoring of the Q*mci*. The third section describes the psychometric properties of the Q*mci* and its subtests using data collected by Professor William Molloy in Canada in order to validate and produce a usable instrument. The third section describes the external validation of the Q*mci* in different clinical settings in Ireland including the development of a shortened version of the Q*mci* called the Quick Memory Check (QMC), validated for use by caregivers as a "home" administered "pre-screen". The fourth section describes additional work conducted during this PhD using the Q*mci* including its use in monitoring change in an Irish sample of patients with MCI and its external validation in other countries. The fifth and final section summarises the PhD, discussing future studies and providing a conclusion.

Chapter 2

Background

2.1 Neurocognitive disorders

Neurocognitive disorders are a broad class of impairments in cognition, usually associated with ageing, that result in a decline from a previously attained level of cognitive functioning [Sachdev et al., 2014],[Foley et al., 2014]. Neurocognitive disorders include mild cognitive impairment (MCI) and dementia. Under the new American Psychiatric Associations' Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) published in 2014, neurocognitive disorders are divided into two types: major incorporating dementia and minor including MCI. The incidence and prevalence of neurocognitive disorders including MCI [Plassman et al., 2008],[Nie et al., 2011] and dementia [Plassman et al., 2007],[Hebert et al., 2013],[Dong et al., 2007],[Prince et al., 2013] has increased in the face of societal ageing. Many challenges are associated with this, particularly in relation to their prompt diagnosis and management. Recent studies have however suggested that cohort effects are evident in dementia prevalence rates, with later-born generations having a lower risk of prevalent dementia [Matthews et al., 2013].

Prevalence of neurocognitive disorders

In the United States, the prevalence of dementia in those aged over 70 years approaches 15%; approximately 5.0% in those aged 71–79 years, increasing to over 35% in those aged 90 and older [Plassman et al., 2007]. This trend is repeated around the world with similar, albeit accelerated, patterns seen in China, India and South East Asia, such that the numbers of people with dementia will double every 20 years to over 80 million by 2040 [Ferri et al., 2006]. In Ireland, it is estimated that there are

approximately 48,000 people with dementia [Department of Health 2014]. This is expected to rise to 152,000 cases by 2046 [Department of Health 2014]. Though sometimes thought of as part of the ageing process, age is not exponentially or inevitably linked to the risk of developing neurocognitive disorders but instead fits an age-related flattened S shaped curve that falls between 80 and 84 years and then plateaus after 95 years at a prevalence rate of 40% [Fjell et al., 2014]. Prevalence rates of MCI are influenced by the definition of MCI used [Ward et al., 2012], ranging from 0.8% to 4.3% (65 years+) for amnestic type MCI (aMCI) in developing countries [Sosa et al., 2012] to 11.1% for aMCI and 16% for any subtype (70+) in developed countries [Petersen et al., 2010].

Diagnostic criteria for neurocognitive disorders

Major neurocognitive disorder describes terms traditionally referred to as dementia, a heterogeneous group of disorders of cognition; minor includes MCI and subjective memory complaints (SMC) or subjective cognitive disorders (SCD). DSM-5 defines six key domains of cognitive function; executive function, perceptual motor function, language, learning and memory, complex attention and social cognition. These neurocognitive domains, each with their own subdomains, can be used to classify and diagnose patients. DSM-5 includes several subtypes of major neurocognitive disorders including Alzheimer's dementia (AD), vascular dementia (VaD), lewy body dementia (LBD), frontotemporal dementia (FTD), Parkinson's disease dementia (PDD), and those associated with HIV infection, Huntington's disease, prion disease, traumatic brain injury and substance/medication-use. It also includes non-specific disorders including mixed dementia subtypes. DSM-5 rates the severity of major neurocognitive disorders as mild, moderate or severe. This classification is commonly

used in clinical practice and is similar to more detailed classifications such as the Functional Assessment Staging (FAST) or the Clinical Dementia Rating (CDR) scales. Minor neurocognitive disorders include the term MCI and like the major neurocognitive disorders these also have subtypes associated with specific cognitive disorders such as Alzheimer's and cerebrovascular disease. Minor neurocognitive disorders are described as either probable or possible and may be accompanied by behavioral disturbance [Foley et al., 2014]. DSM-5 was published in 2014 and DSM-4-R, its predecessor, was used to define dementia in this thesis. While DSM-4 described dementia, it was limited to AD, VaD and mixed dementia subtypes and did not allow for MCI [Foley et al., 2014].

Diagnostic rates

Major neurocognitive disorders such as dementia are frequently under-diagnosed, particularly in older adults. Even in hospital, where at least 40% of patients aged over 70 years have dementia, only half are diagnosed pre-admission [Sampson et al., 2009]. Similarly low detection rates have been found in the community [Valcour et al., 2000]. Diagnostic rates of minor neurocognitive disorders are affected by fluctuations in the conversion rates with many patients reverting to normal or converting to dementia [Sachdev et al., 2013]. Reversion is less likely in participants with more marked cognitive deficits and multiple-domain MCI [Sachdev et al., 2013]. More than 80% of MCI is reported to go unrecognised in primary care [Boustani et al., 2005].

2.1.1 Major neurocognitive disorders

Dementia

Dementia is traditionally defined by the presence of memory impairment and difficulty with at least one of the following: language, coordinating, planning, recognising or personality, and is accompanied by loss of function (social or occupational) usually manifest as impairment in activities of daily living (ADL) [APA 1994]. DSM-5 criteria do not specifiy the need for memory impairment, instead requiring the presence of significant cognitive deficits defined by two or more standard deviations from the mean based on normative data [APA 2013]. Dementia is gradual and persistent, and is diagnosed only when transient or reversible causes including delirium have been excluded. It is associated with increased mortality [Eaker et al., 2002],[Sampson et al., 2009] and other adverse outcomes including institutionalisation [Gaugler et al., 2007] and hospitalisation [Severson et al., 1994].

Major neurocognitive disorder subtypes

Alzheimer`s disease

Alzheimer`s disease is the most prevalent form of dementia [Brunnström et al., 2009]. AD, like all dementia subtypes is associated with age. Early onset AD, before the age of 65 years, represents approximately 5% of cases and is associated with the apolipoprotein E4 allele and genetic mutations in either amyloid precursor protein or the Presenilin (1 or 2) genes [Huang et al., 2012]. Histologically, AD is characterized by the extracellular accumulation of the peptide amyloid-beta that is thought to arise from abnormalities in the cleavage and clearance of amyloid-beta. This process is also

described for those without clinically evident pathology, with approximately 30% of older adults considered cognitively normal, having evidence of amyloid-beta deposition [Savva et al., 2009]. Clinically, AD is classified as a cortical dementia and is associated with early impairment of episodic memory manifesting as an amnestic syndrome of the medial temporal type. It is also associated with language disorders, visuospatial deficits, executive dysfunction and neuropsychiatric disturbances such as apathy and psychotic symptoms [Huang et al., 2012].

Vascular dementia

Vascular dementia is associated with cerebrovascular disease including stroke and is characterised by a broad spectrum of cognitive deficits and focal neurological symptoms including bulbar signs, urinary symptoms and parkinsonism with gait dyspraxia, falls and psychomotor slowing [Korczyn et al., 2012]. Often insidious in onset, it usually follows a progressive "step-wise" deterioration. Personality and insight are relatively preserved in mild and moderate cases. Apart from DSM, the NINDS-AIREN Criteria are the most widely used [Roman et al., 1993].

Parkinson's disease dementia

Parkinson's disease (PD) is a progressive neurodegenerative disease characterised by loss of the dopaminergic neurons of the substantia nigra in the presence of Lewy bodies; clumps of alpha-synuclein and ubiquitin protein in cerebral neurons. Like dementia, the prevalence of PD is projected to increase [Dorsey et al., 2007]. Cognitive impairment is common in PD [Aarsland et al., 2003],[Aarsland et al., 2007] and is the most frequent non-motor symptom [Sitek et al., 2014]. The prevalence of PD increases with age affecting between 0.5 to 5% of the population aged over 65

years [Kis et al]. Prevalence rates of cognitive impairment approach 80% [Aarsland et al., 2003] and PDD increases as persons with PD age. The lifetime incidence of PDD is more than 40% with many people having cognitive impairment from the initial diagnosis. PDD is subcortical such that it is characterised by relatively preserved recognition memory but marked executive dysfunction. It is associated with mood disturbance.

Lewy Body Dementia

LBD, also known as Dementia with Lewy Bodies, is also characterized anatomically by Lewy bodies. Although LBD has similarities to PDD [Weintraub et al 2007] it has its own unique clinical features that help distinguish it. These depend upon the pathway affected; nigrostriatal involvement results in motor features of parkinsonism, cortical involvement in cognitive impairment and neuropsychiatric symptoms and sympathetic nervous system in autonomic failure. LBD is classically described as "Fluctuating" and represents a clinical diagnosis characterised by at least one of the following: visual and/or auditory hallucinations, mild spontaneous parkinsonism, sensitivity to neuroleptics, and repeated unexplained falls and/or transient clouding or loss of consciousness [McKeith et al., 2005].

Frontotemporal dementia

Frontotemporal dementia (FTD), previously called Picks disease, affects the frontal and temporal lobes, preferentially affecting spindle neurons [Seeley et al., 2006]. FTD can be predominantly frontal (frontal variant), characterised by prominent behavior disturbance, or temporal (primary progressive aphasia), characterised by difficulties with speech. Like AD it can occur sporadically but is more likely to have a genetic

predisposition [Ratnavalli et al., 2002]. Clinically it overlaps with motor neuron disease and PD. Core diagnostic features include insidious onset and gradual progression, early decline in social interpersonal conduct with difficulty regulating behavior, early emotional blunting, poor insight and apathy. Other supportive diagnostic features include behavioural disturbance, a decline in personal hygiene, mental rigidity and inflexibility, distractibility, hyperorality and dietary changes, and perseverative or stereotyped behavior (obsessions). Before DSM-5, the Lund-Manchester Criteria were used [Brun et al., 1994].

2.1.2 Minor neurocognitive disorders

Mild cognitive impairment

Minor neurocognitive disorders include MCI and other mild age associated conditions such as SMC. Minor neurocognitive disorders and MCI in particular, represent a significant diagnostic challenge. The most commonly used diagnostic criteria for MCI are the Petersen criteria [Petersen et al.,1999] i.e. those with:

(1) Subjective memory complaint (preferably corroborated by an informant such as carer or clinician),

(2) Objectively abnormal memory function (i.e. assessed using appropriate cut-off scores and adjusting for age or level of education),

(3) General cognition and functional performance (ADL) otherwise sufficiently preserved,

(4) No dementia.

Despite its inclusion in DSM, no "gold standard" criteria for the diagnosis of MCI are widely accepted [Morris 2012]. Several working groups have proposed different

criterion including the report of the International Working Group on Mild Cognitive Impairment [Winblad et al., 2004] which requires the presence of recent, subjective and or corroborated memory loss without obvious loss of social or occupational function with objective evidence of cognitive decline on cognitive testing. More recently, the MCI Working Group of the European Consortium on Alzheimer's Disease [Portet et al., 2006] proposed similar guidelines, although these do not stipulate the requirement for deficits on cognitive testing. More recently, the National Institute on Aging-Alzheimer's Association workgroup [Albert et al., 2011] approved diagnostic guidelines based on Petersens' criteria [Petersen et al., 1999]. These are compared in Table 2.1. Prior to DSM-5, commonly used terms to describe MCI included dementia prodrome, incipient dementia, isolated memory impairment, and cognitive impairment not dementia. The absence of a precise definition has created heterogeneity in the literature with marked inconsistencies in the instruments, methodologies and diagnostic criteria used between clinical trials [Stephen et al., 2013].

Table 2.1. Proposed working group criteria, including defining characteristics, for the classification of mild cognitive impairment.

Criteria	Year Published	Memory Loss	No loss of function	Requirement For objective cognitive test	Reference
International Working Group on Mild Cognitive Impairment	2004	+	+	+	Winblad et al., 2004
European Consortium on Alzheimer's Disease	2006	+	+	-	Portet et al., 2006
National Institute on Aging-Alzheimer's Association workgroup	2011	+	+	+	Albert et al., 2011
DSM V criteria	2013	+	+	+	APA 2013

MCI is reported to be present in 11% of those over 75 years but varies according to its subtype and other demographic factors such as gender, being higher in those with the amnestic type MCI and in men [Petersen et al., 2010]. The annual conversion rate from MCI to dementia is estimated to be between 5-15% [Mitchell et al., 2009]. The reason for this is partly due to variability in the definitions used [Fisk et al., 2003], and may also be due to variations in the diagnostic methods employed. Conversion rates approach 100% at 8-10 years [Morris et al., 2001].

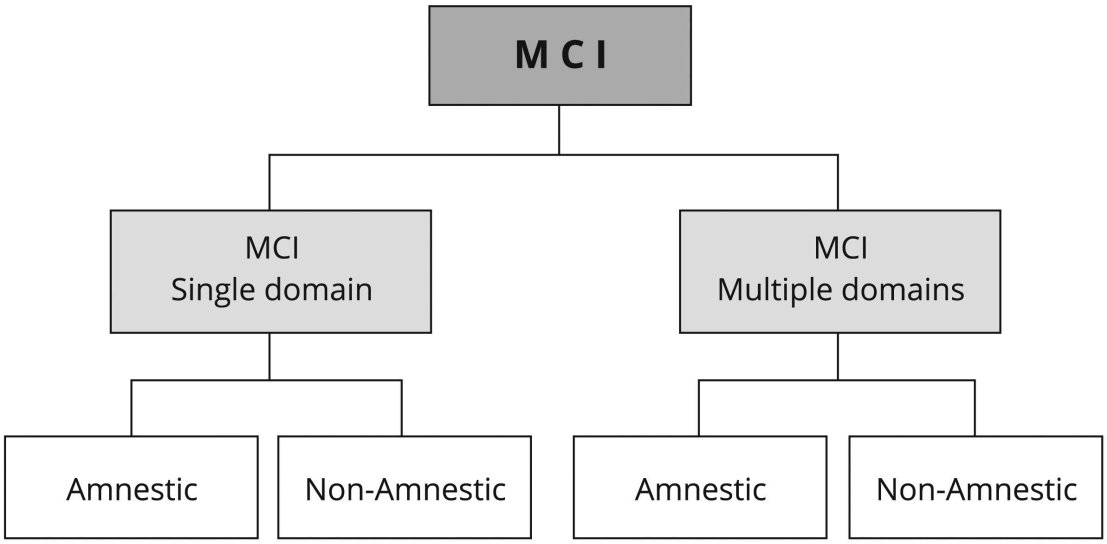
MCI is divided into subtypes, aMCI (amnestic), non-amnestic, mono-domain and multi-domain. This classification is presented in Figure 2.1. The subclassification of MCI into aMCI and non-amnestic subtypes is supported by the utility of different cognitive domains to predict progression to distinct dementia subtypes. For example, people with aMCI, characterized by poor short-term recall, are more likely to progress to Alzheimer's disease pathology [Lyness et al., 2014], whereas those with non-amnestic MCI are more likely to progress to PDD or LBD [Ferman et al., 2013]. DSM-5 criteria also define mild neurocognitive disorders associated with other major neurocognitive disorders including PD-MCI, LBD-MCI and FTD-MCI.

PD-Mild Cognitive Impairment

PD with mild cognitive impairment (PD-MCI) affects approximately 27% of patients with PD [Litvan] and is associated with an increased chance of developing dementia, particularly when already present at diagnosis [Pederson et al., 2013]. Single domain, non-amnestic is the most common subtype of PD-MCI [Litvan et al., 2011]. The diagnosis of PD-MCI is challenging, with uncertainty surrounding the duration of follow-up and the number of repeated cognitive tests required to make the diagnosis [Sitek et al., 2014], with some guidelines suggesting that up to a minimum of 10

repeat assessments are required for PD-MCI subtyping [Sitek et al., 2014]. It differs from MCI associated with Alzheimers disease [Caviness et al., 2007] and typically presents with exaggerated attention and executive function deficits [Petrova et al., 2010].

Figure 2.1. Classification of Mild Cognitive Impairment (MCI) according to its subtypes.



Subjective Memory Complaints

The other class of minor neurocognitive disorders includes SMC. These are characterised by subjective difficulties with cognition, particularly short-term memory, but normal cognition on neuropsychological testing. SMC are common, increase with age and are associated with cognitive decline and depression [Wang et al., 2004][Reisberg et al., 2010]. Prevalence across studies varies from 25-50% in persons aged >65 years [Jonker et al., 2000]. Recent evidence suggests that SMC are not benign and represent a significant independent predictor of progression to dementia. Age is also independently associated with progression from a minor to a major neurocognitive disorder [Waldorff et al., 2012]. As with MCI and dementia age and education affect the presentation of SMC and may affect the results of cognitive screening instruments [Fritsch et al., 2014].

2.2 Principles of cognitive screening

2.2.1 Characteristics of an ideal short cognitive screen

To diagnose neurocognitive disorders healthcare professionals must differentiate normal brain ageing from pathological processes associated with neurocognitive decline. Cognitive screening of symptomatic individuals followed by more detailed assessment with neuropsychological testing is the usual first step. It is important to distinguish between case-finding and screening. Case-finding aims to establish a diagnosis, to rule in or identify a target condition with minimal false negatives. Screening is not a diagnostic process but instead is intended to rule out of a target condition with minimal false positives. The utility of any diagnostic instrument is defined by two conditional probabilities, their sensitivity and specificity, and the utility of most cognitive screens is limited by these [Ritchie et al., 2001]. Sensitivity is the ability to rule in, specificity the ability to rule out disease [Griner et al., 1981],[Gehlbach 1993]. In general, sensitivity and specificity are inversely related and vary with the threshold [Smit et al., 2010]. When an instrument is used as a screen it must be both sensitive and specific [Griner et al., 1981]. High sensitivity, rather than specificity, is preferential for short screens to reduce the rate of false negatives. Further assessment allows the exclusion of false positives. High specificity and the need to avoid false positives are more appropriate in secondary care and in specialised memory clinics. Ideally however, screening tests should strike a balance between both so they can confirm or exclude a disease.

Although sensitivity and specificity are both important, shorts cognitive screens require high sensitivity. Results are interpreted using established cut-off scores but these can be misleading, particularly in older adults, as normal ageing is associated with a decline in test scores that normalise only after correction for

baseline demographics such as age and education [Crum et al., 1993]. Delineating and testing appropriate cognitive domains is also important as their sensitivity and specificity may vary according to the underlying disease process or stage of progression. Several short cognitive screens are currently in use in clinical practice, each with their own advantages and disadvantages.

Apart from sensitivity and specificity, several factors determine the utility of short cognitive screening instruments including clinical and psychometric characteritics. In clinical practice, effective screening instruments must be short, easy to interpret, accurate and administered with only minimal supervision. Another important factor to consider is the setting. Different instruments may be more appropriate in different settings, depending on available time and resources. In busy clinical practice, particularly outpatients and general practice, short instruments are desirable. To use screening tests in clinical practice, cut-off scores, indicating transition points between different cognitive states, are useful. Since cognitive screening instruments provide a range of scores, the challenge is to select cut-off scores to maximise both sensitivity and specificity. Useful instruments should be responsive to change across the cognitive spectrum, from SMC to MCI and dementia.

Where no 'gold standard' exists for the diagnosis of neurocognitive disorders, for example dementia in those with existing intellectual disability and MCI, the traditional approach has been to compare findings with the judgment of clinicians. As clinicians make decisions based upon similar findings and principles as the instruments, it is likely that there will be a high level of agreement, irrespective of validity [Ball et al., 2004]. To overcome this, an important test of the validity of an instrument is concurrent validity, that is, where a test correlates well with a measure that has previously been validated. A further, arguably stronger measure is predictive

validity, when one measure, taken at a starting time, is meant to predict some later outcome. Predictive validity can be determined by examining the degree to which a diagnosis made at time point one predicts decline on cognitive tests and the diagnosis at a second time point, two [Ball et al., 2004]. Analysing large numbers of participants with and without the target condition is required to estimate the overall diagnostic accuracy of any test [Bachmann et al., 2006],[Flahalt et al., 2005]. When multiple tests are performed on the same individual to compare the accuracy of two or more tests, then the proportions (i.e., sensitivity and specificity) are considered dependent. The difference between the two is referred to as the effect size and this can be captured using Cohens σ. A small effect is 0.1-0.3, medium, 0.3-0.5 and 0.5-0.8 or greater is taken as big. Sample size increases if you are looking for a small effect, such that if you expect a big difference in e.g. sensitivity or specificity of a test a priori, you will need a smaller sample size [Fosgate 2009].

Other important psychometric properties include reliability, inter-rater and test-retest, and internal consistencey. Inter-rater reliability (IRR) is a measure of agreement between two or more raters. IRR is measured using Pearsons (best used for interval parametric data) or Spearman's rank (best used for ordinal, non-parametric data) correlation coefficients. Pearsons correlation coefficient (*r*) measures the strength of linear dependence between two variables. Spearman's Rank (rho ρ) measures monotonic relationships. Both can be measured for the same data to examine differences between the data, to confirm whether the assumptions of Pearsons (constant variance and linearity) were met. Correlations are scored between -1 and 1. A score of one or minus one represents perfect linear correlation with scores between suggesting weak to strong correlation. IRR can also be measured using either Cohens weighted Kappa [Cohen 1968], (measures agreement between two raters) or

Fleiss's Kappa [Fleiss et al., 1969] (measures overall agreement between more than two raters). Kappa scores are interpreted as follows: a score of <0.2 is considered poor agreement, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 strong, and more than 0.8 near complete agreement. Internal consistency measures correlations between an instruments subtests or between a test and itself over time. It can be measured using either Cronbach's Alpha or an intraclass correlation coefficient or by measuring correlations between a test and itself over time. Cronbach's Alpha scores above 0.7 indicate a high degree of reliability.

Other useful characteristics include the positive predictive value (PPV) and negative predicitve value (NPV) of a screen, presented in Figure 2.1 The PPV defines the percentage of individuals with a positive test that have the condition, NPV defines the percentage of individuals with a negative that do not have the condition. The PPV and NPV of a test are dependent on the prevalence of the condition assessed [Altman 1994], the higher the prevalence e.g. of cognitive impairment, the higher the PPV and lower the NPV. Provided prevalence is constant PPV and NPV can be compared between tests [Altman 1994]. A high PPV is important for a screening test.

Figure 2.2. Calculation of positive predictive value (PPV) and negaitive predicitive value (NPV).

$$PPV = \frac{sensitivity \times prevalence}{[sensitivity \times prevalence] + [(1 - specificity) \times (1 - prevalence)]}$$

$$NPV = \frac{specificity \times (1 - prevalence)}{[(1 - sensitivity) \times prevalence] + [specificity \times (1 - prevalence)]}$$

Where there is a very high prevalence of a condition, particularly if greater than the true population prevalence such as the prevalence of cognitive impairment in patients attending a memory clinic, it is better to use liklihood ratios [Altman & Bland, 1994]. Positive likelihood ratios (PLR) describe how the probability of disease shifts when the finding is present. A score of between 2-5 suggests a small chance, 5-10 moderate and >10 a large chance of having the condition. Negative likelihood ratios (NLR) describe how the probability shifts when disease is absent [McGee 2002]. A score of 0.2-0.5 suggests a small chance, 0.1-0.2 moderate and <0.1 a large chance.

Receiver operating characteristic (ROC) curve analysis is used to determine the overall diagnostic accuracy of a cognitive screening instrument. Accuracy is measured from the area under the curve (AUC) from ROC curves and these can be compared to determine if instruments differ statistically in accuracy [Hanley et al., 1983],[Alberg et al., 2004]. The AUC is a function of the sensitivity and 1-specificity and is measured from 0 to 1. ROC scores above 0.5 indicate that the component (instrument) has better predictive power than by chance alone. A score greater than 0.8 suggests good accuracy, greater than 0.9 suggest excellent accuracy [Metz 1978]. The interpretation of ROC curves is presented in Table 2.2 and Figure 2.3. Accuracy, while an appealing construct to provide an "overall" marker of sensitivity and specificity, is not equivalent to both which remain the standard for the interpretation of the ability of screens to identify disease states [Alberg et al., 2004]. Finally, cut-off scores to required to allow screening instruments to be used quickly in clinical practice. While the use of cut-off scores is fraught with difficulty have Cut-off can be determined from the scores that offer the best balance between sensitivity and specificity, the "optimal" cut-off or can be calculated using Youden's Index (J) [Larner 2015]. Youden's Index is a method for establishing the maximum potential

effectiveness of a test [Youden 1950],[Ruopp et al., 2008]. It is determined from the ROC curve. The J can be defined mathematically as:

$$J = \max_c \{\mathrm{Se}(c) + \mathrm{Sp}(c) - 1\}$$

Where Se is the sensitivity, Sp is the specificity and c is the optimal cut-off point. The cut-point optimizes the tests ability to differentiate when equal weight is given to sensitivity and specificity [Youden 1950], or mathematically as: J = Sensitivity + Specificity − 1. This is graphically presented in Figure 2.3 [Ruopp et al., 2008].

Figure 2.3. Receiver operating characteristic (ROC) curves showing the reference line and two curves showing high (red) and low (green) accuracy.

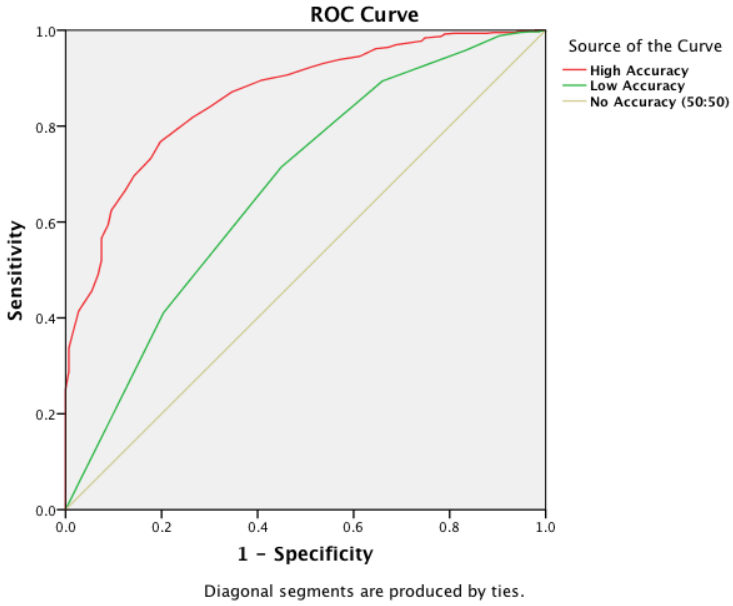
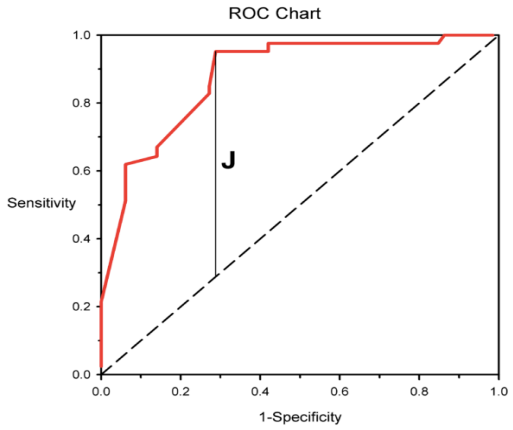


Table 2.2. Table showing interpretation of area under the curve scores for receiver operating characteristics curves.

Area under the curve (AUC) score	Interpretation
0.9-1.0	Excellent
0.8-0.89	Good
0.7-0.79	Fair
0.6-0.69	Poor
05-0.59	Fail

Figure 2.4. Calculation of Youdens Index from receiver operating characteristics curves [Taken from Ruopp et al 2008].



Cognitive domains

Understanding and targeting appropriate cognitive domains is also important for the correct use and interpretation of cognitive screening instruments. As described above, neurocognitive disorders present with different patterns of impairment necessitating the inclusion of the most common cognitive domains. Short instruments can only include a limited number of domains, longer and more comprehensive instruments can include more. Thus, there is a time-accuracy trade-off between different cognitive screening instruments [Larner, Progress in Neurology and Psychiatry 2015]. Instruments can be divided into comprehensive and non-comprehensive based on the

number of cognitive domains covered. Important cognitive domains, commonly incorporated in screens for MCI and early dementia, include orientation, memory, language, attention and calculation, reaction time and visuospatial function (assessed with drawing-copying tests) [Lonie et al., 2009]. A systematic review of short cognitive screens, exclusively in MCI, found that no instrument covers all domains [Lonie et al., 2009].

A complete mental state examination shold target specific cognitive processes or domains [Woodford, 2007]. Domains of interest include attention, memory, language, visuospatial skills and frontal/executive function. Memory is divided into two major categories, declarative and procedural (implicit) memory. Procedural memory is usually preserved, surviving even into advanced dementia. Declarative memory comprises both episodic and semantic memory, which are the main types of memory including short-term memory. Normal ageing is different and although the evidence remains unclear, studies suggest differences in cognitive performance in healthy educated adults between the ages of 18 and 60 years. Longitudinal studies of ageing suggest that one type of memory, episodic memory, for individualized and unique personal experiences, usually declines from about the age of 50–60 years though this is not universal with approximately 20% maintaining their baseline episodic memory [Fjell et al., 2014]. Physical fitness, female gender, and living with someone are protective while less education and not being employed increase the likelihood of memory loss with age. Other cognitive strengths do not appear to decline with age including knowledge, experience and resilience.

2.2.2 Challenges and potential benefits of cognitive screening

Challenges for healthcare professionals

There are many challenges associated with cognitive screening in older adults, particularly in asymptomatic but at risk groups, for example patients with PD. These include physician specific and patient specific challenges. It is known that physicians are poor at predicting patients' cognitive function, especially without the use of formal cognitive (neuropsychological) assessment [Harwood et al., 1997],[Burleigh et al., 2002]. Time is limited in clinical practice and for the majority of busy clinicians this necessiates the use of short cogntive screens [Burleigh et al., 2002],[Harwood et al., 1997]. Studies investigating physicians skills with cognitive screens are limited to examining their ability to predict the scores of common but often inaccurate instruments such as the Abbreviated Mental Test Score [Burleigh et al., 2002]. Studies exploring the views of doctors towards cognitive screening are also limited to those that characterise the perceived utility and popularly of instruments. These reveal that the MMSE is the most widely used instrument [Ismail et al., 2010]. Little is known as to whether physicians feel they have sufficent time or skill to adequately and competantly screen their patients. In Ireland, most GPs (90%) have no dementia specific training and most (83%) express a desire for same [Cahill et al., 2006].

There are other specific challenges for physicians. Cognitive impairment is a heterogeneous disorder and presents in a heterogeneous fashion. Patient populations (normative data) are likewise heterogeneous with different subgroups requiring different cut-off scores, adjusted for age and education [Crum et al 1993],[Rossetti et al., 2011],[Kenny et al., 2013]. The effect of developing and validating these among large populations of patients with different dementia subtypes is also required. People with memory loss most frequently present to their GP with SMC [Speechly et al.,

2008], although little is known about what triggers patients to present in the community [Lin et al., 2013]. Although there is a paucity of evidence for screening in primary care, where cases are often undiagnosed [Bradford et al 2009],[Valcour et al., 2000],[Connolly et al., 2011], research suggests that primary care offers superior post-diagnostic management [Meeuwsen et al., 2012] over secondary care, suggesting that primary care may represent the ideal location to screen as well as manage patients with memory loss. Barriers in primary care include the lack of sufficiently sensitive and specific short screening instruments able to differentiate SMC from MCI and dementia. However, one single screening policy incorporating a single instrument is unlikely to be successful.

Challenges for patients

Similarly, there are challenges for patients. However, little is known about the views of patients themselves. Many report that cognitive screening, neuropsychological testing and the memory clinic experience is probing, demoralizing and in many cases confusing and frightening [Cahill et al., 2008]. Despite this, approximately half of new referrals in an Irish memory clinic found testing to be a positive experience, feeling they performed well [Cahill et al., 2008]. No data is available about the views of caregivers and/or their other family members and friends concerning the use of cognitive screening and their preceptions of whether they could screen others or indeed themselves. However, it is suggested that many patients and caregivers experience anxiety leading up to and while attending a memory clinic, suggesting that many patients may have performed better outside a clinical setting or at a home assessment [Cahill et al., 2008]. Whether shorter but more accurate instruments would be welcomed or beneficial is also unclear.

Evidence for and against screening

It is estimated that only a small number of people meeting the criteria for a neurocognitive disorder are diagnosed [Thies et al., 2011]. Despite this, in 2013 the U.S. Preventive Services Task Force reviewed the evidence base for cognitive screening [Lin et al., 2013] among unselected community-dwelling older adults in primary care, concluding that there is insufficient evidence to recommend cognitive screening nor any single short cognitive screen. This is in part because of lack of sufficiently sensitive and specific screening tests to differentiate normal ageing from major and minor neurocognitive disorders [Winblad et al., 2004],[Boustani et al., 2005]. Indeed, few short screening instruments have been widely validated in primary care and questions remain regarding the ethical [Boustani et al., 2005] and clinical benefits of unselected screening [Lin et al., 2013]. Screening for cognitive impairment doesn't yet meet Wilson's Criteria, recognised as the gold standard for the utility of any screening initiative.

Potential benefits

The potential benefits of screening for cognitive impairment are difficult to measure, which may explain the paucity of evidence to date, particularly with respect to unselected screening. There is however, growing opinion that cognitive screening among selected samples may benefit patients [Clionsky & Clionsky, 2014],[McCartan 2013] particularly at risk populations including those with multiple co-morbidities. Potential advantages include allowing healthcare professionals and families to plan for the future, identify reversible causes and initiate treatment if appropriate. Early diagnosis allows prompt and appropriate initiation of care and treatment. In particular, it allows the physician to differentiate between normal ageing, MCI and early

dementia. Given that different treatments such as cholinesterase inhibitors are appropriate at different stages of disease progression [Tricco et al., 2013],[Cooper et al., 2013], clear staging of cognitive impairment through accurate screening and subsequent assessment is important. Prompt diagnosis allows for the identification and exclusion of reversible causes. These conditions, often misdiagnosed as dementia represent up to 20% of memory clinic referrals [Hejl et al., 2002] but in practice, less than 1.5% of cases of mild to moderate dementia are fully reversible [Boustani et al., 2002]. There is growing recognition of the role cardiovascular (CV) risk factors, such as hypertension [Ligthart et al., 2010],[Tzourio et al., 2010],[Oveisgharan et al 2010], play in the conversion from MCI to dementia and dementia progression [Gao et al 2013],[O'Caoimh, Gao et al., JAD 2014],[O'Caoimh, Kehoe et al., JAD 2014],[O'Caoimh, Kehoe et al., 2013]. Lifestyle factors including obesity, lack of exercise and smoking are also associated with dementia and there is evidence that effectively managing these may prevent cognitive decline [Fillit et al., 2008]. Failure to recognise the presence of MCI, to screen for CV risks or to educate on lifestyle modifications can result in worse outcomes. Finally, prompt assessment gives time for acceptance for patients and families, allowing them to plan for eventualities and access information, resources and supports [Workman et al., 2010].

2.3 Overview of existing cognitive screenings instruments for mild cognitive impairment and early dementia

Systematic reviews [Lonie et al., 2009], have demonstrated that there are an increasing number and variety of short screening instruments available for the early identification and differentiation of MCI and early dementia. Lonie et al found 15 different instruments, the majority of which covered a restrictive range of cognitive

domains. Instruments varied according to their administration time, reliability, sensitivity and specificity. Only one had adequate inter-rater and test-retest reliability. While most reported high levels of sensitivity, most reported low specificity. Further most instruments had small sample sizes. Administration times also differ considerably from as low as 1-2 minutes up to 45 minutes. Available short screening instruments for MCI do not adequately predict the course and eventual outcome of MCI [Lonie et al., 2009]. The authors concluded that none of the identified cognitive screening measures wholly fulfill all of the criteria identified as being important in MCI screening. This may in part relate to a lack of consensus on the definition of MCI and on differences in the characteristics of participants included in studies [Stephan et al., 2013],[Larner, Springer International Publishing 2015].

Multiple cognitive screening tests are available, each with different psychometric properties. Cognitive screening tests can be either direct neuropsychological or observer rated instruments. Observer rated tests are informant guided questionnaires or interviews. There is evidence to support that the addition of an observer rated test improves the diagnostic accuracy of directly administered neuropsychological screen [Roalf et al., 2012]. Observer-rated scales must however, be interpreted with caution as ageing caregivers may be developing cognitive difficulties themselves or may know the subject too well or insufficiently to be objective [Nieuwenhuis-Mark et al., 2009].The advantages and disadvantages of commonly used cognitive screening instruments is presented in Table 2.3. The psychometric characteristics of commonly used instruments for MCI are presented in Table 2.4.

Table 2.3. Comparison of the advantages and disadvantages of commonly used cognitive (observer-rated versus direct neuropsychological) screening instruments.

Classification	Instrument	Accuracy		Advantages	Disadvantages	Timing (mins)	Reference
		Dementia	MCI				
Observer-Rated	**IQCODE-Short Form**	Yes	Low	Short form available Comprehensive	Lengthy Difficult to score	10	Jorm 2004
	AD8	High	High	Short Can be self-administered	Less comprehensive than IQCODE	2	Gavin et al., 2005
Neuro-psychological Instrument	**MMSE (SMMSE)**	High	Low	Widely used translated & validated	Low sensitivity in those with high education;MMSE copyrighted for clinical use, does not assess executive function	5-10	Folstein et al., 1975, Molloy et al., 1991, 1997
	ADAS-cog (SADAS-cog)	Yes	Yes	Gold standard in clinical trials, includes 11 cognitive domains including praxis	Lengthy administration time	45	Rosen et al., 1984
	6CIT	High	Low	Very brief, making it suitable for busy clinics, ward rounds	Little ability to detect MCI	2-3	Katzman et al., 1983; Brookes et al., 1999
	Mini-Cog	High	Low	Little education or language bias	Little ability to detect MCI, No challenging test of recall	4-5	Borsen et al., 2000
	GPCOG	Yes	Yes	Combines observer & neuropsychological components	Age & educational bias, informant required	4-6	Brodaty et al., 2002
	MoCA	High	High	Widely used translated & validated. High sensitivity especially in MCI	Low specificity, floor effects in advanced dementia, educational bias	10-12	Nasreddine et al., 2005
	ABCS 135	High	High	Short administration time. High sensitivity in MCI	Floor effects in advanced dementia, educational bias	3-5	Molloy et al., 2005
	TYM	High	Yes	Can be self-administered	Requires rater supervision	5-10	Brown et al., 2009

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; AD8 = Alzheimer's Disease 8; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive section; MMSE = Mini-Mental State Examination; SMMSE Standardised MMSE; 6CIT = Six-Item Cognitive Impairment Test; GPCOG = General Practicioner Assessment of Cognition; MoCA = Montreal Cognitive Assessment; ABCS 135 = AB Cognitive Screen; TYM = Test Your Memory

Table 2.4. Psychometric properties of commonly used short cognitive screening instruments for mild cognitive impairment (MCI).

Instrument	Administration time (Minutes)	Cut-off	MCI		Reference
			Sensitivity	Specificity	
MMSE (SMMSE)	5-10	<26	18%	100%	Folstein et al., 1975; Molloy, 1991
ADAS-Cog	45	6 (total score)	73%	89%	[Pyo et al., 2006]
6CIT	2-3	>8/28	66%	70%	Katzman et al., 1983; Abdel-Aziz & Larner, 2015
Mini-Cog	4-5	<3	58%	NR	Borson et al., 2005
GPCOG	4-6	NA	NA	NA	NA
MoCA	10-12	<26	90%	87%	Nasreddine et al., 2005
ABCS 135	3-5	NR	80%	50%	Molloy et al., 2005
TYM	5-10	≤42/50	NA	NA	Brown et al., 2009

IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive section; MMSE = Mini-Mental State Examination; SMMSE Standardised MMSE; 6CIT = Six-Item Cognitive Impairment Test; GPCOG = General Practicioner Assessment of Cognition; MoCA = Montreal Cognitive Assessment; ABCS 135 = AB Cognitive Screen; TYM = Test Your Memory
NR = Not Reported; NA = Not Available

Observer rated cognitive instruments

The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) - short form

The Informant Questionnaire on Cognitive Decline in the Elderly -short form (IQCODE) [Jorm 1994] is a widely used observer rated instrument usually scored by families or close contacts. It is limited by its length, albeit shorter than the original version, and its awkward scoring. It not useful in detecting decline in cognition over time [Eramudugolla et al., 2012]. The IQCODE short from is widely validated in MCI and dementia [Perroco et al., 2008] but may be less accurate in MCI [Razavi et al., 2014]. The IQCODE-short form is presented in Appendix 2.1.

The AD8 Dementia Screening Interview

The AD8 [Gavin et al., 2005] is another, more recently developed, observer-rated cognitive instrument (See Appendix 2.2). An informant answers eight questions on whether there has been a recent change (over several years) directly attributable to memory loss in a variety of daily tasks. Informers can respond with 'yes' (a change), 'no' (no change) or 'don't know' answers. A score of one point is given for every score answered 'yes'. A score of two or greater is suggestive of cognitive impairment (sensitivity of 84% and specificity of 80%). The test can also be administered to or self-administered by the patient directly, although an informant is preferable. The AD8 is validated in both MCI and dementia [Razavi et al., 2014].

Direct neuropsychological cognitive instruments

The Mini-Mental State Examination (MMSE) and Standardised MMSE

The Mini-Mental State Examination (MMSE) [Folstein et al., 1975] is the most widely used short cognitive screening instrument [Ismail et al., 2010]. The Standardised Mini-Mental State Examination (SMMSE) is a standardised form of the MMSE that improved inter-rater reliability and reduced administration time by using explicit administration and scoring guidelines [Molloy et al., 1991],[Molloy et al., 1997]. Both screening tests are scored from 30 points. A score of 25 or more suggests that the individual may have normal cognition. Below this, scores can indicate mild (21-24 points), moderate (10-20 points) and severe cognitive impairment (≤9 points) though a cut-off of <24 optimises sensitivity [Molloy et al., 1991],[Molloy et al., 1997]. The MMSE and SMMSE have a limited role in identifying MCI [Mitchell & Shiri-Feshki, 2009], with a 'low' ceiling and 'floor' effects such that a score of 30/30 does not always mean normal cognition and a score of zero does not always support dementia. The MMSE has insufficient sensitivity to differentiate between normal

cognition and MCI particularly where individuals have higher levels of academic achievement [Crum et al 1993]. Despite these limitations, the MMSE remains the most validated short cognitive screening instrument in general practice (primary care) [Lin et al., 2013]. The SMMSE is presented in Table 2.5.

Table 2.5. The Standardised Mini-Mental State Examination (SMMSE) scoring sheet.

Standardised Mini-Mental State Examination		
Maximum Score	Patient`s Score	Questions
5		**Orientation** "What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floor?"
3		**Registration** Ask the subject if you may test his/her memory. Then say "ball", "flag", "tree" clearly and slowly, about 1 second for each. After you have said all 3 words, ask him/her to repeat them - the *first* repetition determines the score (0-3):
5		**Concentration & Calculation** **Serial 7s** Ask the subject to begin with 100 and count backwards by 7. (93,86,79,72,65....). Stop after 5 subtractions. Score the correct subtractions. **Or Spell WORLD backwards** Ask the subject to spell the word "WORLD" backwards. The score is the number of letters in correct position. For example, "DLROW" is 5, "DLORW" is 3, "LROWD" is 0.
3		**Recall** Ask the subject to recall the 3 words you previously asked him/her to remember.
2		**Naming** Show the subject 2 objects, e.g. a wrist watch & pencil and ask him/her what it is.
1		**Repetition** Ask the subject to repeat the following:"No ifs, ands, or buts"
3		**3 Stage Command** following Give the subject a plain piece of paper and say, "Take the paper in your hand, fold it in half, and put it on the floor." 1 point for each TAKES, FOLDS, PUTS
1		**Reading** Hold up the card reading, "Close your eyes", so the subject can see it clearly. Ask him/her to read it and do what it says. Score correctly only if the subject closes eyes **CLOSE YOUR EYES**
1		**Writing** Ask him/her to write a sentence, It must be spontaneous and contain a subject and verb and be sensible. _____
1		**Copying** Give subject a piece of paper and ask him/he to copy a design of two intersecting shapes. One point is awarded for correctly copying it. All angles on both figures must be present, and the figures must have one overlapping angle.
30		Total

Six-item Cognitive Impairment Test (6CIT)

The 6CIT is a short (administration time between 2-3 minutes), cognitive screen including seven questions covering three domains (orientation, episodic memory and attention) [Katzman et al., 1983],[Brookes et al., 1999]. The 6CIT is scored out of 28 points with high scores suggesting cognitive impairment. Initially designed to detect dementia using a cut-off of ≥8/28, it is also validated in MCI [Abdel-Aziz & Larner 2015] though sensitivity (66%) and specificity (70%) are low. The 6CIT is presented in Table 2.6.

Table 2.6. Six-item Cognitive Impairment Test (6CIT).

Question	**Score**	**Patient Score**
1. What year is it?	Correct: 0 points, Incorrect: 4 points	
2. What month is it?	Correct: 0 points, Incorrect: 3 points	
3. Give the patient an address phrase to remember with five components		
4. About what time is it (within one hour)?	Correct: 0 points, Incorrect: 3 points	
5. Count backwards from 20-1	Correct: 0 points, One error: 2 points, More than one error: 4 points	
6. Say the months of the year backwards	Correct: 0 points, One error: 2 points, More than one error: 4 points	
7. Repeat the address	Correct: 0 points One error: 2 points Two errors: 4 points Three errors: 6 points Four errors: 8 points All wrong: 10 points	
Total		/30

Mini-Cog

The Mini-Cog is a brief (3-4 minute) measure including two subtests: three word registration, delayed recall (which serves as an attention test and distracter) and clock drawing [Borson et al., 2000]. The Mini-cog has little education or language bias and is particularly useful as a pre-screen.

The General Practitioner Assessment of Cognition (GPCOG)

The General Practitioner Assessment of Cognition (GPCOG), designed specifically for use in general practice, is short (5-6 mins) and acceptable to patients and physicians alike [Brodaty et al., 2002]. It is criticised for having age and educational bias [Cullen et al., 2007],[Brodaty et al., 2004]. The GPCOG is presented in Appendix 2.3.

The Montreal Cognitive Assessment (MoCA)

The MoCA is a short cognitive screening test with high sensitivity for detecting cognitive impairment, over and above the MMSE [Nasreddine et al., 2005]. It has seven subtests covering five cognitive domains; memory, language, visuospatial, attention and cognitive control, scored out of 30 points [Nasreddine et al., 2005].

The MoCA is widely validated in multiple languages and different clinical settings [see http://www.mocatest.org/]. Its high sensitivity makes it useful as a cognitive screen. It low ceiling makes it particularly useful in those with subtle cognitive deficits such as in MCI. Although the MoCA is increasingly accepted as one of the short cognitive screens of choice, its use presents some challenges. It is long, taking at least 10 minutes to complete [Nasreddine et al., 2005] and is considered by some to be too difficult to use in those with significant cognitive impairment [O'Caoimh & Molloy, 2013]. No age or education specific cut-offs are available for those with cognitive impairment and the utility of its recommended cut-off score (<26/30) has been questioned [Luis et al., 2008]. The specificity of the MoCA at a cut-off score of <26 is low, with studies demonstrating specificities between 35% [Luis et al., 2008] and 50% [Smith et al., 2007]. Recently, it has been suggested that lowering its cut-off will improve its specificity without adversely affecting sensitivity [McLennan et al., 2011], [Freitas et al., 2013]. However, uncertainty remains as to which cut-off is

most appropriate and in which setting. In addition, the MoCA subtest scores have also been criticised for having unacceptably poor levels of accuracy when predicting impairment in their respective cognitive domains [Moafmashhadi et al., 2013]. The MoCA is presented in Appendix 2.4.

Alzheimer`s Disease Assessment Scale-Cognitive section (ADAS-cog)

The existing accepted standard for measuring cognitive function in clinical trials in dementia, is the Alzheimer`s Disease Assessment Scale-Cognitive section (ADAS-cog) [Rosen et al., 1984],[O'Halloran et al., 2011],[Weyer et al., 1997]. The ADAS-cog has 11 domains, including: word recall, object naming, command following, construction, orientation, word recognition, language, speech comprehension, word finding and recall, and takes 30-40 minutes to complete [Rosen et al., 1984]. Total scores range from 0–70; higher scores (≥ 18) indicate greater cognitive impairment. The minimal important change has been determined to be approximately four points and many regulatory authorities, including the Food and Drug Authority, require evidence of such change at six months to confirm the benefit of any new medication [McKhann et al., 1984],[Matthews et al., 2000],[Aisen et al., 2003]. The ADAS-cog, although comprehensive and useful at different stages of dementia, has limitations. The ADAS-cog is long, requires training and there is concern about the instruments` inter-rater reliability [Connor et al., 2008]. It also has a ceiling effect, limiting usefulness in the initial stages of dementia [Mohs et al., 1997]. To overcome these limitations, the Standardised Alzheimer`s Disease Assessment Scale-cognitive section (SADAS-cog) was developed, to improve inter-rater reliability using explicit administration and scoring guidelines [Standish et al., 1996]. The SADAS-cog, is equally lengthy, taking up to 45 minutes. The SADAS-cog is presented in Appendix 2.5.

The AB Cognitive Screen 135 (ABCS 135)

The ABCS 135 was developed to improve the accuracy of diagnosing MCI [Molloy et al., 2005]. The ABCS 135 has five domains: orientation, registration, clock drawing, delayed recall (DR) and verbal fluency (VF) [Molloy et al., 2005]. Administered in three to five minutes, it is more sensitive in differentiating MCI from normal controls and dementia compared with the SMMSE [Molloy et al., 2005], although floor effects were suggested in those with advanced dementia. Like other instruments, age and education affect ABCS135 median scores and accuracy [Molloy et al., 2005]. While its accuracy and sensitivity is high (80%), its specificity (50%) is low [Molloy et al., 2005]. Its DR and VF subtests were best at distinguishing MCI from those with normal controls (NC) [Standish et al., 2007]. Analysis of the subtests suggests that although all of the domains are useful, orientation, registration and clock drawing did not enhance the ability of the test to differentiate normal from MCI. For this reason, the Quick Mild Cognitive Impairment (Q*mci*) screen was developed, to enhance the sensitivity of the ABCS 135, particularly for MCI. Thus, the ABCS 135 is the predecessor of the Q*mci*.

Test Your Memory (TYM)

The Test Your Memory (TYM) [Brown et al., 2009] scored by patients, under supervision of trained raters, the TYM is validated in memory clinics against the MMSE [Brown et al., 2009], Addenbrooke's Cognitive Examination-Revised [Hancock & Larner, 2011] and detailed neuropsychological testing [Koekkoek]. It is composed of 25 items scored out of 50 points and requires five to ten minutes to complete. It is validated in different languages [Hanyu et al., 2011],[Szczesniak er al., 2013].

2.4 The Quick Mild Cognitive Impairment (Q*mci*) Screen

Development of the Q*mci*

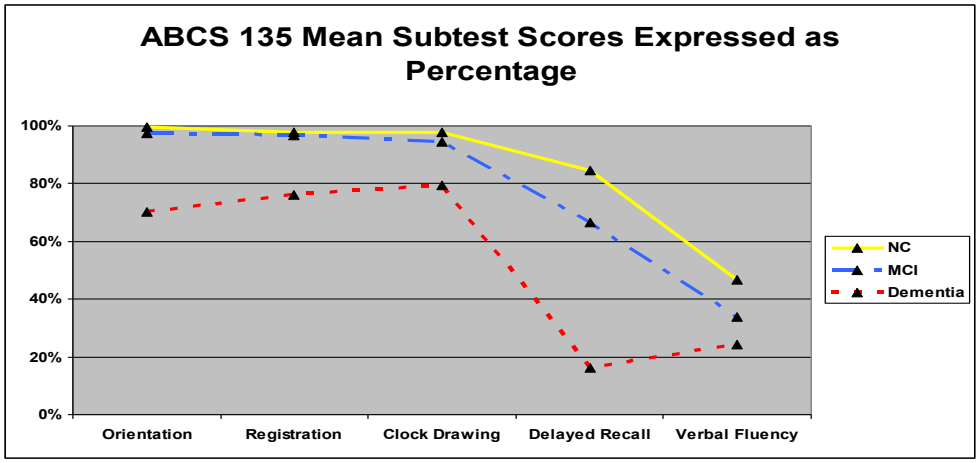
The Q*mci*, originally called the ABCS 100 after its predecessor, is a modified version of the ABCS 135. It is scored out of 100 points and places greater emphasis on verbal fluency and memory including recall compared to the 135 version. Although, the ABCS 135 is a sensitive and quick test to differentiate subtypes of cognitive impairment from normal cognition, much of the test is inadequate at detecting MCI. Given this, the scores of the ABCS 135 subtests were re-weighted to accomadate the introduction of an additional subtest logical memory (LM) and to reduce the total score to 100 points [O'Caoimh et al., 2013]. The scores of the ABCS 135 and Q*mci* are presented by way of comparison in Table 2.6 in sub-section 2.4.

Figure 2.5, which has been previously published by another research team [Standish et al., 2007], shows the mean subtest scores for the ABCS 135 expressed as a percentage for subjects with normal cognition, MCI and established dementia. The orientation, registration and clock drawing subtests did not enhance the discriminatory properties of the test. Further, while sensitivity was high, specificity was low, approximately 50%. For this reason the Q*mci* was developed to enhance the sensitivity of the ABCS 135. To do this, the weightings of delayed recall and verbal fluency were increased, and a logical memory subset was added to the original score (see Table 2.7). Thus, on the basis of these results, orientation was reweighted from 25 to 10 points, registration from 25 to 5 points, clock drawing from 30 to 15 and VF from 30 to 20. DR was increased in weighting to 20 and a test of LM was added at a weight of 30 points.

Table 2.7: Comparison of the weightings of the AB Cognitive Screen 135 (ABCS 135) and the Quick Mild Cognitive Impairment (Q*mci*) screen.

ABCS 135	Score	Q*mci*	Score
Orientation	25	Orientation	10
Registration	25	Registration	5
Clock drawing	30	Clock drawing	15
Delayed recall	25	Delayed recall	20
Verbal fluency	30	Verbal fluency	20
		Logical memory	30

Figure 2.5. Mean subset scores for the AB Cognitive Screen 135 (ABCS 135) expressed as a percentage for normal controls (NC), and patients with mild cognitive impairment (MCI) and dementia [Standish et al., 2007].



Q*mci* Scoring and administration guidelines

The Q*mci* is then scored out of a total of 100 points. The Q*mci* has a short administration time, median time 4.24 minutes [O'Caoimh et al., 2013], which if scored according to the administration guidelines cannot take more than five minutes to complete. The Q*mci* screening instrument includes six subtests, covering five cognitive domains: orientation, working memory, sematic memory (verbal fluency for animals), visuo-spatial (clock drawing) and two tests of episodic memory, delayed recall and logical memory (immediate verbal recall of a short story).

Orientation

The first subtest, orientation, has five items (country, year, month, day and date). Two points for the correct answer, 1 point for wrong answers, and 0 points for no answer or a conceptually unrelated answer. Maximum of 10 seconds for each answer to a total time of 30 seconds. The maximum score is 10 points.

Registration

The second subtest is word registration. It is composed of five items to be repeated back immediately. Three alternative word sets are provided. One point is scored for each word recalled after the first reading. If subject recalls all five, the five items are repeated once before proceding to the next subtest. If a subject does not repeat all 5, the 5 items are repeated. This is done until the subject correctly recalls all 5 items or for a maximum of 3 trials. Trials 2 and 3 do not count. These trials are to help the person learn in preparation for the delayed recall (DR) subtest. Ten seconds are allowed for recall. The maximum score is 5 points.

Clock Drawing Test

The third subtest is a one minute clock drawing test. The clock drawing subtest is a moderately sensitive and specific test, in its own right, to screen for executive dysfunction and visuospatial problems. Clock drawing is a popular short screening test for dementia, in both community [Sager et al., 2006] and hospital settings [Death et al., 1993], and can be scored reliably by both trained and untrained raters [Lessig et al., 2008]. There is excellent IRR for clock drawing between specialists in dementia [Nair et al., 2010]. It can be abnormal despite, a normal SMMSE [Juby et al., 2002]. It is also included in other short screening test batteries including the Mini-Cog [Borson

et al., 2000]. A blank circle "clock face" and scoring template are provided to the test subject. This transparent scoring template is placed over the circle of the patient's completed clock. The template is rotated so that the "12"s align. One point is scored if the 1, 2, 4, 5, 7, 8, 10, and 11 numbers are drawn in the correct quadrants. One point is also scored if the 12, 3, 6, and 9 touch their quadrant lines. One point is subtracted for each number repeated or for numbers above 12. One point is given for each hand between the dashed lines (see Appendix 1.1.). One point is scored for hands connecting at the pivot. The maximum score is 15 points.

Delayed Recall (DR)

The fourth subtest, delayed recall (DR), relates to the five words in the registration subtest using the clock subtest as a distractor. The patient is asked to remember the five words from the registration task. DR is timed at 20 seconds and words may be recalled in any order. The maximum score is 20 points.

Verbal Fluency (VF)

The fifth subtest is a test of verbal fluency (VF). Subjects must name as many words as possible relating to a named category within 60 seconds. A half a point is given for each word named to a maximum of 40 words. The final score is rounded up. Words with different suffixes are not counted twice (e.g. fish / fishes, mouse / mice, etc.). Alternate species (e.g. blue jay, robin, sparrow, duck, etc.) are accepted. Alternate validated forms include fruits and vegetables, cities and towns [Cunje et al., 2007]. The maximum score is 20 points.

Logical Memory (LM)

The sixth and final subtest is logical memory (LM). LM is a highly sensitive and specific test to differentiate normal cognition from MCI [Cunje et al., 2007]. LM is a linguistic memory test (for verbal stories) [Wechsler 1997] and tests immediate verbal recall. LM is unaffected by age or education [Lichtenberg & Christensen, 1992].

Two points are given for each correct word item recalled verbatim. All bolded words within each section of the short story must be recalled to score 2 points. Otherwise score 0. Recall may be in any order. In total 30 seconds are allowed for administration and 30 seconds for response. Again alternative validated alternatves are available. The maximum score is 30 points.

Thus, the Q*mci* can be performed and scored in less than five minutes. Alternative, validated forms of the Q*mci* are available: VF (plants and flowers or fruits and vegetables) and LM (different stories) [Cunje et al., 2007]. The Q*mci* scoring template is presented in Figure 2.6. The doubled sided scoring sheet including alternative versions and the clock scoring template are presented in Appendix 1.1. Detailed scoring and administration guidelines are presented in Appendix 1.2.

Figure 2.6. The Quick Mild Cognitive Impairment (Q*mci*) screen, single page scoring template.

Quick *Mild Cognitive Impairment* screen (Q*mci*)

Name: DOB: Gender: Years in Education: Date: Time:

1. Orientation

To begin ask 5 questions.

◷ One minute.

✎ Give **2 points for correct answer**, 1 if attempted but incorrect, 0 if no attempt.

		Score
What country is it?	___ / 2	
What year is it?	___ / 2	
What month is it?	___ / 2	
What is todays date?	___ / 2	
What day of the week is it?	___ / 2	__/ 10

2. Word Registration

To begin say…

"I am going to say 5 words. After I have said these 5 words, repeat them back to me. Are you ready?"

◷ 30 seconds.

✎ Give **1 point per word** repeated, in any order, no hints.

Dog **Rain** **Butter** **Love** **Door**

Alternate word groups include…

Cat	**Dark**	**Pepper**	**Fear**	**Bed**
Rat	**Heat**	**Bread**	**Round**	**Chair**

Score __/ 5

3. Clock Drawing

"Use the circle provided over page to draw a clock face, set the time to 'ten past eleven'."

◷ One minute approximately.

✎ Give 1 mark for each number, 1 for each hand & 1 for the pivot correctly placed or close to their ideal location. Loose 1 mark for each number duplicated or greater than 12, e.g, 15 or 45, i.e. errors.

Score:	Numbers	Correct	+ _____/ 12	
		Errors	- _____	
	Hands		+ _____/ 2	
	Pivot		+ _____/ 1	
	Total		+ _____/ 15	__/ 15

Score

4. Delayed Recall

"A few minutes ago I named five words. Name as many of those words as you can remember."

◷ 30 seconds.

✎ Recall in any order, within 30 seconds, giving **4 points per word**, no hints.

Dog **Rain** **Butter** **Love** **Door**

Alternate word groups include…

Cat	**Dark**	**Pepper**	**Fear**	**Bed**
Rat	**Heat**	**Bread**	**Round**	**Chair**

Score __/ 20

5. Verbal Fluency

"Name as many animals as you can in one minute. Ready? Go."

◷ One minute.

✎ Give **half a point per animal** named; to a maximum of 40. Accept all 'creatures' including birds, fish, insects etc. Do NOT count suffixes twice, e.g. mouse/mice but allow points for similar names calf, cow, bull.

Alternative forms include: ***fruit & veg*** or ***towns & cities***.

Score 0.5 x number of animals =

List here, in 'shorthand' if required:

Score __/ 20

6. Logical Memory

"I am going to read you ONE short story. After I have finished reading it completely, I want you to tell me as much of the story as you can. OK?"

◷ 30 seconds.

Give **2 points per highlighted word**, recalled exactly, immediately within 30 seconds, in any order, no hints. Two alternatives are provided.

Story 1		Alternative version 1		Alternative version 2	
The **red**	It was a **hot**	The **brown**	It was a **cold**	The **white**	It was a **warm**
fox	**May**	**dog**	**October**	**hen**	**September**
ran across the	**morning**.	**ran across**	**day**.	**walked across**	**afternoon**.
ploughed	**Fragrant**	the **metal**	**Ripe**	the **concrete**	**Dry**
field.	**blossoms**	**bridge**.	**apples**	**road**.	**leaves**
It was **chased** by	were **forming** on	It was **hunting**	were **hanging** on	It was **followed** by	were **blowing** in
a **brown**	the **bushes**.	a **white**	the **trees**.	a **black**	the **wind**.
dog.		**Rabbit.**		**cat.**	

Score __/ 30

Q*mci* Total score *___/ 100

*adjust score for age & education (see over). **Administered by:**_____

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2.5 The Memory Clinic

The main external validation of the Q*mci* in this PhD was conducted in the memory clinic in the Assessment and Treatment Centre in St Finbarrs Hospital, Cork City. An additional "out-reach" memory clinic was created in Mallow Primary Healthcare Centre, Mallow Co Cork, to facilitate diagnosis of patients in the community-general practice setting. Historically, the earliest memory clinic prototype emerged in America in the early 1980s. Clinics have since emerged across Europe, first reaching Ireland in 1991. The importance of memory clinics is well established [Philips & O'Brien, 2004],[Passmore & Craig, 2002].Memory clinics are specialised medical clinics focusing on identifying, investigating and managing memory disorders, including dementia [Jolley et al., 2006].

Referral pathways

Memory clinics see patients across the spectrum of memory problems from normal ageing to MCI and dementia. Acceptance criteria vary between clinics but early referral is desirable. Advanced dementia, presenting for the first time, although representing less of a diagnostic challenge, can be referred, especially if the diagnosis is uncertain. Patients with advanced dementia with behaviours that challenge are usually not accepted and are often redirected to the old age psychiatry team. Memory clinics usually accept referral directly from GPs or other physicians. Standardised referral letters have been developed but are not typical. A small number of appointments are usual, allowing time for comprehensive assessment. A waiting period of three months has been observed in Ireland [Cahill et al., 2011].. Referral should ideally be made after screening for depression and initial blood work, provided this doesn`t cause unnecessary delay (See Figure 2.7).

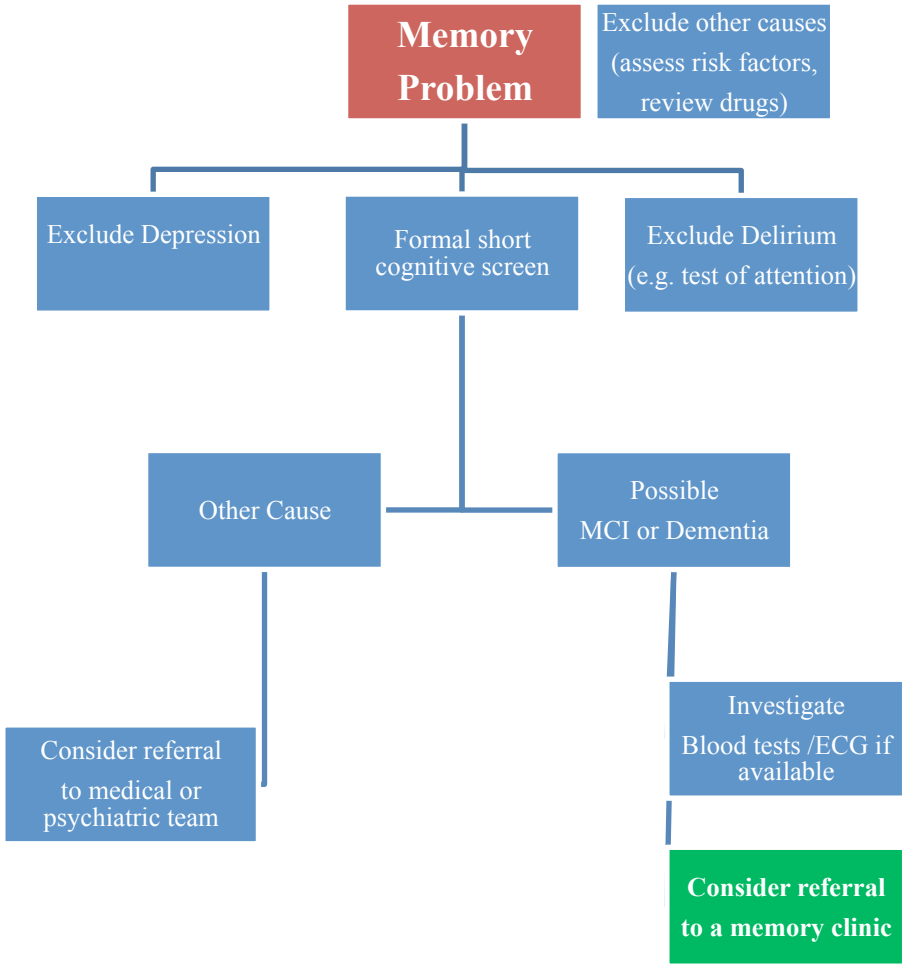
The role of the Memory clinic

Memory clinics, co-ordinated by psychiatry or geriatrics usually accept referrals directly from GPs or other physicians, seeing patients with a spectrum of memory problems, including people with SMC. New presentations of advanced dementia should be referred if the diagnosis is uncertain. Acceptance criteria vary between clinics but as a rule early referral is desirable. Referral should ideally be made after screening for depression and initial blood work, provided this doesn`t cause unnecessary delay. When a diagnosis is made, depending upon the stage of progression and the extent to which a patient or their family accept the diagnosis, advice and literature can be provided regarding creating a will, an enduring power of attorney, advanced care directives or home supports. Memory clinic assessment is usually completed over a short period before patients are discharged back to their primary physician. Some patients are followed for longer where the diagnosis is uncertain or close monitoring is desirable particularly for MCI.

The exclusion of reversible causes of cognitive impairment, which can represent between 13% [Clarfield 1988] and 20% [Hejl et al., 2002] of referrals, is paramount. Fewer reversible cases are now presenting to memory clinics [Clarfield 2003]. The most common, primary reversible causes are depression followed by hydrocephalus and alcohol dependency, all more likely in younger than older patients. Where patients have symptoms that meet the diagnostic criteria for dementia (marked cognitive and functional impairment), a reversible cause is found in less than 5% [Hejl et al., 2002]. Individuals with self-reported memory loss are the most likely to have reversible cognitive impairment. A major challenge for memory clinics lies is differentiating symptomatic patients with normal cognition from those with MCI. Prevalence of normal cognition varies considerably between clinics; 4% in Ireland

[Popoola et al., 2008] but up to 50% in the United States [Steenland]. Diagnosis is based on a multi-disciplinary assessment taking into account the results of investigations, using cognitive screening tools as an adjunct. Delirium and subsyndromal delirium, a common cause of new onset cognitive impairment particularly in hospitalised older adults [Ryan et al., 2013],[Meagher et al., 2015] are an infrequent cause of memory problems in memory clinics [Hejl et al., 2002]. Four cardinal features, history of recent onset, fluctuating confusion, inattention, disorganised thinking and altered consciousness [Inouye et al., 1990] combined with short tests of attention help distinguish delirium from dementia.

Figure 2.7. Suggested referral algorithm to a memory clinic for patients with memory problems, referred from primary care.



2.6 Rationale for the study

From the review above, six key reasons for undertaking the project emerged:

1) At present there is insufficient evidence for suitably accurate, sensitive and specific short cognitive screening instruments that can differentiate MCI from normal ageing but SMC and early dementia, for use in busy clinical practice (hospital clinics and general practice).

2) While patients often present to general practice with SMC, GPs are poor at differentiating these from patients with MCI and early dementia. Few short screens are validated in general practice and it is not clear which instruments are most useful. In particular, little is known about the reliability (inter-rater) of short screens in primary care.

3) It is not clear if a single, short cognitive screen are accurate across different neurocognitive disorders (across the cognitive spectrum), particularly in different dementia subtypes. Although the MMSE and MoCA are brief and widely validated instruments, their use presents challenges. In particular, the MoCA is rarely compared to tests designed specifically to detect MCI.

4) While normative data is increasingly available for some short screens, little is known to what extent instruments need to be adjusted for demographic details in those presenting with symptomatic memory loss and what effects these have on cut-offs for different tests.

5) At present it is not known whether a short cognitive screen can substitute for more detailed instruments and whether brief screens have similar responsiveness to change over time.

6) Can short cognitive screening instruments be shortened further, based upon analysis of their subtests, to provide a "home" caregiver-administered screen, without loosing their diagnostic accuracy?

In summary, this PhD sets out to investigate the characteristics of an ideal short cognitive screen and explores the psychometric properties of a new instrument, the Q*mci* and its subtests, in different clinical settings with a view to demonstrating its construct validity as an easy to use, short screen to differentiate normal ageing from MCI and early dementia. The rationale for each study undertaken as part of this PhD is provided in detail in each chapters' introduction

Section 2

Development of the Quick Mild Cognitive Impairment (Q*mci*) Screen

Chapter 3

Validation of the Quick Mild Cognitive Impairment screen; Comparison to the AB Cognitive Screen 135 and Standardised Mini-Mental State Examination.

3.1 Introduction

As discussed in Chapter 2, MCI represents a heterogeneous group of disorders of memory impairment [Petersen et al., 2004]. Individuals with MCI have variable, subtle cognitive changes and although many go on to develop dementia, the rate of progression differs considerably. When people present with memory loss, it is important to differentiate between MCI and dementia as treatment choices differ. In particular, patients with dementia benefit from cholinesterase inhibitors while those with MCI do not have a sustained response [Petersen et al., 2005]. Clinical and functional assessment has been used to differentiate between these two groups. While those with MCI generally do not have functional impairment, evidence suggests that subtle functional changes are present in 31% [Artero et al., 2001]. Several cognitive screening tools have been used in an attempt to differentiate between normal controls, MCI and dementia [Lonie et al., 2009]. Not all of these are able to distinguish between MCI and dementia, and it has been suggested that no single screening tool will fit all situations [Cullen et al., 2007].

The MMSE and SMMSE, while widely used and validated have a limited role in identifying MCI [Mitchell 2009], lacking the sensitivity to differentiate between

those with normal cognition and MCI, in particular where individuals have higher levels of academic achievement [Crum et al., 1993]. To address this problem the ABCS 135 was developed [Molloy et al., 2005]. Despite its superior sensitivity, its specificity was low and a new subtest (LM) was added and the remaining subtest scores reweighted favouring the most accurate domains: delayed recall DR and VF, producing the Q*mci*. The rationale for and development of the Q*mci* is described in Chapter 2.

The primary objective of this study was to compare the accuracy of the Q*mci* with that of the SMMSE and its predecessor, the ABCS 135, in distinguishing individuals with normal cognition from those with MCI and dementia.

3.2 Methods

Participants

The population is similar to that studied in the validation of the ABCS 135 and was sampled in the same fashion [Molloy et al., 2005]. Patients with MCI and dementia were recruited from patients attending four memory clinics across Ontario, Canada (Hamilton, Paris, Niagara Falls, and Grand Bend) for investigation of cognitive loss between 2004 and 2010. Caregivers and those attending with the patients were asked to participate as controls. A diagnosis of dementia was based upon NINCDS [McKhann et al., 1984] and DSM-IV criteria [APA 1994]. Dementia severity was correlated to the Reisberg Functional Assessment Staging (FAST) scale. A diagnosis of MCI was made by a consultant geriatrician if patients had subjective but corroborated memory loss without obvious loss of function. While in keeping with previous working group criteria this definition does not require the demonstration of cognitive deficits on objective cognitive testing [Winblad et al., 2004]. Patients were

excluded if they were aged under 55 years, if they were unable to communicate verbally in English or had depression as defined by a Geriatric Depression Scale (GDS) greater than seven [Yesavage 1988],[Marc et al., 2008].

The Reisberg Functional Assessment Staging (FAST) scale

The Reisberg FAST is a global measure designed to stage dementia severity. The Reisberg FAST scale presented in Table 3.1.

Table 3.1. Reisberg Functional Assessment Staging (FAST) scale.

Functional Assessment Staging (FAST) scale stage	Description
Stage 1 - Normal adult	No functional decline evident.
Stage 2 - Normal older adult	Insight and awareness into some functional decline.
Stage 3 - Early Alzheimer's disease	Some noticeable deficits with demanding tasks.
Stage 4 - Mild Alzheimer's	Requires assistance in complicated instrumental activities including handling medications & finances, etc.
Stage 5 - Moderate Alzheimer's	Requires assistance with dressing.
Stage 6 - Moderately severe Alzheimer's	Requires assistance with dressing, bathing, and toileting. Experiences urinary and fecal incontinence.
Stage 7 - Severe Alzheimer's	Decline in speech. Progressive loss of ability to walk, sit up, smile and hold head up.

The Geriatric Depression Scale (GDS)

The GDS is a clinician-administered measure of depression. It has two accepted forms, the long form with 30 questions and a short form with 15. The GDS-30 was originally validated with standard research diagnostic criteria for depression. With a cut-off score of 11/30 it provides a sensitivity of 84% and specificity of 95% for depression. Test retest reliability is satisfactory with a correlation of 0.85. The 15 item GDS-Short Form has a cut-off 0 to 5 score of ≥5 for depression [Yesavage 1988],[Marc et al., 2008]. While the performance of the GDS is compromised by severe cognitive impairment (approximately 14 or less out of 30 on the MMSE), it is suitable as a brief screen for depression in those with mild to moderate dementia. The GDS Short Form is presented in Table 3.2.

Table 3.2. The Geriatric Depression Scale (Short Form).

Geriatric Depression Scale (Short Form)

Patient's Name: _____ Date: _____

Instructions: Choose the best answer for how you felt over the past week. Note: when asking the patient to complete the form, provide the self-rated form (included on the following page).

No.	Question	Answer	Score
1.	Are you basically satisfied with your life?	YES / ***NO***	
2.	Have you dropped many of your activities and interests?	***YES*** / NO	
3.	Do you feel that your life is empty?	***YES*** / NO	
4.	Do you often get bored?	***YES*** / NO	
5.	Are you in good spirits most of the time?	YES / ***NO***	
6.	Are you afraid that something bad is going to happen to you?	***YES*** / NO	
7.	Do you feel happy most of the time?	YES / ***NO***	
8.	Do you often feel helpless?	***YES*** / NO	
9.	Do you prefer to stay at home, rather than going out and doing new things?	***YES*** / NO	
10.	Do you feel you have more problems with memory than most people?	***YES*** / NO	
11.	Do you think it is wonderful to be alive?	YES / ***NO***	
12.	Do you feel pretty worthless the way you are now?	***YES*** / NO	
13.	Do you feel full of energy?	YES / ***NO***	
14.	Do you feel that your situation is hopeless?	***YES*** / NO	
15.	Do you think that most people are better off than you are?	***YES*** / NO	
		TOTAL	

(Sheikh & Yesavage, 1986)

Scoring:

Answers indicating depression are in bold and italicized; score one point for each one selected. A score of 0 to 5 is normal. A score greater than 5 suggests depression.

Sources:

- Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clin Gerontol*. 1986 June;5(1/2):165-173.
- Yesavage JA. Geriatric Depression Scale. *Psychopharmacol Bull*. 1988;24(4):709-711.
- Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982-83;17(1):37-49.

Data collection

Each patient had demographic data collected including age, gender and years of education. Each underwent a comprehensive evaluation including a physical examination and work-up for causes of cognitive impairment including a brain computerised tomogram (CT) scan, an electrocardiograph and blood tests. Caregivers were asked to score caregiver burden, ADL, behaviour, depression and safety scores. All patients had the SMMSE and the Q*mci* administered in random order by a trained rater, who was blind to the diagnosis.

Statistical analysis

Data were entered into SPSS version 16.0. Subjects were subdivided according to age, > or ≤ 75 years (to provide a balance in the numbers in each group – most patients were aged over 75) and educational level achieved, ≥ or < 12 years (approximating high school / secondary school level in North America). A subset labeled as having "everything else", incorporating patients with normal and MCI, was used to compare the ability of the tools to select for dementia. A subset of patients called "cognitive impairment" was included to compare those with any cognitive deficits to normal controls. Data were analysed using ROC curves. Students t tests compared mean scores were data were parametric; Mann-Whitney U tests were used to compare non-parametric data, between different conditions.

3.3 Results

A total of 965 participants were included in the study; 561 males (43 %) and 424 females (57%). In all, 630 participants had normal cognition (65.3%), 154 had MCI (16%) and 181 (19%) had dementia. The mean age of the total population was 70.5

years; those with normal cognition had a mean age 67.4 years compared to 73.3 for the MCI group and 78.7 for dementia group. The dementia group was older than the normal cognition (p <0.001) and MCI (p <0.001) groups. They also had spent less time in education, 11 years (95% CI: 10.4-11.5) compared to the normal (13.8 years; 95% confidence intervals (CI): 13.6-14.1, p <0.001) and MCI (12.2 years; CI 11.6-12.8, p <0.005) groups. Dementia was divided into mild (n=141), moderate (n=33) and severe cognitive impairment (n=7). Table 3.3 summarises the demographics and Table 3.4 the median screen scores of the patients and controls.

Table 3.3. Demographic characteristics of the normal controls, mild cognitive impairment (MCI) dementia and combined groups.

Group		**Normal Controls**	**MCI**	**Non Dementia**	**Dementia**
		630	154	784	181
Age					
	Mean	67.4	73.6	68.6	78.1
	95% CI	66.7 – 68.1	72.2 – 75.0	68.0 – 69.3	77.0 – 79.2
	Range	44 - 92	50 - 88	44 - 92	49 - 93
Proportion female (57.0%) n=561					
	Mean age	67.0	73.3	68.1	78.7
	95% CI	66.1 – 68.0	71.1 – 75.4	67.2 – 69.0	77.1 – 80.3
	Range	50 - 92	50 - 87	50 - 92	49 - 93
Proportion male (43.0%) n=424					
	Mean Age	68.0	73.9	69.4	77.6
	95% CI	66.9 – 69.1	71.9 – 75.9	68.4 – 70.4	76.1 – 79.1
	Range	44 - 85	51 - 88	44 - 88	53 - 92
Education (years in education)					
	Mean	13.8	12.2	13.5	11.0
	95% CI	13.6 – 14.1	11.6 – 12.8	13.3 – 13.8	10.4 – 11.5
	Range	5 - 29	5 - 26	5 - 29	3 - 20

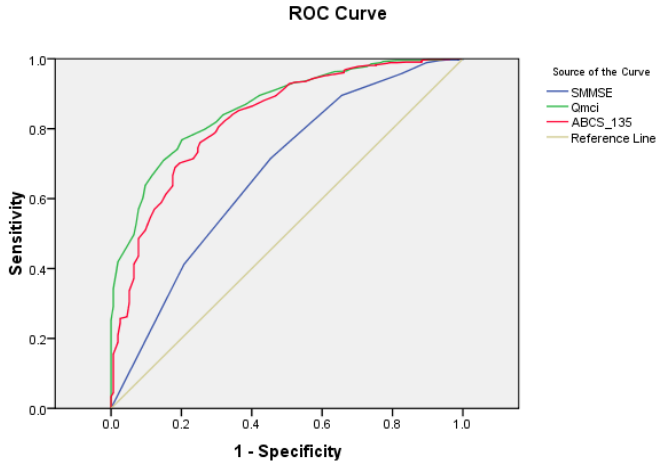
Table 3.4. Median Quick Mild Cognitive Impairment (Q*mci*), AB Cognitive 135 Screen (ABCS 135) and SMMSE scores with 95% Confidence Intervals (CI) for normal controls, mild cognitive impairment (MCI) and Dementia.

Instrument	**Normal Controls**	**MCI**	**Dementia**
Q*mci* (median with 95% CI)	76 (83-69=14)	62 (68-53=15)	36 (45-23=22)
ABCS 135 (median with 95% CI)	115.5 (121-109=12)	102 (111-94=17)	70 (83.5-45.5=38)
SMMSE (median with 95% CI)	29 (30-28=2)	28 (29-27=2)	22 (25-18=7)

Normal controls had a median SMMSE score of 29 and a median Q*mci* score of 76, the MCI group scored 28 and 62 and the dementia group scored 22 and 36 on the SMMSE and Q*mci*, respectively. All three cognitive tests (SMMSE, ABCS 135 and the Qmci) were sensitive in differentiating MCI from controls. The Q*mci* was best able to do this in a clinically useful way. The median difference in scores between those with MCI or controls was one for the SMMSE compared with 14 for the Q*mci*. This represents a diffe ence of 3.33% of the total score of 30 with the SMMSE and a 14% difference for the Q*mci* (scored out of 100 points). All three tests distinguished dementia from MCI. Patients with MCI scored a median 26 points more on the Q*mci* than those with dementia ($p < 0.001$), whereas there was a 40-point difference in the Q*mci* between controls and those with dementia ($p < 0.001$).

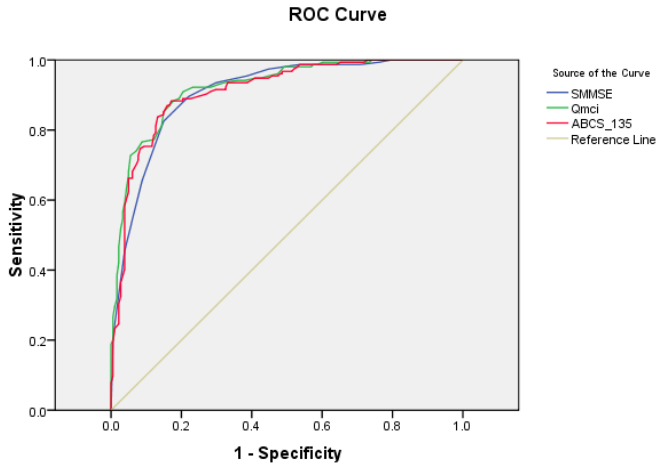
Although the Q*mci*, ABCS 135 and the SMMSE were able to distinguish MCI from NC, the Q*mci* was more accurate with an AUC of 0.86 (95% CI: 0.83–0.89) compared with 0.83 (95% CI: 0.79–0.86) for the ABCS 135 and 0.67 (95% CI: 0.62–0.72) for the SMMSE. The Q*mci* was statistically significantly more accurate than the SMMSE, $z=7.1$, $p<0.001$.The difference between the ABCS 135 and Q*mci* although small, was of borderline statistical significance, $z=1.9$, $p=0.059$. The Q*mci* had similar accuracy at differentiating MCI from dementia, AUC of 0.92 (95% CI: 0.89–0.95) versus 0.91 (95% CI: 0.88– 0.94) for the ABCS 135 and 0.91 (95% CI: 0.88–0.94) for the SMMSE. When moderate and severe dementia cases were removed from analysis, the AUC of the Q*mci* and SMMSE for differentiating MCI from mild dementia cases alone was unchanged at 0.92 (95% CI: 0.89–0.95) and 0.90 (95% CI: 0.85–0.93), respectively. Figure 3.1 and 3.2 present ROC curves demonstrating the accuracy of the Q*mci*, ABCS 135 and SMMSE in differentiating MCI from controls and MCI from dementia respectively.

Figure 3.1. Receiver Operating Characteristic curve demonstrating sensitivities and specificities of Quick Mild Cognitive Impairment (Q*mci*) screen, AB Cognitive Screen 135 (ABCS 135) and Standardised Mini-Mental State Examination (SMMSE) in differentiating mild cognitive impairment from normal controls.



Instrument	Area Under the Curve
Q*mci*	0.86
ABCS 135	0.82
SMMSE	0.67

Figure 3.2. ROC curve demonstrating sensitivities and specificities of Quick Mild Cognitive Impairment (Q*mci*) screen, AB Cognitive Screen 135 (ABCS 135) and Standardised Mini-Mental State Examination (SMMSE) in differentiating mild cognitive impairment and dementia.



Instrument	Area Under the Curve
Q*mci*	0.92
ABCS 135	0.91
SMMSE	0.91

Subanalysis for age (> or < 75 years of age) and education (> or <12 years) showed that the Q*mci* was more accurate with a larger AUC than the SMMSE. The Q*mci* was best for distinguishing MCI from controls in an older age group, (>75 years), with more time, (>12 years), in education, with an AUC of 0.86 (95% CI: 0. 79–0.92) compared with 0.55 (95% CI: 0.44–0.66) for the SMMSE. The only participants where the difference in accuracy between the Q*mci* and SMMSE was less obvious was for younger individuals, (<75 years) with less than 12 years in education, AUC of 0.72 (95% CI: 0.62–0.82) for the Q*mci* versus 0.65 (95% CI: 0.54–0.76) for the SMMSE. The SMMSE, ABCS 135 and Q*mci* were all able to differentiate MCI from dementia, irrespective of age or educational status ($p < 0.001$).

3.4 Discussion

This study compares a new short cognitive screening instrument called the Q*mci* to its predecessor, the ABCS 135, and the established SMMSE in their ability to discriminate controls from MCI and dementia. The results presented here show that the Q*mci* is more accurate than the SMMSE in differentiating MCI from NC, while all three are able to distinguish NC from dementia. Although the Q*mci* had a higher AUC score this was modestly greater than the ABCS 135 and of only borderline statistical significance. Although, the SMMSE was useful in differentiating MCI and NC groups, from dementia subjects, it was not able to separate MCI from NC. The small percentage difference (3.33%) of the total score for the SMMSE between those with NC and MCI, shows that the SMMSE is not clinically useful in distinguishing MCI from normals. The Q*mci* had a wider and more clinically significant percentage difference in median scores to help discriminate MCI from dementia. Similarly, the median SMMSE score for MCI cases and controls, even taking the IQR into account,

at 28 out of 30 (IQR 29-27=2) lies within the accepted cut off interval for normal cognition , at greater than 25 out of 30 [Molloy et al., 1997],[Mungas 1991].This again suggests that the SMMSE is not adequately sensitive in detecting MCI. The Q*mci* was also more sensitive than the SMMSE in differentiating MCI from NC among older adults, over 75 years, especially those with more than 12 years in education.

Of note, age and educational level did not affect the ability of the Q*mci* or SMMSE to discriminate between MCI and dementia. The dementia group in this study was significantly older and had spent less time in formal education than either the MCI or NC group. The dementia group was weighted towards the mild spectrum of dementia. This is important, as differentiating MCI from mild dementia is more challenging than differentiating it from severe dementia. Removing moderate and severe dementia cases from analysis, showed that the Q*mci* retains and even improves its increased sensitivity, for differentiating MCI from mild dementia, confirming that this tool is useful across the whole range of the cognitive impairment spectrum.

Our paper has several limitations. First we cannot be certain that all patients were classified appropriately as having normal or impaired cognition. This is difficult to do, especially where controls are drawn from a sample of convenience. Controls in this study did not have any complaints of memory loss. We acknowledge that one of the major clinical challenges is to separate symptomatic patients with NC from those with MCI, especially as approximating 50%, attending some memory clinics with subjective memory problems, have NC [Steenland et al., 2010]. However, within the confines of a sample of convenience, the subjects chosen as normal controls were tested rigorously, screened for cognitive impairment and depression and underwent the same detailed assessment as cases with MCI and dementia. Future validation of

the Q*mci*, will also investigate sensitivity and specificity in patients presenting with SMC. Another limitation is that we used NINCDS and DSM IV criteria to make a diagnosis of dementia, and while there is no defined gold standard, these criteria are broadly accepted and have been validated internationally [O'Connor et al., 1996]. Third, the diagnosis of dementia was based upon a single assessment which may have reduced accuracy, while one rater scored both cognitive tests which may have led to 'practice' effects. However, the raters were blind to the eventual diagnosis made at the clinical assessment. Finally, we compared the Q*mci* to the SMMSE and ABCS 135 which are not gold standards for differentiating MCI from NC or dementia. This said, the SMMSE is the most widely used screen for dementia and no gold standard yet exists for the diagnosis of MCI and the objective of this study within the PhD was to validate the instrument. The strengths of this study are the large sample size, comprehensive assessment, and bigger number of controls than the original ABCS 135 validation paper. The diagnosis of MCI and diagnosis and grading of dementia are based upon both functional and cognitive assessments. This study was performed at multiple sites.

In summary, this study confirms that the Q*mci*, a short cognitive screen, is more sensitive in differentiating normal controls from those with MCI, than the widely used SMMSE. Compared to the ABCS135, the Q*mci* is slightly more accurate in differentiating MCI, takes a similar albeit longer (by 30 seconds to one minute) time to complete and is conveniently scored out of 100 making it easy to interpret in clinical practice. However, based upon this initial analysis it remains unclear if the addition of LM to the ABCS 135 has improved the accuracy of the instrument. The next study will investigate the accuracy of the individual Q*mci* subtests.

Chapter 4

Investigation of the Quick Mild Cognitive Impairment (Q*mci*) Screen subtests

4.1 Introduction

As time is limited in clinical practice, short screening instruments help improve diagnostic efficiency. One of the major challenges in cognitive testing has been the development of rapid screening tests that can differentiate MCI from normal cognition. As demonstrated in Chapter 3, instruments such as the SMMSE are useful in distinguishing normal cognition and MCI from dementia but take time to complete and are less able to distinguish MCI from normal than instruments such as the ABCS 135 and the Q*mci*. Previous analysis of the Q*mci*'s predecessor, the ABCS 135, showed that its verbal fluency (VF) and delayed recall (DR) subsets best distinguished between MCI and normal controls [Standish et al., 2007]. It is not known which of the subtests of the Q*mci* is best at doing this or what is the impact of the reweighting of the subtests and addition of a logical memory (LM) component on the sensitivity and specificity of the instrument.

Given this, the primary objective of this study was to assess which of the individual subtests of the Q*mci* most affects its accuracy in differentiating between normal cognition, MCI and dementia, in order to help further refine the development of this rapid screening tool for detecting MCI in clinical practice. The secondary objectives were to assess whether age and educational attainment also affect the accuracy of individual subtests of the Q*mci* and determine test-retest reliability.

4.2 Methods

Participants

As this is a secondary analysis of the Q*mci* validation database, the recruitment of subjects is the same as that described in Chapter 3. In summary, subjects were recruited between 2004 and 2010 from patients attending four memory clinics in Ontario, Canada. Caregivers and those attending with the subjects were recruited as controls that is, those with normal cognition. In total 965 individuals were included. 16% (n=154) had MCI, 19% (n=181) had dementia, the majority of which had mild dementia as defined by the SMMSE with 65% (n=630) having normal cognition. Ethical approval was obtained and subjects provided verbal consent. Assent was obtained in the case of individuals with cognitive impairment.

Data analysis

Data were analysed using SPSS 16.0. Subjects were classified as normal controls, MCI or dementia. Subgroup analysis was performed for age (greater and less than 75 years) and for years in formal education (greater or less than 12 years). ROC curves were constructed to determine the accuracy of the subtests of the Q*mci*. Area Under the Curve (AUC) was calculated for each of the subsets and was analysed for age and for total years in education. Normality was tested using the Shapiro–Wilk test. The majority of the data were not normally distributed and were analysed using a Mann–Whitney U test. Normally distributed data were analysed using Student's t-tests. Pearson Chi-squared tests were used to establish the difference between the distributions when it was impossible to analyse differences in medians. Test–retest reliability had been collected and was analysed using Pearson's correlation coefficient.

4.3. Results

Figure 4.1 shows box plot distributions for each Q*mci* subtest with the median and IQR scores for those with dementia, MCI and normal cognition. The VF and LM subtests of the Q*mci* clearly distinguish between dementia, MCI and controls. Orientation and registration did not show a median difference between MCI and NC. All individual subtests had statistically significant differences, $p < 0.001$, in distributions between NC, MCI and dementia. Figure 4.2 and Table 4.1 show the median Q*mci* subtest scores expressed as percentages. Table 4.2 shows the median scores and IQR's for the Q*mci* subtests. Although there were statistically significant differences between Q*mci* subtests scores, they were not all able to differentiate MCI and NC in a clinically useful way; DR (four point difference), VF (four points) and LM (7.5 points) all had clinically useful median score differences between patients with MCI and controls. These differences, expressed as a percentage of the total score for each subtest, are 20% (four point difference out of a total score of 20) for DR, 20% for VF and 25% for LM. There was a median one-point difference for clock drawing (6.66%), and no difference (0%) for orientation and registration, suggesting that these three subtests are clinically less useful.

The best performing SMMSE subtest was short-term memory (0.66), the worst registration (0.51). ROC curves with AUC values for the SMMSE subtests are presented in Tables 4.5 and 4.6, and in Figure 4.3 and 4.4. Table 4.2 also shows AUC values for the SMMSE compared with the best performing subtest, LM after adjusting for age and education. The AUC for the LM was superior to the SMMSE in differentiating MCI from NC, irrespective of the educational level or age (over or under 75 years) of subjects. The improved performance of LM over the SMMSE was more evident for the older age group (age over 75) who had more than 12 years

education, AUC of 0.79 (95% CI: 0.71– 0.88) versus 0.55 (95% CI: 0.44–0.66). There was a significant difference between the median scores for LM, for the MCI and NC groups, irrespective of age or educa- tional status. This difference was not significant for the SMMSE for older people, >75 years with >12 years in education (p =0.350).

Taken in isolation, the LM (AUC 0.80) component of the Q*mci* scored had similar accuracy to the ABCS 135 and greater accuracy then the SMMSE (AUC of 0.80 and 0.67, respectively). Comparing the ability of the Q*mci* subtests to discriminate between MCI and NC showed that the most accurate subtest was LM (AUC of 0.80), followed by VF (0.77) and DR (0.73). Registration (0.56), orientation (0.57) and clock drawing (0.66) were the least accurate subtests. These AUC values, comparing the Q*mci* subtests in their ability to differentiate MCI from NC and MCI from dementia are summarised in Tables 4.5 and 4.6 and presented in Figures 4.5 and 4.6 respectively.

Test–retest reliability was also obtained from the database by analysing the correlation between patients who had the Q*mci* scored on two separate occasions, a minimum of one week apart, (n=20). Pearson's correlation coefficient showed good test–retest correlation, (r =0.86).

Figure 4.1 Box plots showing the distribution for each subtest of the Quick Mild Cognitive Impairment (Q*mci*) screen.

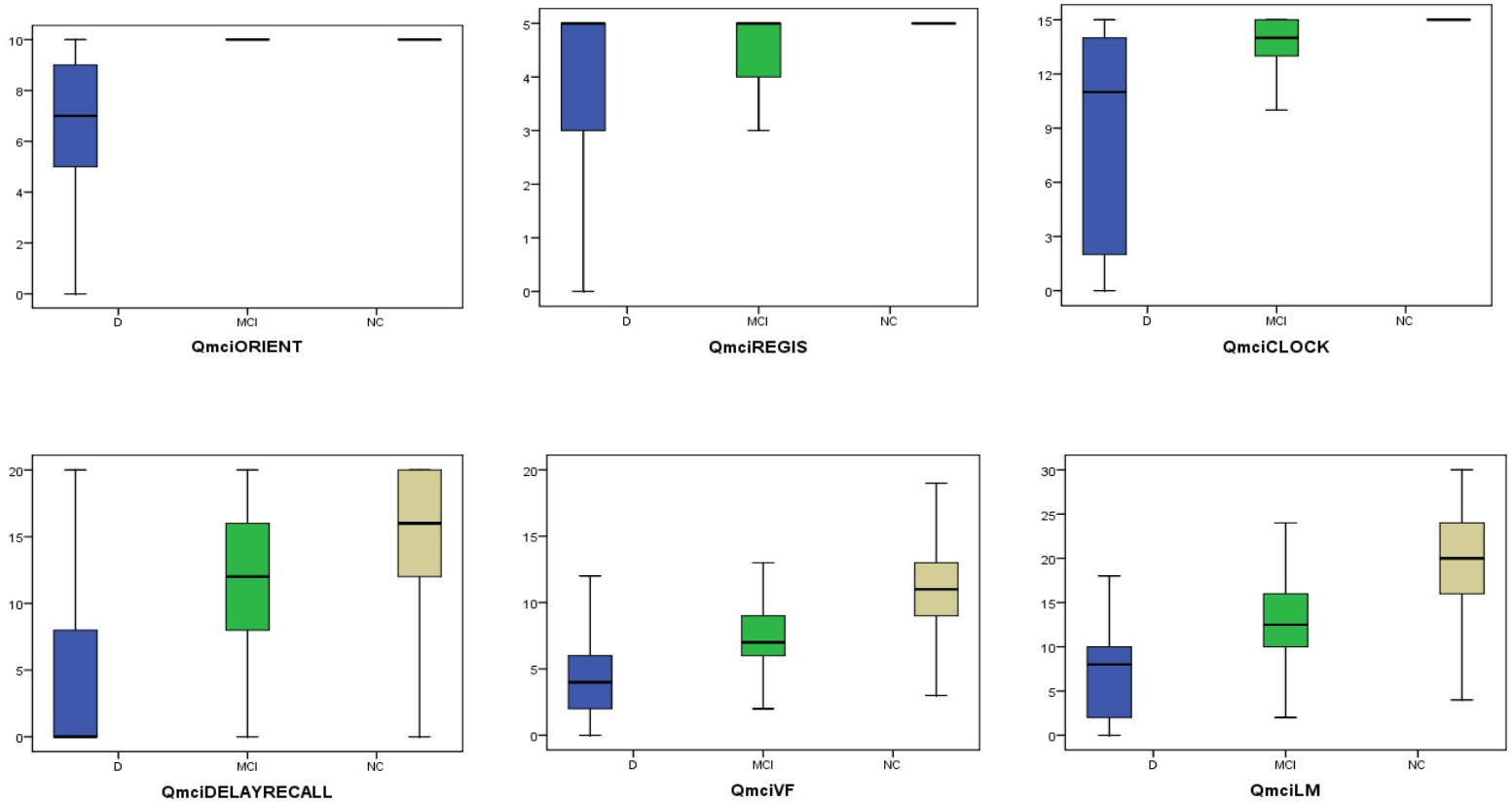


Figure 4.2. Median Q*mci* subtest scores expressed as percentages.

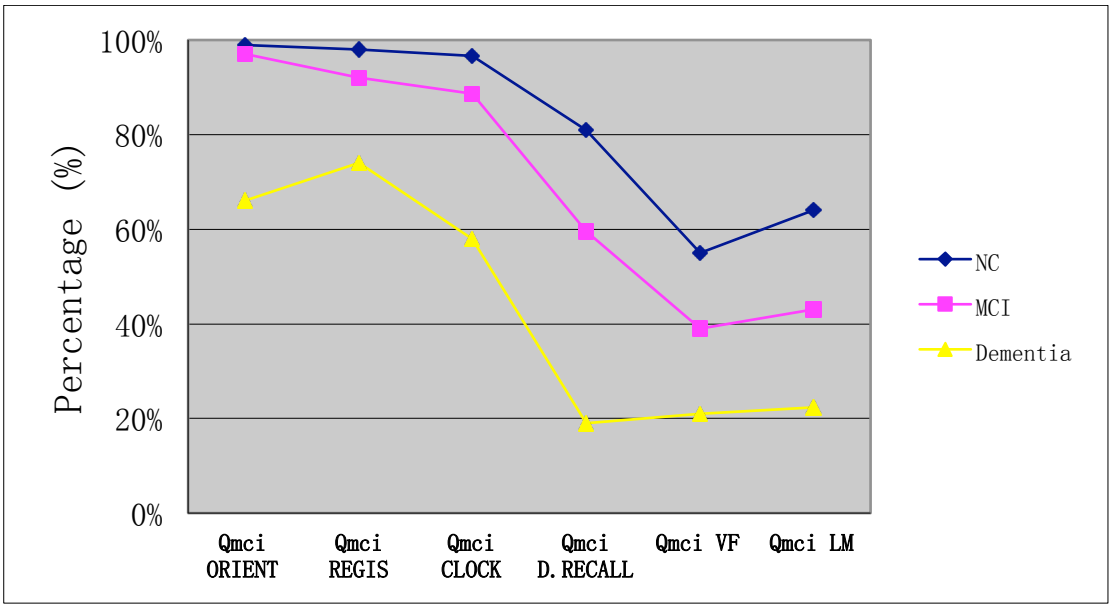


Table 4.1. Median Q*mci* subtest scores expressed as percentages

	Q*mci* Orientation	Q*mci* Registration	Q*mci* Clock	Q*mci* Delayed Recall	Q*mci* Verbal Fluency	Q*mci* Logical Memory
NC	99%	98%	97%	81%	55%	64%
MCI	97%	92%	89%	60%	39%	43%
Dementia	66%	74%	58%	19%	21%	22%

Table 4.2. Q*mci* Subtests: Median scores and IQR, (Q1 = 1st Quartile, Q3= 3rd Quartile) by diagnosis, and p value of the median difference between MCI and NC, dementia and MCI, along with AUC scores for SMMSE and the best performing *Qmci* subtest, LM, by age and education, for differentiating NC from MCI.

Item	NC Median (Q3-Q1= IQR) (n=630)	MCI Median (Q3-Q1= IQR) (n=154)	Dementia Median (Q3-Q1= IQR) (n=181)	p value of the median diff between MCI-NC	p value of the median diff between MCI-Dementia
Q*mci* Total	76 (83-69=14)	62 (68-53=15)	36 (45-23=22)	p<0.001	p<0.001
Qmci Subtests (score out of)					
Orientation (10)	10 (10-10=0)	10 (10-9=1)	7 (9-5=4)	p<0.001	p<0.001
Registration (5)	5 (5-5=0)	5 (5-4=1)	5 (5-3=2)	p<0.001	P=0.002
Clock drawing (15)	15 (15-15=0)	14 (15-13=2)	11 (14-2=12)	p<0.001	p<0.001
Delayed recall (20)	16 (20-12=8)	12 (16-8=8)	0 (8-0=8)	p<0.001	p<0.001
Verbal fluency (20)	11 (13-9=4)	7 (9-6=3)	4 (6-2=4)	p<0.001	p<0.001
Logical memory (30)	20 (24-16=8)	12.5 (16-10=6)	8 (10-2=8)	p<0.001	p<0.001

Group (MCI & NC, N=X)	Test variables	Area Under Curve (95% CI)	Median Diff MCI and NC (p value)
Age <= 75 with education < 12 years N = 127	SMMSE	0.65 (0.54 – 0.76)	29 (p = 0.011)
	LM	0.72 (0.62 – 0.82)	15.49 * (mean) (p < 0.001)
Age <= 75 with education > = 12 years N = 449	SMMSE	0.66 (0.57 – 0.75)	29 (p < 0.001)
	LM	0.79 (0.73 – 0.86)	20 (p < 0.001)
Age > 75 with education < 12 years N = 71	SMMSE	0.64 (0.51 – 0.77)	28 (p = 0.034)
	LM	0.74 (0.62 – 0.85)	14.35 * (mean) (p < 0.001)
Age > 75 with education > = 12 years N = 127	SMMSE	0.55 (0.44 – 0.66)	29 (p = 0.350)
	LM	0.79 (0.71 – 0.88)	16.91* (mean) (p < 0.001)
Overall	SMMSE	0.67 (0.62 – 0.72)	29 (p < 0.001)
	LM	0.80 (0.76 – 0.84)	18 (p < 0.001)

*Normally distributed data.

Figure 4.3. Receiver operating characteristic curves showing the ability of the Standardised Mini-Mental State Examination to differentiate normal controls from mild cognitive impairment (MCI) compared with the Quick Mild Cognitive Impairment (Q*mci*) screen total score and logical memory (LM) subtest.

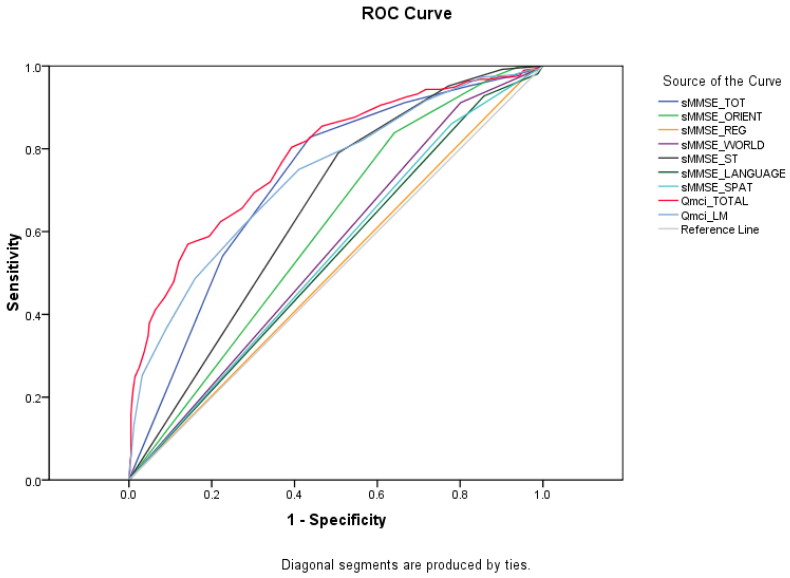


Table 4.3. Comparision of the subtests of the Standardised Mini-Mental State Examination (SMMSE) in their ability to differentiate normal controls from mild cognitive impairment, compared with the Quick Mild Cognitive Impairment (Q*mci*) screen total score and logical memory (LM) subtest.
(Area under the curve = AUC).

SMMSE Subtest	**AUC**
Orientation	0.60
Registration	0.51
WORLD	0.56
Short-term memory	0.66
Language	0.53
Spatial	0.54
SMMSE Total	0.67
Q*mci* Total	0.86
LM	0.80

Figure 4.4. Receiver operating characteristic curves showing the ability of the Standardised Mini-Mental State Examination to differentiate MCI from dementia, compared with the Quick Mild Cognitive Impairment (Q*mci*) screen total score and logical memory (LM) subtest.

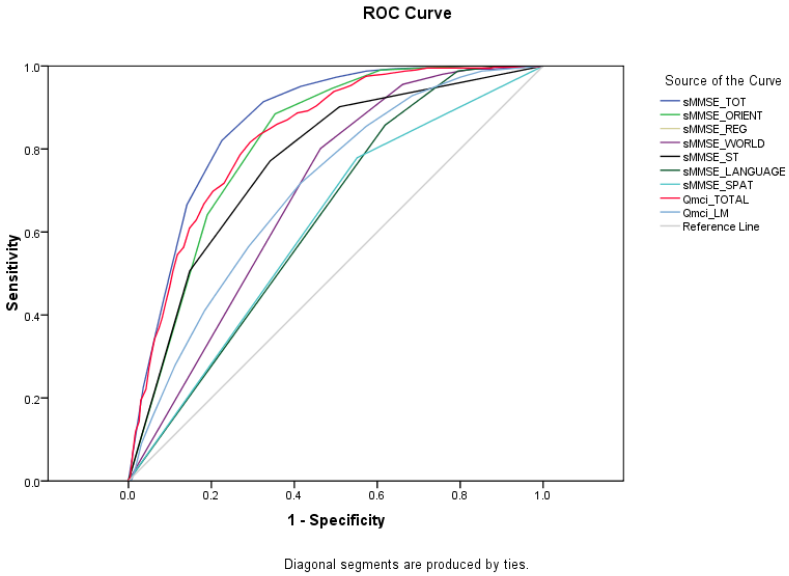


Table 4.4. Comparision of the subtests of the Standardised Mini-Mental State Examination (SMMSE) in their ability to differentiate mild cognitive impairment from dementia, compared with the Quick Mild Cognitive Impairment (Q*mci*) screen total score and logical memory (LM) subtest.
(Area under the curve = AUC).

SMMSE Subtest	**AUC**
Orientation	0.82
Registration	0.54
WORLD	0.69
Short-term memory	0.77
Language	0.63
Spatial	0.61
SMMSE Total	0.91
Qmci Total	0.92
LM	0.82

Figure 4.5. Reciever Operating Characteristic curves for the Quick Mild Cognitive Impairment (Q*mci*) subtests for normal controls vs MCI.

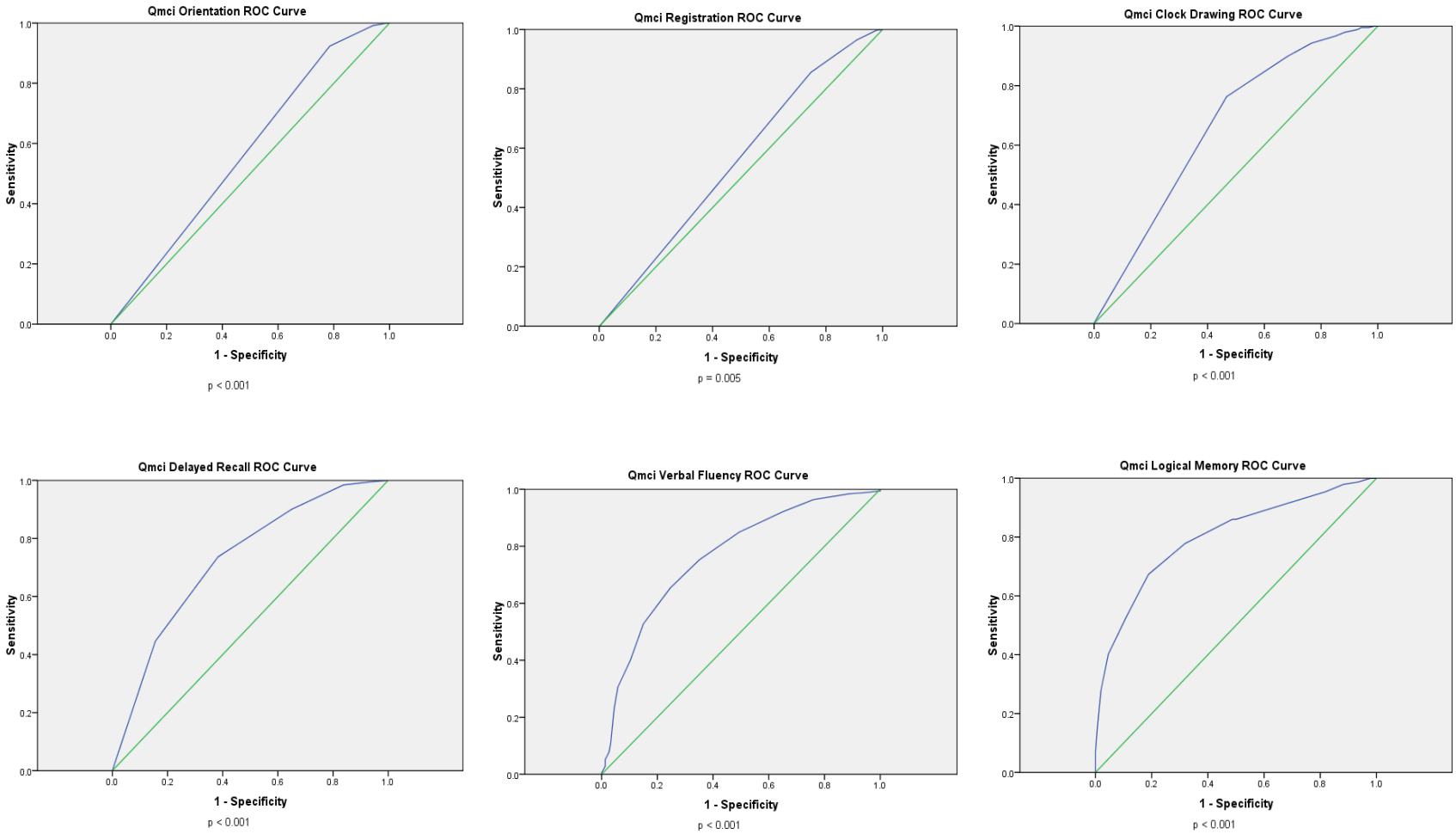


Figure 4.6. Reciever Operating Characteristic curves for the Quick Mild Cognitive Impairment (Q*mci*) subtests – MCI vs Dementia.

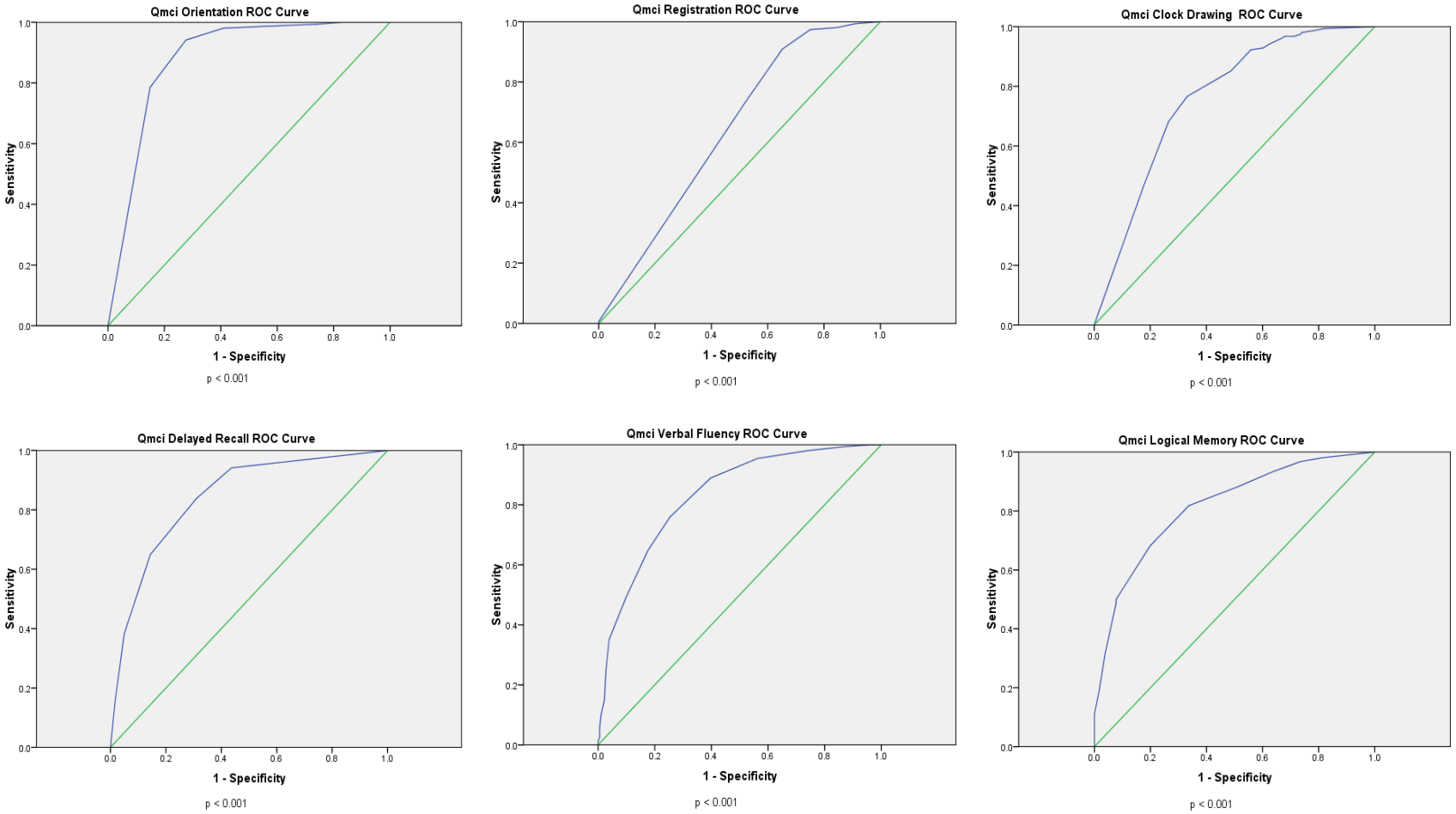


Table 4.5. Receiver operating characteristic curves illustrating the area under the curve (AUC) scores for each of the Q*mci* subtests in differentiating MCI from normal controls.

Q*mci* Subtest	**AUC**
Q*mci* Orient	0.57
Q*mci* Reg	0.56
Q*mci* Clock	0.66
Q*mci* DR	0.73
Q*mci* VF	0.77
Q*mci* LM	0.80

Table 4.6. Receiver operating characteristic illustrating the area under the curve (AUC) scores for each of the Q*mci* subtests in in differentiating dementia from MCI.

Q*mci* Subtest	**AUC**
Q*mci* Orient	0.88
Q*mci* Reg	0.64
Q*mci* Clock	0.76
Q*mci* DR	0.84
Q*mci* VF	0.83
Q*mci* LM	0.82

4.4 Discussion

The analysis presented in this chapter shows the ability of each of the individual Q*mci* subtests to differentiate normal controls from MCI and patients with MCI from those with dementia. The Q*mci* includes a battery of subtests (n=6), but not all differentiate MCI from NC in a clinically useful way. This study found that subtests with the greatest median differences between MCI from normal controls, expressed as percentage of their total scores, were DR, VF and LM. The addition of LM, explored in Chapter 3 in the original validation study [O'Caoimh et al., 2012], added to the original ABCS 135, improving the accuracy of the test in differentiating MCI from NC and is the most useful subtest of the Q*mci*. Orientation, registration and clock drawing, as individual subtests, do not enhance the discriminating power of the tool to the same extent. These subtests have lower ceilings and are insensitive to early cognitive changes [Standish et al., 2007]. When age and education were taken into account, the best performing subtest, LM, was more accurate than the entire SMMSE in differentiating MCI from normal controls, suggesting that alone, it may be better at distinguishing MCI in the oldest and most educated subjects.

All Q*mci* subtests could differentiate dementia from MCI and normal. None of the SMMSE subtests performed better than the complete SMMSE or LM.

From the results we conclude that tests targeting episodic memory (DR and LM) best discriminate MCI from NC whereas orientation is best for assessing dementia, allowing the Q*mci* accurately monitor disease progression. The remaining subtests, further enhance sensitivity, structure the test and may enhance its ability to identify MCI syndromes that convert to different dementia subtypes.

The strength of this study is that it included large numbers of patients with MCI and dementia, and that the tool was validated in a clinical sample in a busy memory clinic, increasing the generalisability of these results. A weakness is that it compares the Q*mci* to the SMMSE and ABCS 135, which are not gold standards for diagnosing MCI or dementia. No objective cognitive testing was used in the diagnosis of MCI which may also have led to bias, although when data collection began MCI consensus guidelines did not stipulate the requirement for independent cognitive testing [Winblad et al., 2004]. Furthermore, the diagnosis was supported by patients clinical history, examination and the opinion of an independent, senior, consultant physician specialised in the diagnosis of cognitive impairment. Where doubt existed patients had an independent neuropsychological assessment providing MCI criteria not inconsistent with Petersen's criteria (see section 2.1.2). The GDS Short Form, used to support a diagnosis of depression, is limited in advanced dementia [Burke et al., 1989], although the majority of subjects in this study were at an early stage. Subjects were only classified with MCI if there was no evidence of functional impairment. This may have created bias given that evidence suggests that up to 30% of subjects with MCI may have subtle impairment in instrumental ADL [Artero et al., 2001]. Another limitation is that the reweighting of the subtests in favour of DR, VF and LM, may have overestimated their contribution to the sensitivity of the Q*mci*, minimising the role of the other subtests. However, the overall improved accuracy of the Q*mci* over the ABCS 135, in differentiating MCI from normal, suggests that the reweighting and addition of LM have enhanced the test as a whole. Only including caregivers attending with subjects as normal controls could also have led to bias as the challenge in diagnosing MCI lies in differentiating MCI from persons with subjective memory complaints (SMC) but who have normal cognition. This

population accounts for up to 50% of referrals in memory clinics [Steenland et al., 2010], but accounted for less than 10% of our clinic population.

In summary, this chapter confirms that reweighting the Q*mci* subtests and the addition of LM, improved the ability of the original ABCS 135 to differentiate subjects with MCI and normal cognition. This secondary analysis of the original Q*mci* validation database presented in chapter 1, further highlights and describes some attributes of an ideal short cognitive screening test for MCI that can be used in everyday clinical practice. As presented in chapter 1, the Q*mci* was more accurate than its predecessor, the ABCS 135 and the SMMSE in distinguishing MCI from NC and dementia. The Q*mci* incorporates several important cognitive domains, across the spectrum of cognition and its subtests allow discrimination of MCI from both normal cognition and dementia, potentially allowing the Q*mci* to continue monitoring patients throughout the stages of cognitive impairment. The Q*mci* also has the advantage of being quick to administer and has excellent test-retest reliability and of having alternative forms. Other tools such as the SMMSE and the ABCS 135 are less sensitive and because of their scoring range, are less practical for use clinically. The development of cut-off scores for the Q*mci*, to increase its usability, and comparison with other rapid screening tools, such as the MoCA, is now required.

Chapter 5

Developing cut-off scores for the Quick Mild Cognitive Impairment (Q*mci*) Screen

5.1 Introduction

While screening for symptomatic cognitive impairment is advocated [Boustani et al., 2003], [Cordell et al., 2013], there is limited evidence supporting routine screening in clinical practice [Boustani et al., 2005], [Lin et al., 2013]. This is in part because most cognitive screens lack sufficient sensitivity and specificity to differentiate symptomatic memory loss with normal cognition from MCI and dementia, [Winblad et al., 2004], [Boustani et al., 2005] particularly in those with low education [Cordell et al., 2013], but also because of the effects of age and education on scoring variability [Crum et al 1993], [Freitas et al., 2012]. Misclassifying may be harmful as treatments that are indicated at one stage may not benefit at another [Peterson et al., 2005],[Tricco et al., 2013], [Cooper et al., 2013]. Cut-off scores, transitions points along the spectrum of cognitive impairment, are useful in busy clinical practice. Although age and educational cut-offs, based upon population-based norms are available for some widely used short cognitive screens, including the MMSE [Crum et al., 1993] and MoCA [Rosetti et al., 2011], [Kenny et al., 2013], few studies have published usable cut-off scores for patients presenting with symptomatic memory loss. Given this, we sought to define cut-off scores for symptomatic MCI and dementia in patients populating three clinical and research cohorts (derived in Canada by Prof William Molloy), including the original Q*mci* validation data set, and investigate if these needed adjustment for age and education.

5.2 Methods

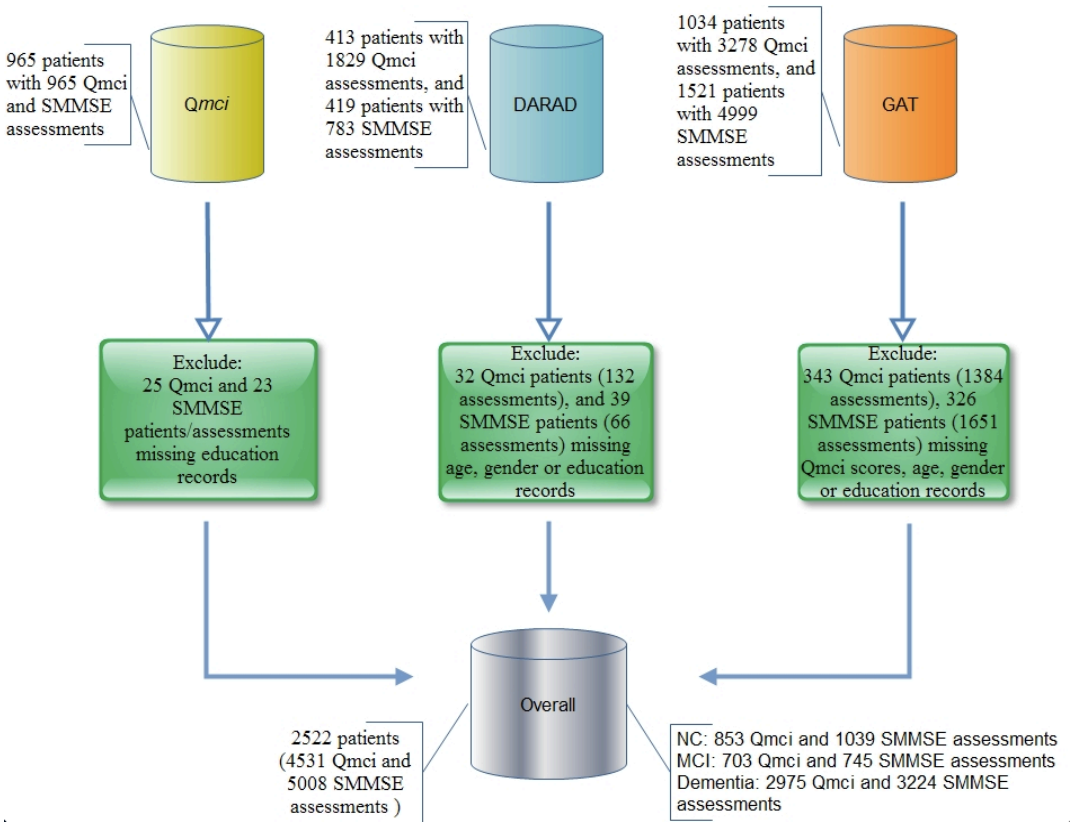
Participants

We pooled data from two outpatient databases: the GAT (Geriatric Assessment Tool) [Gao et al., 2013] and the Q*mci* validation databases [O'Caoimh et al., 2012], with the DARAD (Doxycycline And Rifampicin for Alzheimers Disease) [Molloy et al., 2012] clinical trial database. Participant characteristics and recruitment from all three studies have been published previously [O'Caoimh et al., 2012],[Gao et al., 2013],[Molloy et al 2012]. In summary, the GAT is a customised software application that automates clinicians' outpatient reviews [Gao et al., 2013]. GAT data were collected in outpatient geriatric and memory clinics in two university hospitals in Ontario, Canada between 1999 and 2010. The GAT contains over 8000 individual assessments from 1749 people aged 41–104 years including SMMSE and Q*mci* screen scores. The Q*mci* validation database, presented in Chapter 3 and 4, includes patients referred for assessment of cognition, aged ≥55 years and recruited from four memory clinics in Ontario Canada [O'Caoimh et al., 2012]. The DARAD was a multi-centre, blinded, randomised trial conducted between 2006 and 2010, comparing the effect of rifampicin and doxycycline to placebo on the progression of AD [Molloy et al., 2012]. The DARAD database includes patients ≥50 years with mild to moderate AD recruited from 14 Canadian centres.

Participants were included in this analysis if both their SMMSE and Q*mci* scores were available. Participant selection is presented in Figure 5.1. All data were collected under the supervision of the same principle investigator (Prof William Molloy) and each participant underwent similar comprehensive work-up including laboratory investigations, neuropsychological assessment and neuroimaging where appropriate [Gao et al., 2013],[Molloy et al., 2012]. MCI was diagnosed in patients

Peter presenting with subjective and objective memory loss, without loss of function. This was consistent with Petersen's criteria, described in section 2.1.2 (minor neurocognitive disorders), where patients present with subjective memory complaints, objective abnormal memory function but preservation of ADL and have no evidence of dementia [sen 1999]. Dementia was diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (4th-edition) [APA 1994]. Those with active depression screened using the GDS-Short Form [Yesavage 1988] were excluded. Participants were English literate. Persons attending with patients (mainly caregivers) without memory loss were recruited by convenience sampling were available as controls.

Figure 5.1. Flow chart demonstrating the recruitment of patients from the three databases: the Quick Mild Cognitive Impairment screen validation (Q*mci*), Doxycycline And Rifampicin for Alzheimers Disease (DARAD) study and Geriatric Assessment Tool (GAT), including the number of Q*mci* and Standardised Mini-Mental State Examination (SMMSE) assessments available, for participants with normal cognition (NC), mild cognitive impairment (MCI) and dementia (Kindly prepared by Dr Yang Gao).



Measures

The SMMSE and Q*mci* were common to all three databases. Alternative forms of its subtests were used to avoid learning effects [Cunje et al., 2007].

Analysis

Pooled data were grouped according to age (≤75 or >75 years) and education (≤12 or >12 years), to create four subgroups. An age cut-off of 75 years provided the best balance in numbers between the four subgroups and represents the accepted age cut-off for CI using the MMSE [Ylikoski et al., 1992], above which scores must be adjusted to account for age. The cut-off for education was 12 years, the average length of formal schooling in North America [http://hdr.undp.org/en/content/mean-years-schooling-adults-years]. Accuracy was calculated from the area under the curve (AUC) of receiver operating characteristic curves. Optimal cut-off scores were estimated using Youden's Index [Youden 1950]. Likelihood ratios for the probability of having MCI and dementia were determined. As described in Chapter 2, a PLR of between 2-5 suggests a small chance, 5-10 moderate and >10 a large chance of having cognitive impairment. A NLR of 0.2-0.5 suggests a small chance, 0.1-0.2 moderate and <0.1 a large chance of not having the condition. The Mann–Whitney *U* test compared non-parametric data and student's *t*-tests compared parametric data. The Kruskal-Wallis test was used for comparisons between two or more non-normally distributed groups.

5.3 Results

Characteristics

In all, 2,074 patients representing 3,387 assessments were included. The median age of all participants was 76 years, interquartile range (IQR) of +/-12. The median age of those with dementia was 78 (+/-8) years, older than those with normal cognition, 69 (+/-14) ($p<0.001$) or MCI, 76 (+/-10) ($p<0.001$). Half (49%) were male. The median number of years education was 12 (+/-5) for those with dementia compared with 13 (+/-4) ($p<0.001$) for controls and 12 (+/-4) ($p=0.46$) for those with MCI. The median SMMSE score for controls was 29 (+/-2) points, compared to 28 (+/-3) for MCI and 23 (+/-7) for dementia. The scores were significantly different in the three groups, $\chi^2(2) = 615$ ($p<0.001$). The median Q*mci* scores were 74 (+/-15) points for controls, 57 (+/-20) for MCI and 37 (+/-26) for dementia. Q*mci* scores were also significantly different in the three groups, $\chi^2(2) = 811$ ($p<0.001$). The number and characteristics of those included in each database is presented in Table 5.1. There was no statistically significant difference in age or gender between those with MCI or dementia. Median age, gender, education, SMMSE and Q*mci* screen scores, though similar, were significantly different between the three databases, irrespective of diagnosis. These comparisons are presented in Table 5.2. The characteristics of patients according to their age and educational level are presented in Table 5.3.

Table 5.1. Baseline characteristics of participants included from the Quick Mild Cognitive Impairment (Q*mci*) screen validation, Doxycycline And Rifampicin for Alzheimers Disease (DARAD) study and Geriatric Assessment Tool (GAT) databases, divided according to their Standardised Mini-Mental State Examination (SMMSE) and Q*mci* screen scores, including numbers included with normal cognition (NC), mild cognitive impairment (MCI) and dementia. (SD= Standard Deviation).

Database	**Diagnosis**	**Assessments (n=X)**	**Age Median +/-IQR (Q3-Q1)**	**Gender (% male)**	**Education** Median +/-IQR (Q3-Q1)	**SMMSE** Median +/-IQR (Q3-Q1)	**Q*mci*** Median +/-IQR (Q3-Q1)
DARAD	All (Dementia)	339	79 +/-9 (82-73)	49%	12 +/-4 (14-10)	21 +/-7 (24-17)	34 +/-22 (44-22)
GAT	NC	252	73 +/-14 (80-66)	49%	13 +/-5 (15-10)	29 +/-2 (30-28)	69 +/-18 (78-60)
	MCI	619	76 +/-9 (80-71)	53%	12 +/-4 (14-10)	28 +/-4 (29-25)	55 +/-22 (66-44)
	Dementia	1242	78 +/-8 (82-74)	53%	11 +/-4 (13-9)	23 +/-8 (26-18)	38 +/-26 (50-24)
	All	2113	77 +/-9 (81-72)	53%	12 +/-5 (14-9)	26 +/-8 (29-21)	47+/-29 (61-32)
Q*mci* (validation)	NC	623	67 +/-14 (74-60)	40%	13 +/-4 (16-12)	29 +/-2 (30-28)	76 +/-13.5 (82.5-69)
	MCI	147	75 +/-13.5 (80.5-67)	52%	12 +/-4.5 (14.5-10)	28 +/-2 (29-27)	62 +/-13.5 (67-53.5)
	Dementia	165	79 +/-8 (83-75)	46%	10 +/-3 (12-9)	22 +/-7 (25-18)	36 +/-22 (45-23)
	All	935	71 +/-15 (78-63)	43%	13 +/-6 (16-10)	29+/-3 (30-27)	70 +/-21.5 (79-57.5)
Total	NC	875	69 +/-14 (76-62)	43%	13 +/-4 (16-12)	29 +/-2 (30-28)	74 +/-15 (81-66)
	MCI	766	76 +/-10 (80-70)	53%	12 +/-4 (14-10)	28 +/-3 (29-26)	57 +/-20 (66-46)
	Dementia	1,746	78 +/-8 (82-74)	52%	12 +/-5 (14-9)	23 +/-8 (26-18)	37 +/-26 (49-23)
	All	3387	76 +/-12 (81-69)	49%	12 +/-5 (15-10)	26 +/-7 (29-22)	51 +/-33 (67-34)

Table 5.2. Comparison of participant characteristics: age, education, gender and Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment (Q*mci*) screen scores, according to diagnosis: normal controls, mild cognitive impairment (MCI) and dementia. (Non-parametric data compared using Mann Whitney- U test or Krushal Wallis H test; Chi-Square test comparing frequencies).

Diagnosis	**Age**	**Education**	**Gender**	**SMMSE**	**Q*mci***
Controls	Z=-7.8, p<0.001	Z=-2.5, p=0.01	$X^2(1)=5.9$, p=0.02	Z=-0.88, p<0.34	Z=-8.3, p<0.001
MCI	Z=-1.2, p=0.23	Z=-0.44, p=0.66	$X^2(1)=0.06$, p=0.8	Z=-3.7, p<0.001	Z=-4.5, p<0.001
Dementia	$X^2(2)=1.8$, P=0.39	$X^2(2)=21$, p<0.001	$X^2(2)=4.2$, p=0.12	$X^2(2)=37.2$, p<0.001	$X^2(2)=17.2$, p<0.001
Total	$X^2(2)=288$, p<0.001	$X^2(2)=81$, p<0.001	$X^2(2)=24$, p<0.001	$X^2(2)=615$, p<0.001	$X^2(2)=811$, p<0.001

Table 5.3. Descriptive statistics for patients with Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment (Q*mci*) scores available, comparing patients with normal controls (NC), mild cognitive impairment (MCI) and dementia, grouped according to age (≤75, >75 years) and education (<12, ≥12 years).

Subgroup (years)	**Diagnosis**	**SMMSE** (Number)	**Gender** (Male)	**Age Median** (IQR)	**Education Median** (IQR)	**SMMSE Median** (IQR)	**Q*mci*** (Number)	**Gender** (Male)	**Age Median** (IQR)	**Education Median** (IQR)	**Q*mci* Median** (IQR)
Overall	**NC**	157	50.3%	68 (7)	10 (1)	29 (2)	853	43.0%	69 (14)	13 (4)	75 (15)
	MCI	135	57%	71 (6)	9 (2)	28 (2)	703	56.2%	78 (10)	12 (4)	57 (20)
	Dementia	476	58.4%	72 (5)	9 (2)	21 (9)	2975	50.3%	79 (9)	12 (5)	37 (23)
Age ≤ 75 Edu < 12	**NC**	550	40%	65 (11)	15 (4)	30 (1)	133	51.9%	68 (7)	10 (1)	70 (15)
	MCI	188	51.1%	69 (10)	14 (4)	28.5 (3)	109	57.8%	71 (8)	9 (2)	57 (19)
	Dementia	571	53.9%	70 (9)	14 (4)	23 (8)	369	59.9%	72 (5)	9 (2)	32 (21)
Age ≤ 75 Edu ≥ 12	**NC**	114	52.6%	81 (8)	9 (2)	29 (2)	487	37.8%	64 (11)	15 (4)	78 (13)
	MCI	200	45.0%	81 (7)	9 (2)	28 (3)	159	50.9%	69 (12)	14 (4)	63 (20)
	Dementia	1134	44.6%	82 (5)	9 (2)	22 (7)	530	58.6%	70 (8)	14 (4)	38 (24)
Age > 75 Edu < 12	**NC**	218	48.2%	81 (8)	14 (4)	29 (2)	68	45.6%	79.5 (7)	9 (2)	67.5 (13)
	MCI	222	58.6%	81 (5)	14 (4)	29 (2)	197	58.4%	81 (7)	9 (2)	55 (21)
	Dementia	1043	49.5%	81 (6)	13 (4)	23 (6)	969	45.6%	82 (5)	9 (2)	37 (22)
Age > 75 Edu ≥ 12	**NC**	1039	44.7%	70 (15)	13 (5)	29 (1)	165	50.3%	81 (6)	14 (5)	70 (15)
	MCI	745	52.8%	77 (11)	12 (5)	28 (2)	238	57.1%	81 (5)	14 (3)	56 (20)
	Dementia	3224	49.9%	79 (9)	12 (5)	22 (7)	1107	47.2%	81 (6)	13 (4)	38 (22)

Effects of age and education on median scores

Table 5.4 presents the results of comparisons between median SMMSE and Q*mci* scores, where age was constant and education varied and vice versa, for controls, MCI and dementia. This table shows that median SMMSE scores were similar between these subgroups classified by age or education, although some statistical differences were seen. Age influenced median Q*mci* scores for patients with more compared to those with less education, for controls (78 versus 70 points, p <0.001) and MCI (63 versus 56 points, p <0.001), but not dementia, (38 versus 38 points, p =0.884).

Table 5.4. Comparisons between median and interquartile range (IQR) scores for the Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment (Q*mci*) screen, where age (≤75, >75 years) was constant and education (<12, ≥12 years) varied and vice versa of patients with normal cognition (NC), mild cognitive impairment (MCI) and dementia.

Age (years)	**Education** (years)	**Diagnosis**	**SMMSE score** Median (IQR)	**p-value**	**Q*mci* score** Median (IQR)	**p-value**
≤75	≥12 vs <12	NC	29 (2) vs 30 (1)	<0.001	78 (13) vs 70 (15)	0.001
		MCI	28 (2) vs 28.5 (3)	0.002	63 (20) vs 57 (19)	0.001
		Dementia	21 (9) vs 23 (8)	<0.001	38 (24) vs 32 (21)	0.001
>75	≥12 vs <12	NC	29 (2) vs 29 (2)	0.004	70 (15) vs 67.5 (13)	0.11
		MCI	28 (3) vs 29 (2)	<0.001	56 (20) vs 55 (21)	0.11
		Dementia	22 (7) vs 23 (6)	<0.001	38 (22) vs 37 (22)	0.08
≤75 vs >75	<12	NC	29 (2) vs 29 (2)	<0.001	70 (15) vs 67.5 (13)	0.05
		MCI	28 (2) vs 28 (3)	0.621	57 (19) vs 55 (21)	0.30
		Dementia	21 (9) vs 22 (7)	0.312	32 (21) vs 37 (22)	0.002
≤75 vs >75	≥12	NC	30 (1) vs 29 (2)	0.405	78 (13) vs 70 (15)	0.001
		MCI	28.5 (3) vs 29 (2)	0.252	63 (20) vs 56 (20)	0.001
		Dementia	23 (8) vs 22 (7)	0.008	38 (24) vs 38 (22)	0.884

For subjects with less education differences in median Q*mci* scores between older and younger patients were only significant for dementia, 32 (21) vs 37 (22) points, p =0.002. Contrasting this, for those with more education, Q*mci* score differences between older and younger patients were only significant for controls and MCI, but not for dementia, 38 (24) vs 38 (22) points, p =0.884. Education affected median Q*mci* score for older patients but there were no significant differences in median Q*mci* scores between more and less educated individuals whereas scores were significantly different for younger patients irrespective of the diagnosis. There were statistically significant differences between median SMMSE scores for controls, MCI and dementia, irrespective of age.

Cut-off scores for the SMMSE

The cut-off scores that provided the best balance between sensitivity and specificity for the SMMSE are presented in Table 5.5. A cut-off of <28 for cognitive impairment (MCI or dementia) produced a sensitivity of 90% and specificity of 81%, and yielded an AUC of 0.91, (95% CI: 0.90-0.92). The optimal cut-off for MCI was higher at <29, with a lower sensitivity of 75% and specificity of 56%, AUC 0.69 (0.67-0.72). The optimal cut-off for dementia was <27, sensitivity 89%, specificity 86% with an AUC of 0.94 (0.93-0.94). The SMMSE more accurately identified cognitive impairment for older adults (>75 years) with less formal education (<12 years), sensitivity 90% and specificity of 81% (AUC 0.91, 95% CI: 0.89-0.93), than for younger patients (≤75) with more education (≥12), sensitivity 84%, specificity 83%, although this did not reach significance, p =0.43. This preferential accuracy for older and less educated patients was reversed for those with established dementia: sensitivity 82%, specificity 82% (AUC of 0.89, 95% CI: 0.87-0.92) compared with a sensitivity of 90% and

specificity of 90%, AUC 0.95 95% CI: 0.93-0.95) for younger patients with more education, p<0.001. The SMMSE was also more accurate for younger patients with more education in differentiating MCI from normal cognition. These results are summarised in Table 5.5 and presented in Figure 5.2. Few clinically meaningful differences in SMMSE cut-offs were found. There was only a one-point difference between normal cognition and dementia SMMSE cut-offs for younger patients with more education (<29 to <28), and a one-point difference for older subjects with less education (<27 to <26).

Cut-off scores for the Q*mci*

The Q*mci* cut-off scores selected using the maximal approach (AUC of ROC) were <60 for cognitive impairment, <65 for MCI and <50 for dementia (see Table 5.5). At a cut-off of <60 the Q*mci* had a sensitivity of 89% and specificity of 86% for cognitive impairment and excellent accuracy in differentiating normal cognition from MCI and dementia, AUC 0.95 (0.94-0.95). This was selected using the AUC of the ROC curve. However, using Youden's index the optimal cut-off was calculated at <62. This provided a sensitivity of 87% and specificity of 88% (AUC 0.94), see Figure 5.2.

At <65 the Q*mci* produced a sensitivity of 81% and specificity of 70% for distinguishing MCI from normal cognition, AUC 0.84 (0.82-0.86). A score <50 yielded a sensitivity of 84% and specificity of 79% for dementia, AUC of 0.89 (0.88-0.90). The cut-off for dementia using Youden's index was also <50. For older adults with less education the optimal Q*mci* cut-off for cognitive impairment fell from <60 (for the total population) to <54 points, providing a sensitivity of 81% and specificity of 85%. In contrast to the SMMSE, the Q*mci*'s sensitivity (86%) and specificity (89%)

for cognitive impairment was higher for younger patients with more education, AUC of 0.95 (0.94-0.96) at a cut-off of <67 and lower for older patients with less formal education, 81% and 85% respectively at a cut-off of <54, AUC of 0.89 (0.85-0.94), p <0.001. The accuracy of the Q*mci* for detecting MCI was lower for older adults with less education (AUC 0.76; 0.69-0.83) compared with younger patients with more education (AUC 0.85; 0.81-0.88), p <0.001. The Q*mci* also had lower accuracy for detecting dementia for older adults with less education, AUC of 0.81 (0.78-0.84) with a cut-off of <42, compared with younger more educated adults, AUC of 0.95 (0.94-0.96) using a cut-off of <53, p <0.001. These results are summarised in Table 5.5 and presented in Figures 5.2 and 5.3. There were more clinically useful differences in cut-offs between patients with normal cognition and dementia for the Q*mci* compared with the SMMSE. Overall, the range of cut-off scores were narrow for both instruments. This mirrors the results other screening cognitive instruments including the MoCA, which have a similarly narrow range between diagnostic categories and reflects the challenges of using cut-off scores in isolation from clinical evaluation. Cut-offs, were however wider for younger subjects with more education, (range from <67 to <53), a 14-point spread and narrower for older subjects with less education, (range from <54 to <42), (12-point).

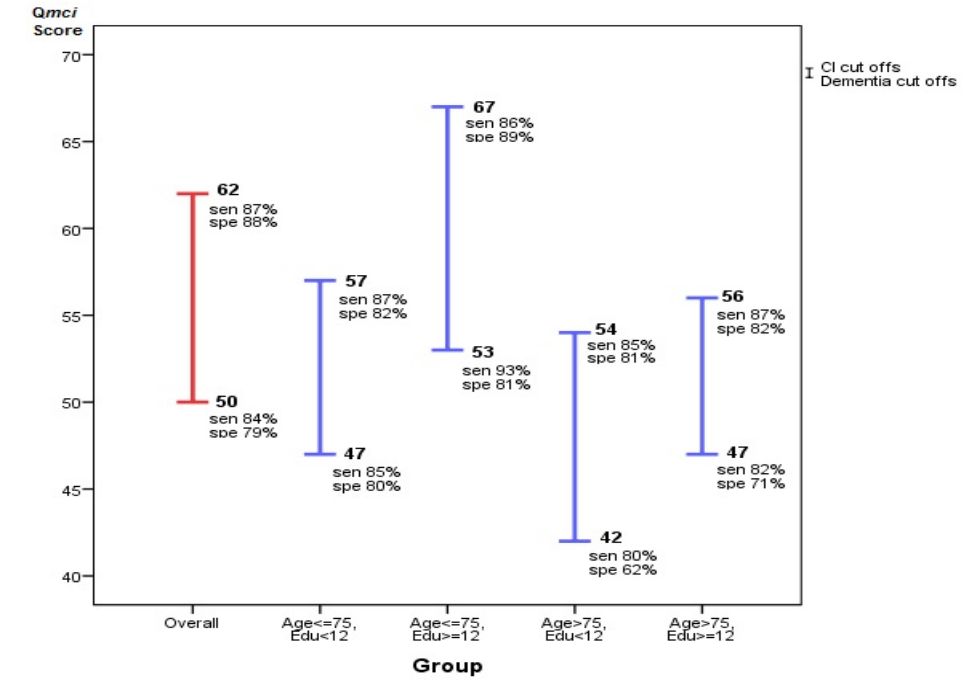
Table 5.5. Cut-off scores* for the Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment (Q*mci*) screen with sensitivity, specificity and area under the curve (AUC) values, grouped by age (≤75, >75 years) and education (<12, ≥12 years), comparing patients with normal controls (NC) to those with cognitive impairment (CI), those with dementia compared to the rest, those with NC versus mild cognitive impairment (MCI) and those with MCI versus dementia. (*cut-off scores selected using the AUC).

Subgroup (Years)	**SMMSE** (n=X vs X)	**Optimal SMMSE Cut-off**	**Sensitivity**	**Specificity**	**AUC** (95% Confidence Interval)	**Q*mci*** (n=X vs X)	**Optimal Q*mci* Cut-off**	**Sensitivity**	**Specificity**	**AUC** (95% Confidence Interval)
Overall	**NC vs CI** (1039 vs 3969)	<28	90%	81%	0.91 (0.90-0.92)	**NC vs CI** (853 vs 3678)	<60	89%	86%	0.95 (0.94-0.95)
	MCI (1039 vs 745)	<29	75%	56%	0.69 (0.67-0.72)	**MCI** (853 vs 703)	<65	81%	70%	0.84 (0.82-0.86)
	MCI vs Dementia (745 vs 3224)	<27	81%	86%	0.90 (0.89-0.91)	**MCI vs Dementia** (703 vs 2975)	<44	80%	66%	0.80 (0.78-0.82)
	Dementia (3224vs 1784)	<27	89%	86%	0.94 (0.93-0.94)	**Dementia** (2975 vs 1556)	<50	84%	79%	0.89 (0.88-0.90)
Age ≤ 75 Edu < 12	**NC vs CI** (157 vs 611)	<28	80%	81%	0.89 (0.86-0.91)	**NC vs CI** (133 vs 478)	<57	87%	82%	0.93 (0.91-0.95)
	MCI (157 vs 135)	<29	65%	63%	0.66 (0.60-0.72)	**MCI** (133 vs 109)	<62	80%	62%	0.80 (0.74-0.85)
	MCI vs Dementia (135 vs 476)	<26	89%	79%	0.91 (0.88-0.93)	**MCI vs Dementia** (109 vs 369)	<45	78%	76%	0.82 (0.78-0.87)
	Dementia (476 vs 292)	<27	84%	87%	0.93 (0.91-0.95)	**Dementia** (369 vs 242)	<47	85%	80%	0.90 (0.88-0.93)
Age ≤ 75 Edu ≥ 12	**NC vs CI** (550 vs 759)	<29	84%	83%	0.90 (0.88-0.92)	**NC vs CI** (487 vs 689)	<67	86%	89%	0.95 (0.94-0.96)
	Dementia (571 vs 738)	<28	90%	90%	0.95 (0.93-0.96)	**Dementia** (530 vs 646)	<53	93%	81%	0.95 (0.94-0.96)
	MCI (550 vs 188)	<29	84%	50%	0.71 (0.66-0.75)	**MCI** (487 vs 159)	<69	83%	69%	0.85 (0.81-0.88)
	MCI vs Dementia (188 vs 571)	<27	87%	83%	0.90 (0.88-0.93)	**MCI vs Dementia** (159 vs 530)	<50	79%	75%	0.85 (0.81-0.88)

Age > 75 Edu < 12	**NC vs CI** (114 vs 1334)	<27	90%	81%	0.91 (0.89-0.93)	**NC vs CI** (68 vs 1166)	<54	81%	85%	0.89 (0.85-0.94)
	Dementia (1134 vs 314)	<26	85%	82%	0.89 (0.87-0.92)	**Dementia** (969 vs 265)	<42	80%	62%	0.81 (0.78-0.84)
	MCI (114 vs 200)	<28	79%	41%	0.67 (0.60-0.73)	**MCI** (68 vs 197)	<64	69%	77%	0.76 (0.69-0.83)
	MCI vs Dementia (200 vs 1134)	<25	84%	73%	0.86 (0.83-0.89)	**MCI vs Dementia** (197 vs 969)	<45	73%	70%	0.77 (0.73-0.81)
Age > 75 Edu ≥ 12	**NC vs CI** (218 vs 1265)	<28	87%	79%	0.89 (0.87-0.91)	**NC vs CI** (165 vs 1345)	<56	87%	81%	0.91 (0.89-0.93)
	Dementia (1043 vs 440)	<27	91%	84%	0.94 (0.92-0.95)	**Dementia** (1107 vs 403)	<47	82%	71%	0.85 (0.83-0.88)
	MCI (218 vs 222)	<29	70%	48%	0.62 (0.57-0.67)	**MCI** (165 vs 238)	<59	80%	55%	0.77 (0.73-0.82)
	MCI vs Dementia (222 vs 1043)	<27	90%	84%	0.92 (0.91-0.94)	**MCI vs Dementia** (238 vs 1107)	<45	78%	66%	0.79 (0.76-0.82)

Figure 5.2. The distribution of a. the Quick Mild Cognitive Impairment screen (Q*mci*) and b. the Standardised Mini-Mental State Examination (SMMSE) cut-off scores (using Youden's Index), together with sensitivity and specificity levels for controls versus cognitive impairment (CI) and dementia, for the total sample and four subgroups, stratified according to age (≤75 or >75 years) and education (≤12 or >12 years).

a.



b.

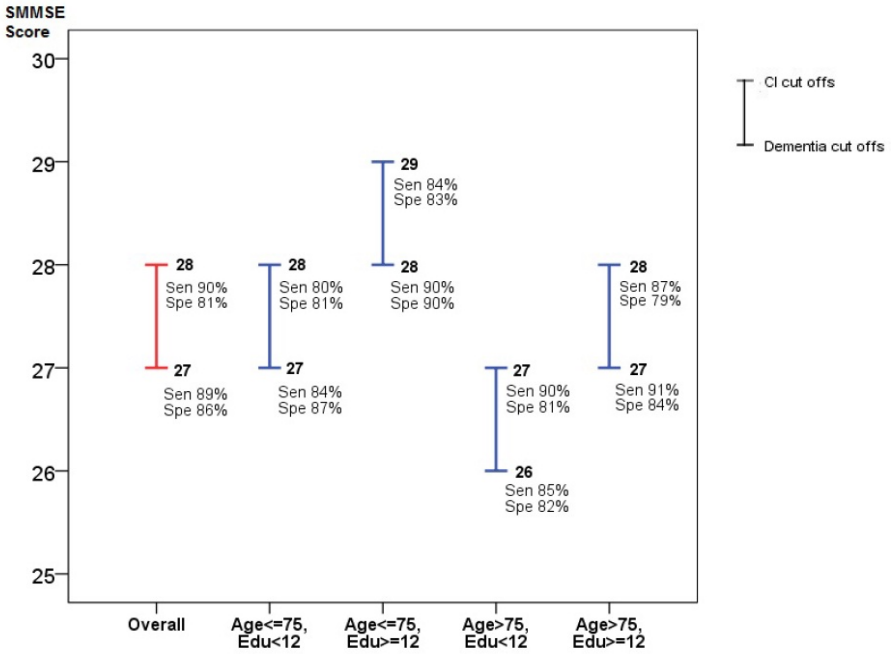
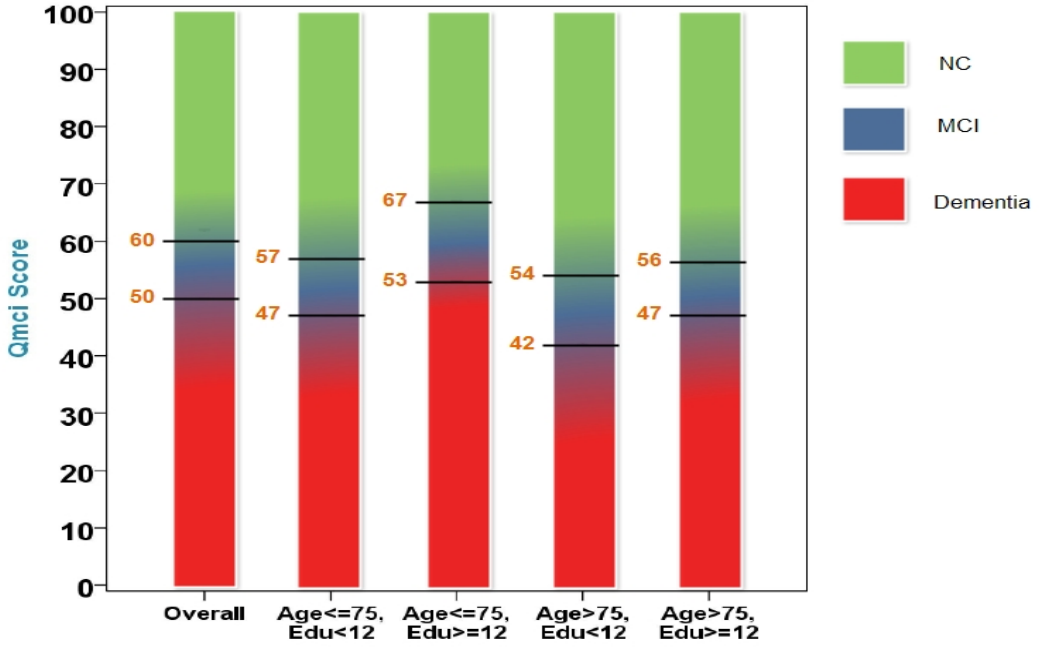


Figure 5.3. Age and educational cut-off scores for the Quick Mild Cognitive Impairment (Q*mci*) screen.



Likelihood ratios

Likelihood ratios were calculated for several cut-off scores for the total population and according to age and education. At the optimal Q*mci* cut-off for CI (<60), patients had a moderate chance of having cognitive impairment (NLR 0.17). Above 60 points, there was a moderate chance of having normal cognition (PLR 7.88). Above 65 points there was a 'large' chance (PLR >10) of being normal whereas at or below 65 the chance of having normal cognition was small (NLR 0.23). Those scoring <50, the optimal Q*mci* cut-off score for dementia, had a moderate chance of having dementia (PLR 5.0) while at a score >50 there was a small chance of having dementia (NLR 0.28). Liklihood ratios also confirmed the choice of cut-off scores for each subgroup. For example, the cut-off above which younger subjects (≤75) with more formal education (≥12) had a large chance of being normal was <70. Below 70, the chance of not being normal was also small, confirming that the optimal Q*mci* cut-off for these patients (≤67) lies below this.

5.4 Discussion

This paper presents cut-off scores for two short cognitive screens, the SMMSE and Q*mci*, adjusted for age and education, based upon a large population of patients in three pooled databases. The results showed small albeit significant, differences in median SMMSE and large and significant differences in median Q*mci* scores, which clearly separated normal cognition, MCI and dementia. Twenty years after Crum et als' [Crum et al., 2013] work exploring population-based norms for the MMSE by age and education, this paper presents adjusted cut-off scores for the SMMSE for a large sample of patients with symptomatic memory loss. It is also the first to compare the differential effects of age and education on two short cognitive screens, one designed specifically to screen for MCI (Q*mci*).

Using Youdens Index, a cut-off score for cognitive impairment (i.e. either MCI or dementia) of <28 for the SMMSE and <62 for the Q*mci* provided the best balance between sensitivity and specificity. At these cut-offs, the SMMSE had a sensitivity of 90% and specificity of 81%, while the Q*mci* had an 87% sensitivity and 88% specificity. At a cut-off score of <27 the SMMSE had a sensitivity of 89% and specificity of 86% for dementia while at <50 the Q*mci* had a sensitivity of 84% and specificity of 80%. For MCI, a higher cut-off of <65 was found for the Q*mci* (sensitivity 81%, specificity 70%), but the SMMSE cut-off remained similar at <29 but provided lower sensitivity (75%) and specificity (56%).

In this study, both age and education affected the cut-off scores for all cognitive categories. Differences were more marked between younger patients with more education and older patients with less education. For younger adults with more education, the best performing SMMSE cut-off for cognitive impairment was <29, compared to <67 for the Q*mci*. For older adults with the less education this dropped to

<27 for the SMMSE and <54 for the Q*mci*, a difference of two and 13 points respectively, suggesting that the Q*mci* cut-offs may be more clinically useful. The discriminating ability of the Q*mci* to detect cognitive impairment was lower in older adults with less time in formal education (AUC 0.89) and higher in younger adults with more education (AUC 0.95). There was no difference in accuracy for the SMMSE AUC 0.91 and 0.90 respectively) suggesting that it is less responsive to the effects of age and education than the Q*mci*. Cut-off scores for dementia were less affected by age and education.

For younger adults with more education, the best performing cut-offs for dementia were <28 for the SMMSE and <53 for the Q*mci*, compared to <26 and <42, respectively for those older with less education. Only median differences in Q*mci* scores for MCI, between younger adults with more education and older adults with less education, were sufficient to change diagnosis, (63 versus 55). No median differences in SMMSE scores were sufficient to change diagnosis irrespective of age or education. Individuals with more education required Q*mci* cut-off score adjustment for age when they presented with normal cognition and MCI, but not dementia. Participants with less education only required age-adjustment when they developed dementia. Therefore, age is an important factor to consider in people with more education and only becomes relevant for those with less education when they present with dementia, suggesting a "falling off the cliff" phenomenon. These results also suggest that only symptomatic younger adults should have their cut-off scores adjusted for education, irrespective of their stage at presentation. Although statistical differences between median SMMSE scores were seen, values were similar irrespective of age or education.

Irrespective of age and education, all but one of the SMMSE cut-offs for patients with symptomatic memory loss presented here, were above the recommended cut-off of <25 [Molloy et al., 1997], suggesting that any failure to fully complete the test should prompt more detailed assessment. As expected, the Q*mci* was more accurate than the SMMSE in distinguishing MCI from normal cognition. This supports the results of the Q*mci* validation study presented in Chapter 3 [O'Caoimh et al., 2012]. The Q*mci* was more accurate for differentiating MCI, irrespective of age or education, supporting evidence that screening tests designed to identify MCI should be used in preference to the SMMSE when subtle cognitive changes are suspected. Based upon these results, the Q*mci* compares favourably with other short cognitive screens, including the MoCA, which has a similar sensitivity of 90% [Nasreddine et al 2005] but similar or lower specificity of between 35% [Luis et al 2008] and 87% [Nasreddine et al., 2005] for CI, at its recommended cut-off of <26. Given that the Q*mci* is shorter (median 4.24 [O'Caoimh et al., 2013] compared to 10-12 minutes [Nasreddine et al., 2005]), it may be a more useful instrument in those presenting to memory clinics where time is at a premium. The results of this study suggest that the Q*mci* is particularly useful for differentiating MCI from normal cognition in older adults. The results also support evidence that while education may protect against the development of cognitive impairment [Mortimer & Graves, 1993],[Ott et al., 1995],[Stern et al., 1994], once developed, it does not protect against a fall in cognitive scores towards the level of those with less education. Indeed, patients with more education may also experience a greater decline in cognitive scores, relative to those with less education, as they age. This supports previous research suggesting that some cognitive domains decline irrespective of baseline education [Leibovici et al., 1996].

Strengths and weaknesses

Strengths of this study include the inclusion of a large sample of patients presenting with memory loss in a clinic setting, allowing analysis of subgroups according to age and education. Another strength is that cut-offs were confirmed as clinically meaningful using likelihood ratios. The study includes patients with different dementia subtypes, all of whom underwent comprehensive assessments using standardised diagnostic criteria, across multiple sites. This paper has a number of limitations. This study included pooled data from three sources, a clinical trial and two outpatient databases, potentially resulting in spectrum bias. The findings are drawn from a single country, potentiallt reducing the generalisability of results. However, Canada is an ethnically diverse country with similar demographics to many other industrialised nations and data were drawn from multiple clinics spread over a large geographic area. The age and educational level cut-offs chosen could also limit the external validity of these results. Although 12 years is the average number of years of education for older adults in North America, this figure is lower in other countries. Another potential limitation is that the SMMSE was used as an inclusion criteria for patients entering the DARAD trial.

Conclusions

In summary, this study provides usable cut-off scores for the SMMSE and Q*mci* and illustrates the effects of age and education on cut-off scores for patients presenting with symptomatic memory loss. The results suggest that the SMMSE may be less sensitive to these effects than the Q*mci*, likely reflecting the poor discriminating power of the SMMSE. This study also suggests that educational levels are less important in older adults. Thus, this study suggests that while SMMSE

population norms, in unselected community dwellers, require adjustment for age and education [Crum et al., 1993], smaller adjustments are required for older adults who present with symptomatic memory loss. The type of test selected also determines the extent to which adjustments in age and education are required. Based upon this analysis, the authors recommend overall SMMSE cut-offs of <28 for cognitive impairment, <29 for MCI and <27 for dementia. The recommended Q*mci* cut-offs are <60, <65 and <50 respectively.

From the clinicians perspective this study shows the importance of selecting the appropriate instrument in the appropriate context. In busy clinics the instrument chosen should reflect the pre-test probability so as to avoid unnecessary delays and inconvenience to the patient. Where mild deficits such as MCI are expected e.g. in younger, functionally independent patients screens such as the Q*mci* should be used in preference to the SMMSE. Once the appropriate instrument is selected, age and education should be further considered to provide context. It must be remembered however, that although cut-offs are useful in clinical practice and the effects of age and education are important, they should act only as a guide and not replace clinical judgment [Cullen et al., 2007]. Further study is required to confirm these findings in different cultural groups and with different cognitive tests.

Chapter 6

Performance of the Q*mci* Screen and its Subtests in Different Dementia Subtypes, MCI and Depression

6.1 Introduction

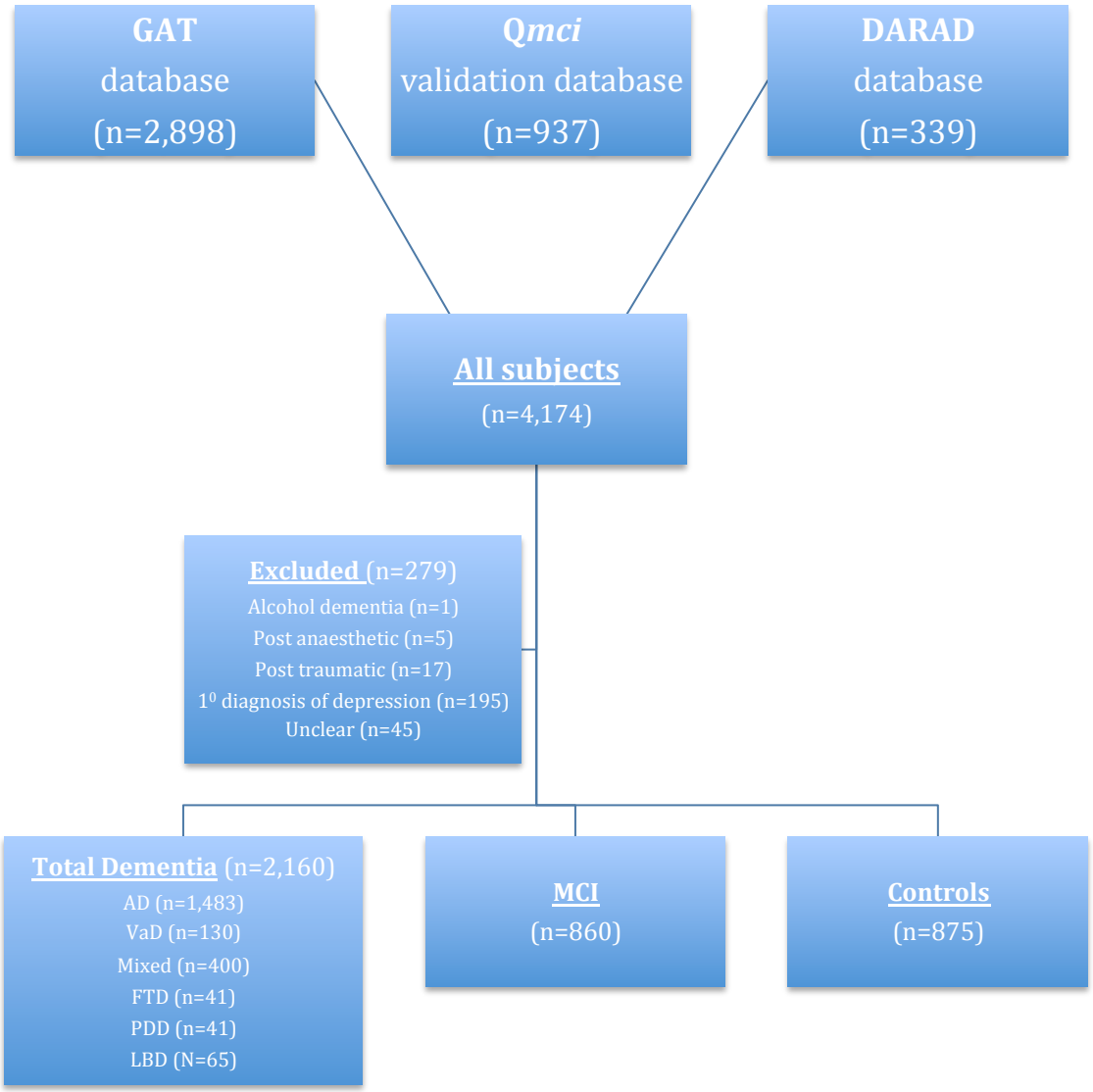
Although short cognitive screening instruments such as the MMSE are widely used in clinical practice and research studies, their accuracy and hence suitability for use in different dementia subtypes is poorly characterised [Woodford 2007]. Given that the MMSE and the Standardised MMSE contain a limited number of cognitive domains, their use in particular dementia subtypes, and in MCI is unclear. Both lack a subtest measuring executive function, something that screens such as the Q*mci* and MoCA include. The pentagon task may lack accuracy in post-stroke, frontotemporal and subcortical dementias [Bak et al.,2005]. Although evidence suggests that depression in MCI is associated with disease progression, the effects of depression on scoring cognitive screening is poorly characterised [Van der Mussle et al., 2014]. The extent to which depression affects the results of cognitive screening instruments is poorly understood and it is not known the extent to which different dementia subtype scores are influenced by the presence of comorbid depression.

The objective of this study is to explore the performance (accuracy) of the Q*mci* and SMMSE in different dementia subtypes, to reaffirm the superior accuracy of Q*mci* over the SMMSE in a large, pooled sample of patients and to examine the subtests of the Q*mci* and their accuracy in different dementia subtypes, MCI and patients with depression.

6.2 Methods

This study compared the SMMSE and the Q*mci* screen in patients (n=3,020) pooled from three memory clinic databases in Canada including those with MCI (predominantly aMCI), AD, VaD, FTD, LBD and PDD, with and without a history of comorbid depression. Patients without cognitive impairment and with depression as the primary symptom were excluded. Caregivers (n=875), without cognitive symptoms, were included as normal controls. Data from the three data sets (original Q*mci*, GAT and DARAD) were pooled and analysed using simple descriptive statistics, ROC curve analysis and the Mann-Whitney U test. Only those with both a Q*mci* and SMMSE scores at the same visit were included. Comparisons between participant characteristics in each database are presented in Chapter 5. Available participants are presented in Figure 6.1

Figure 6.1 Flow chart presenting the recruitment of participants pooled from three data sets: The Geriatric Assessment Tool (GAT), Quick Mild Cognitive Impairment (Qmci) screen and Doxycycline and Rifampicin for Alzheimer's Disease (DARAD) trial databases; it includes the number of controls, those with mild cognitive impairment (MCI) and specific dementia subtypes: Alzheimer's disease (AD), Vascular dementia (VaD), Mixed dementia, Frontotemporal dementia (FTD), Parkinson's disease dementia (PDD) and Lewy Body dementia (LBD) subtypes.



6.3 Results

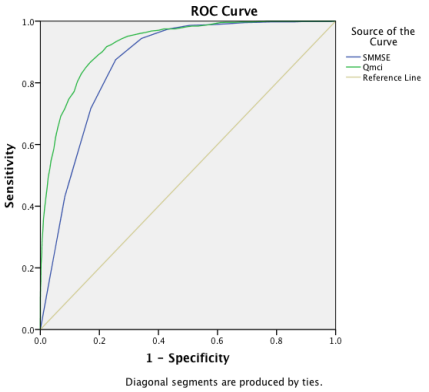
The median age of patients was 77 years (Interquartile = +/-9), controls 69 (+/14). Median SMMSE scores were 23/30 (+/-8) for dementia, 28/30 (+/-4) for MCI and 29/30 (+/-2) for controls. Median Q*mci* scores were 38/100 (+/-26) for dementia, 56/100 (+/-20) for MCI and 74/100 (+/-15) for controls. Differences in gender were seen between diagnosis with the percentage of males ranging from as high as 73% in those with VaD to as low as 41% in those with dementia and comorbid depression. Both instruments accurately differentiated cognitive impairment from normal. The SMMSE most accurately differentiated AD (AUC 0.94) and LBD (AUC 0.94) and least accurately identified MCI (AUC 0.73), VaD (AUC 0.74) and PDD (AUC 0.81). Characteristics of participants are presented in Table 6.1. The Q*mci* had statistically similar or greater accuracy in distinguishing all dementia subtypes but particularly MCI (AUC 0.85). ROC curves demonstrating the accuracy of both instruments in each type of dementia, in MCI and in those with and without depression are presented in Figure 6.2. Comorbid depression did not affect the accuracy of either instrument for dementia but improved accuracy in those with MCI. Comparison of median scores for MCI with and without depression showed that scores were significantly different for both the Q*mci*, 51.5 and 57 respectively ($z=-2927$, $p=0.003$) and SMMSE 26 and 28 respectively, ($z=-3302$, $p=0.001$). There were no statistically significant differences in age, education or gender between MCI patients with and without a history of comorbid depression and in fact patients without depression were older (median 76 years compared to a median of 73 years of age for those with comorbid depression). Similarly, significant differences were found between median scores for dementia alone (excluding MCI), with (n=2,160) and without (n=1879) depression, for the Q*mci* ($z=-4.771$, $p<0.001$) and the SMMSE ($z=-5.627$, $p<0.001$).

Table 6.1. Characteristics of participants from the Quick Mild Cognitive Impairment (Q*mci*) screen validation, Doxycycline And Rifampicin for Alzheimer's Disease study and Geriatric Assessment Tool databases, divided according to diagnosis: depression, controls, mild cognitive impairment (MCI) and dementia (AD= Alzheimer's disease, VaD= Vascular dementia, FTD= Frontotemporal dementia, PDD= Parkinson's dementia, LBD= Lewy Body dementia), including their Standardised Mini-Mental State Examination (SMMSE) and Q*mci* screen scores; comparison of SMMSE and Q*mci* score accuracy in differentiating each diagnosis from controls.

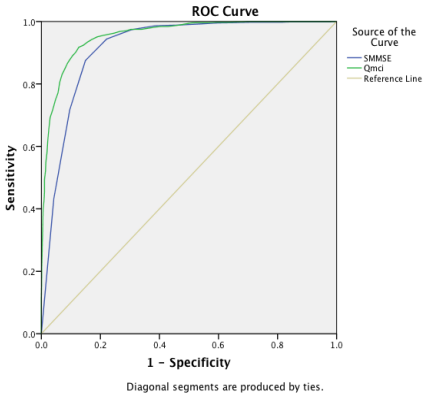
Diagnosis	**Number** (n=x)	**Age** (Median & IQR)	**Education** (Median & IQR)	**Gender** (% male)	**SMMSE** (Median & IQR)	**Q*mci*** (Median & IQR)	**SMMSE** AUC NC v CI (95% confidence intervals)	**Q*mci*** AUC NC v CI (95% confidence intervals)	**p=x**
Total (All subtypes **including** comorbid depression & MCI)	3,020	77 (81-72=9)	12 (14-9=5)	1537/2997* (51%)	25 (28-20=8)	43 (56-29=27)	0.87 (0.85-0.88)	0.93 (0.92-0.94)	**
Dementia (All subtypes **including** comorbid depression)	2,160	77 (82-73=9)	12 (14-9=5)	1087/2145* (51%)	23 (26-18=8)	38 (50-24=26)	0.92 (0.91-0.93)	0.96 (0.95-0.96)	**
Dementia (All subtypes **excluding** comorbid depression)	1,879	78 (82-74=8)	11 (14-9=5)	971/1864* (52%)	23 (26-18=8)	37 (49-24=25)	0.92 (0.91-0.93)	0.96 (0.95-0.97)	**
AD	1,483	78 (83-74=9)	12 (14-9=5)	651/1475* (44%)	23 (25.5-18=7.5)	37 (48-23=25)	0.94 (0.93-0.95)	0.97 (0.96-0.97)	**
VaD	130	74 (79-69=10)	12 (14-10=4)	95 (73%)	27 (29-25=4)	53 (64-40=24)	0.74 (0.68-0.69)	0.87 (0.84-0.91)	**
Mixed (AD/VaD)	400	77 (81-74=7)	11 (13-9=4)	256/393* (65%)	22 (27-19=8)	35.5 (51-23=28)	0.91 (0.89-0.93)	0.95 (0.94-0.96)	**
AD, VaD & Mixed	2,013	78 (82-74=4)	12 (14-9=5)	1002/1998* (50%)	23 (26-18=8)	38 (50-24=26)	0.92 (0.91-0.93)	0.96 (0.95-0.97)	**
FTD	41	69 (71-62=9)	12 (14-10=4)	25/41 (61%)	23 (27-19=8)	42 (52-28=24)	0.90 (0.85-0.96)	0.96 (0.94-0.98)	
PDD	41	75 (77-71=6)	12 (12-9.5=2.5)	28/41 (68%)	26 (29-21=8)	46 (61-32=29)	0.81 (0.72-0.90)	0.92 (0.88-0.95)	
LBD	65	78 (82-73=9)	10 (14-8=6)	32/65 (49%)	24 (27-18=9)	37 (54-24=30)	0.94 (0.92-0.97)	0.94 (0.91-0.97)	
MCI	860	75 (80-70=10)	12 (14-10=4)	450/852* (53%)	28 (29-25=4)	56 (66-46=20)	0.73 (0.71-0.75)	0.85 (0.83-0.87)	**
Comorbid depression (Dementia not MCI)	281	75 (81-70=11)	12 (14-10=4)	116/281 (41%)	25 (27-21=6)	44 (56-30=26)	0.88 (0.86-0.91)	0.93 (0.91-0.95)	**
MCI with comorbid depression	94	73 (75-68=7)	12 (14-9=5)	50/92* (54%)	26 (29-23=6)	51.5 (62-40=22)	0.79 (0.73-0.85)	0.90 (0.86-0.93)	**
MCI without comorbid depression	766	76 (80-70=10)	12 (14-10=4)	400/760* (53%)	28 (29-26=3)	57 (66-46=20)	0.72 (0.70-0.75)	0.84 (0.82-0.86)	**
Controls	875	70 (76-62=14)	13 (16-12=4)	372/875 (43%)	29 (30-28=2)	74 (81-66=15)	NA	NA	NA

NC = Normal Controls
CI = Cognitive Impairment
IQR = Interquartile Range
AUC = Area Under the Curve
NA = Not applicable
*Missing data
**Significantly different, $p<0.05$

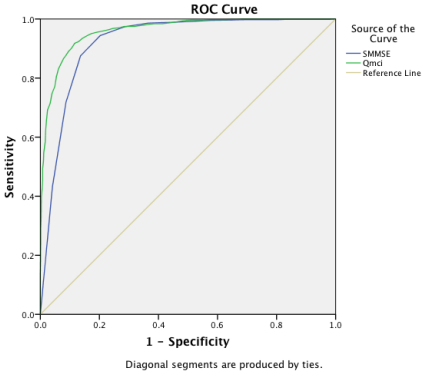
Figure 6.2. Receiver operating characteristic curves (a-l) comparing the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen and Standardised Mini-Mental State Examination in differentiating normal controls (n=875) from those with mild cognitive impairment (MCI), different dementia subtypes and comorbid depression for participants included within the Q*mci* screen validation, Doxycycline And Rifampicin for Alzheimer's Disease study and Geriatric Assessment Tool databases.



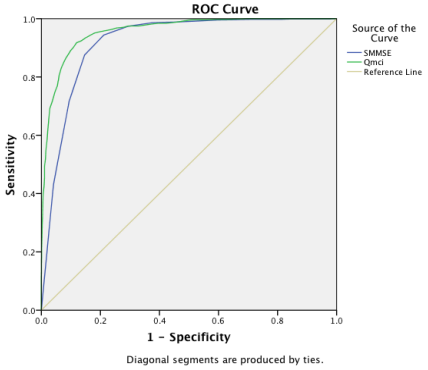
a. All patients (n=3020)



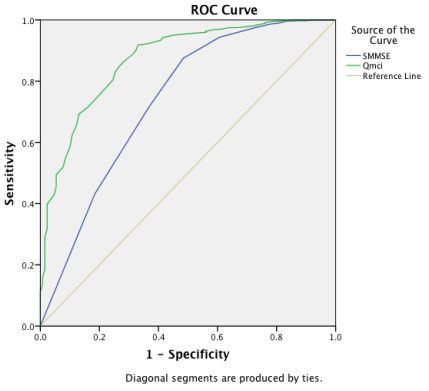
b. All patients with dementia (n=2,160)



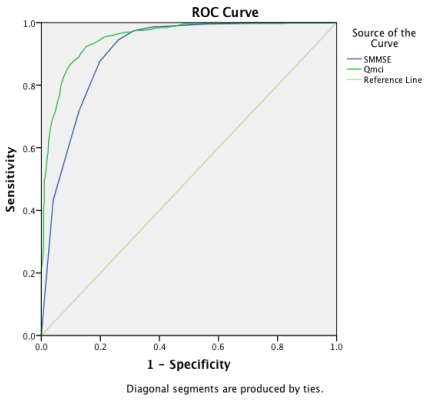
c. Dementia excluding depression (n=1,879)



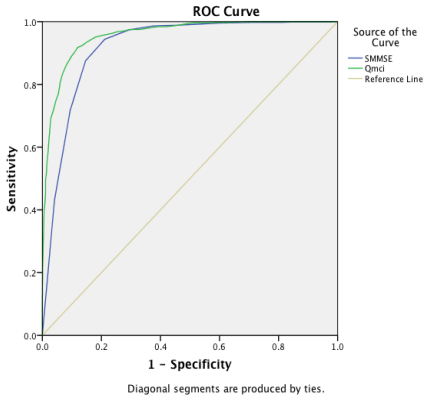
d. Alzheimer's dementia (n=1,483)



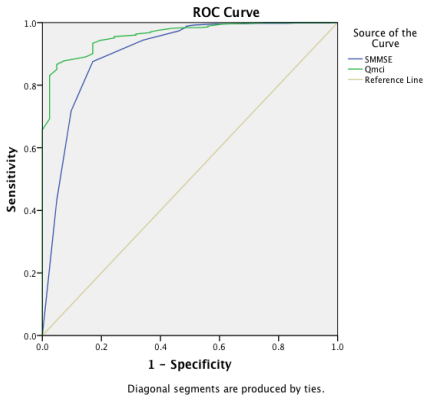
e. Vascular dementia (n=130)



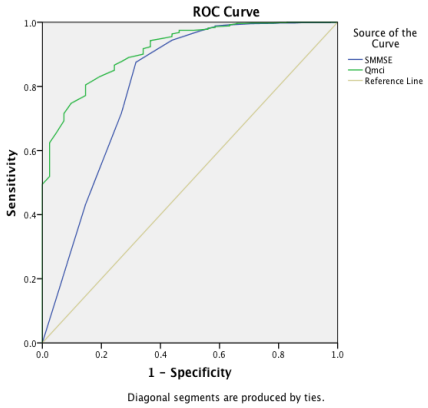
f. Mixed dementia (n=400)



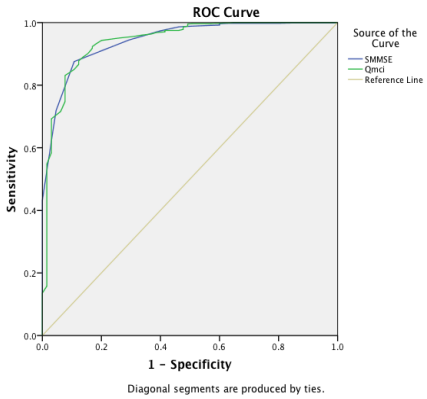
g. Alzheimer's, vascular, mixed dementia (n=2,013)



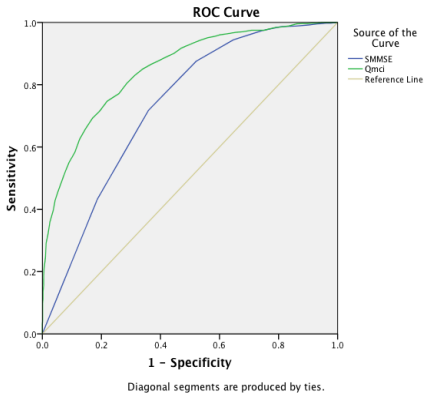
h. Frontotemporal dementia (n=41)



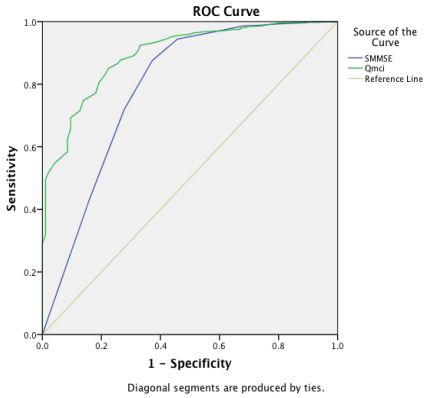
i. Parkinson's disease dementia (n=41)



j. Lewy Body dementia (n=65)



k. All MCI (n=860)



l. MCI excluding depression (n=766)

The median subtest scores and AUC scores derived from ROC curves according to diagnosis are presented in Tables 6.2 and 6.3 respectively. ROC curves comparing the subtests of the Q*mci* are presented in Figure 6.3. The highest median score for the clock drawing subtest was found in those with VaD (14/15), the lowest was in LBD (7/15). All subtest scores were less accurate for MCI in those with comorbid depression. LM was again the most accurate for most dementia subtypes and MCI (AUC 0.80). Orientation was accurate for AD (AUC 0.88) but had particularly low accuracy in VaD (AUC 0.71), FTD (AUC 0.78), PDD (AUC 0.71) and MCI (AUC 0.68).

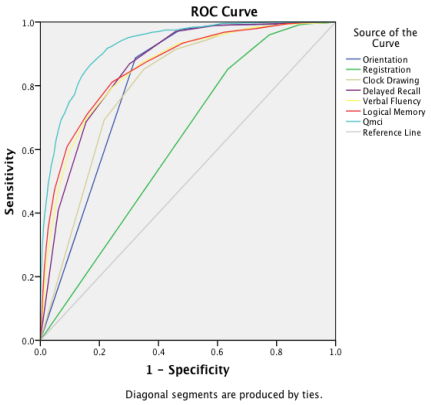
Table 6.2. Median scores for the Quick Mild Cognitive Impairment (Q*mci*) screen subtests divided according to diagnosis: depression, mild cognitive impairment (MCI) and dementia (AD= Alzheimer's disease, VaD= Vascular dementia, FTD= Frontotemporal dementia, PDD= Parkinson's dementia, LBD= Lewy Body dementia).

Diagnosis	**Number** (n=x)	**Orientation** (Median & IQR)	**Registration** (Median & IQR)	**Clock** (Median & IQR)	**Delayed Recall** (Median & IQR)	**Verbal Fluency** (Median & IQR)	**Logical Memory** (Median & IQR)	**Q*mci* Total** (Median & IQR)
Total (All subtypes **including** comorbid depression & MCI)	3,020	8 (10-6=4)	5 (5-4=1)	12 (14-5=9)	4 (12-0=12)	5 (7-3=4)	8 (12-4=8)	43 (56-29=27)
Dementia (All subtypes **including** comorbid depression)	2,160	7 (9-5=4)	5 (5-3=2)	11 (14-3=11)	4 (8-0=8)	5 (7-3=4)	8 (12-4=8)	38 (50-24=26)
Dementia (All subtypes **excluding** comorbid depression)	1,879	7 (9-5=4)	5 (5-3=2)	11 (13-3=10)	0 (8-0=8)	4 (6-3=3)	8 (12-4=8)	37 (49-24=25)
AD	1,483	7 (9-5=4)	5 (5-3=2)	11 (13-3=10)	0 (8-0=8)	4 (6-3=3)	8 (12-4=8)	37 (48-23=25)
VaD	130	9 (10-7=3)	5 (5-4=1)	14 (15-11=4)	8 (12-0=12)	7 (9-4=5)	10 (14-8=6)	53 (64-40=24)
Mixed (AD/VaD)	400	7 (10-5=5)	5 (5-3=2)	10 (14-2=12)	0 (8-0=8)	5 (7-3=4)	8 (12-4=8)	35.5 (51-23=28)
AD, VaD & Mixed	2,013	7 (9-5=4)	5 (5-3=2)	11 (14-3=11)	0 (8-0=8)	5 (7-3=4)	8 (12-4=8)	38 (50-24=26)
FTD	41	9 (10-6=4)	5 (5-3=2)	12 (13-5=8)	4 (8-0=8)	4 (7-3=4)	8 (12-4=8)	43 (55-30=25)
PDD	41	9.5 (10-7=3)	5 (5-4=1)	12.5 (15-7=8)	8 (12-0=12)	5.5 (7-4=3)	10 (14-8=6)	46 (61-32=29)
LBD	65	8 (10-6=4)	5 (5-3=2)	7 (12-1=11)	8 (12-0=12)	4 (6-3=3)	8 (10-4=6)	37 (54-24=30)
MCI	860	10 (10-8=2)	5 (5-5=0)	14 (15-12=3)	12 (16-4=12)	7 (9-5=4)	12 (16-8=8)	56 (66-46=20)
Comorbid depression	281	8 (10-6=4)	5 (5-4=1)	11 (14-4=10)	4 (12-0=12)	6 (8-3=5)	10 (14-4=10)	44 (56-30=26)
MCI with comorbid depression	94	9 (10-7=3)	5 (5-4=1)	13 (15-10=5)	8 (12-4=8)	8 (8-4=4)	12 (14-8=6)	51.5 (62-40=22)
MCI without comorbid depression	766	10 (10-8=2)	5 (5-5=0)	14 (15-12=3)	12 (16-4=12)	7 (9-5=4)	12 (16-8=8)	57 (66-46=20)
Controls	875	10 (10-10=0)	5 (5-5=0)	15 (15-14=1)	16 (20-12=8)	10 (13-8=5)	18 (22-14=8)	74 (81-66=15)

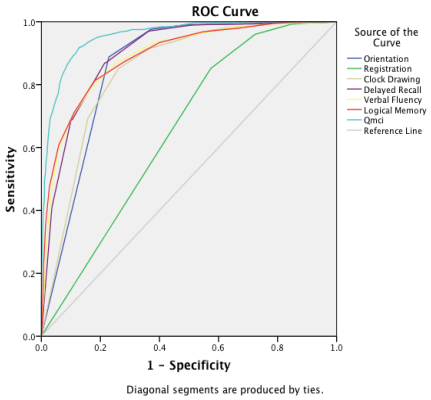
Table 6.3. Comparison of the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen subtests in differentiating each diagnosis from normal controls (n=875): depression, mild cognitive impairment (MCI) and dementia (AD= Alzheimer's disease, VaD= Vascular dementia, FTD= Frontotemporal dementia, PDD= Parkinson's dementia, LBD= Lewy Body dementia). (AUC= area under the curve).

Diagnosis	**Number** (n=x)	**Orientation** AUC (95% Confidence Intervals)	**Registration** AUC (95% Confidence Intervals)	**Clock** AUC (95% Confidence Intervals)	**Delayed Recall** AUC (95% Confidence Intervals)	**Verbal Fluency** AUC (95% Confidence Intervals)	**Logical Memory** AUC (95% Confidence Intervals)	**Q*mci* Total** AUC (95% Confidence Intervals)
Total (All subtypes **including** comorbid depression & MCI)	3,020	0.81 (0.79-.82)	0.62 (0.60-0.64)	0.80 (0.79-0.82)	0.86 (0.85-0.87)	0.85 (0.84-0.87)	0.87 (0.85-0.88)	0.93 (0.92-0.94)
Dementia (All subtypes **including** comorbid depression)	2,160	0.86 (0.85-0.87)	0.65 (0.63-0.67)	0.85 (0.83-0.86)	0.90 (0.89-0.91)	0.89 (0.88-0.90)	0.89 (0.88-0.91)	0.96 (0.95-0.96)
Dementia (All subtypes **excluding** comorbid depression)	1,879	0.87 (0.85-0.88)	0.66 (0.64-0.68)	0.85 (0.84-0.87)	0.90 (0.89-0.92)	0.90 (0.88-0.91)	0.90 (0.89-0.91)	0.96 (0.95-0.97)
AD	1,483	0.88 (0.87-0.90)	0.66 (0.64-0.68)	0.85 (0.84-0.87)	0.91 (0.90-0.93)	0.91 (0.89-0.92)	0.91 (0.89-0.92)	0.97 (0.96-0.97)
VaD	130	0.71 (0.66-0.77)	0.56 (0.50-0.61)	0.72 (0.67-0.77)	0.80 (0.75-0.84)	0.80 (0.77-0.84)	0.81 (0.77-0.85)	0.87 (0.84-0.91)
Mixed (AD/VaD)	400	0.84 (0.82-0.87)	0.65 (0.61-0.68)	0.85 (0.82-0.87)	0.90 (0.88-0.92)	0.89 (0.87-0.91)	0.89 (0.87-0.91)	0.95 (0.94-0.96)
AD, VaD & Mixed	2,013	0.86 (0.85-0.88)	0.65 (0.63-0.67)	0.84 (0.83-0.86)	0.90 (0.89-0.91)	0.90 (0.88-0.91)	0.90 (0.88-0.91)	0.96 (0.95-0.97)
FTD	41	0.78 (0.69-0.87)	0.63 (0.53-0.73)	0.88 (0.81-0.94)	0.90 (0.87-0.95)	0.85 (0.78-0.92)	0.88 (0.83-0.93)	0.96 (0.94-0.98)
PDD	41	0.71 (0.61-0.81)	0.68 (0.58-0.77)	0.73 (0.63-0.82)	0.84 (0.77-0.91)	0.85 (0.79-0.91)	0.83 (0.77-0.88)	0.92 (0.88-0.95)
LBD	65	0.82 (0.74-0.88)	0.66 (0.58-0.74)	0.92 (0.87-0.96)	0.84 (0.79-0.90)	0.89 (0.85-0.93)	0.86 (0.81-0.92)	0.94 (0.91-0.97)
MCI	860	0.68 (0.65-0.70)	0.54 (0.51-0.57)	0.69 (0.67-0.72)	0.76 (0.74-0.78)	0.76 (0.74-0.78)	0.80 (0.77-0.81)	0.85 (0.83-0.87)
Comorbid depression	281	0.80 (0.77-0.84)	0.62 (0.57-0.66)	0.81 (0.78-0.84)	0.86 (0.84-0.89)	0.84 (0.82-0.87)	0.84 (0.82-0.87)	0.93 (0.91-0.95)
MCI with comorbid depression	94	0.75 (0.69-0.82)	0.59 (0.52-0.65)	0.75 (0.70-0.81)	0.82 (0.78-0.87)	0.80 (0.76-0.85)	0.80 (0.75-0.84)	0.90 (0.86-0.93)
MCI without comorbid depression	766	0.67 (0.64-0.69)	0.53 (0.50-0.56)	0.69 (0.66-0.71)	0.75 (0.73-0.77)	0.76 (0.73-0.78)	0.80 (0.76-0.81)	0.84 (0.82-0.86)

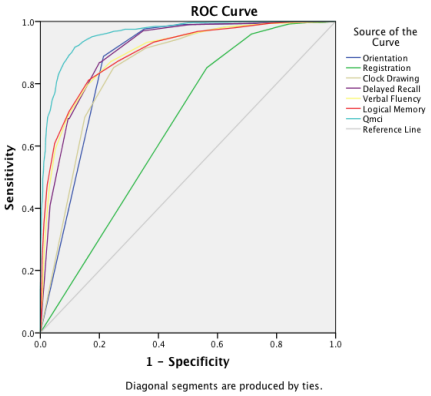
Figure 6.3. Receiver operating characteristic curves (a-l) comparing the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) subtests in differentiating normal controls (n=875) from those with mild cognitive impairment (MCI), different dementia subtypes and comorbid depression for participants included within the Q*mci* screen validation, Doxycycline And Rifampicin for Alzheimer's Disease study and Geriatric Assessment Tool databases.



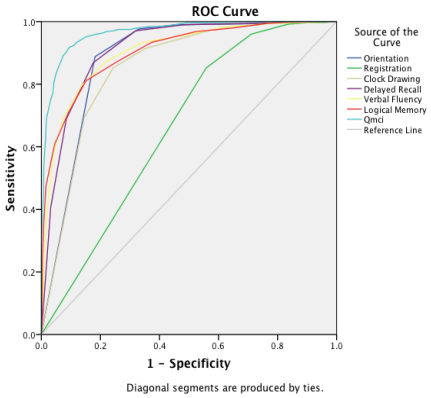
a. All patients (n=3020)



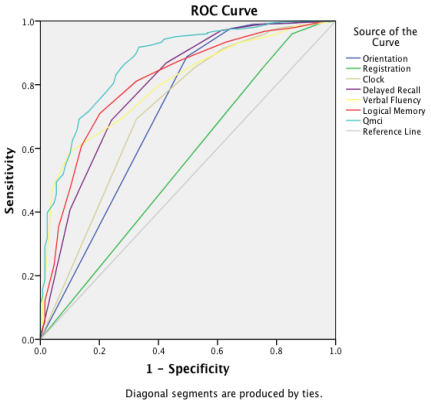
b. All patients with dementia (n=2,160)



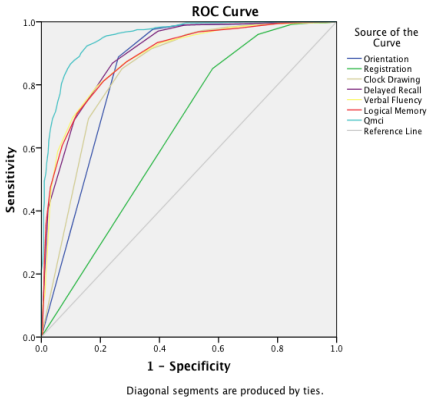
c. Dementia excluding depression (n=1,879)



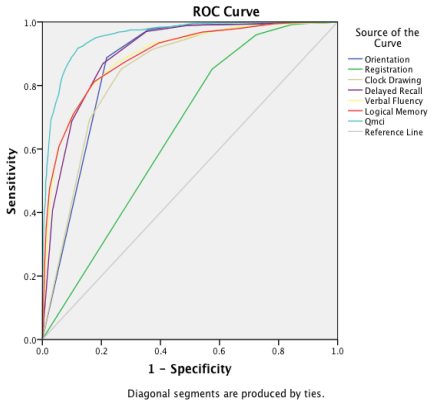
d. Alzheimer's dementia (n=1,483)



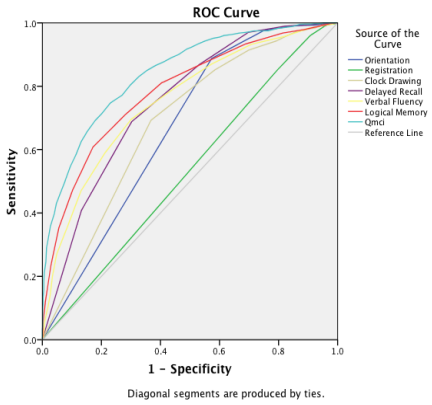
e. Vascular dementia (n=130)



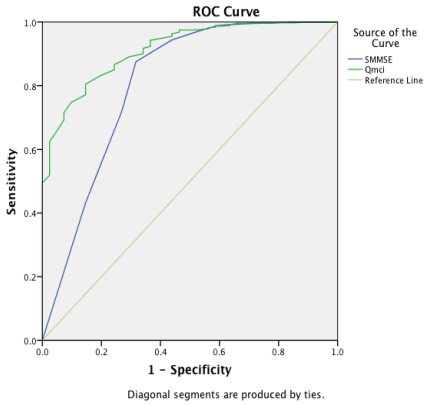
f. Mixed dementia (n=400)



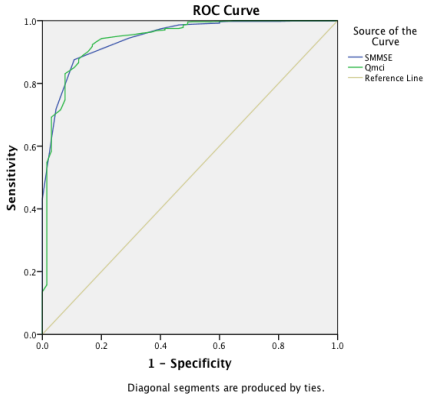
g. Alzheimer's, vascular, mixed dementia (n=2,013)



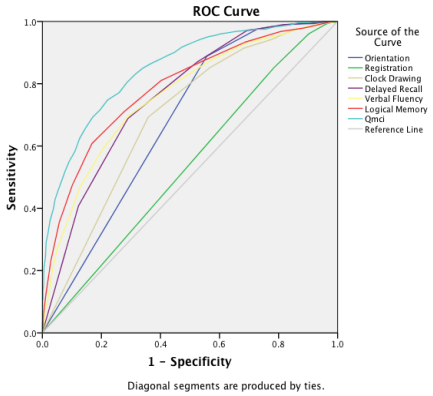
h. Frontotemporal dementia (n=41)



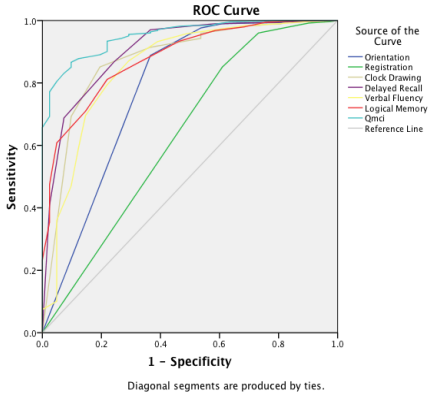
i. Parkinson's disease dementia (n=41)



j. Lewy Body dementia (n=65)



k. All MCI (n=860)



l. MCI excluding depression (n=766)

6.4 Discussion

This study compares the accuracy of the Q*mc*i and the SMMSE in different dementia subtypes using a large sample of patients pooled from three different data sets. The SMMSE and Q*mci* are both accurate cognitive screens in those with dementia. Like the original validation data [O'Caoimh et al., 2013], this analysis confirms the Q*mci* is more accurate and LM its most accurate subtest in MCI. It also has high levels of accuracy for most dementia subtypes and patients with comorbid depression. The SMMSE again is less suitable in MCI [O'Caoimh et al., 2012], VaD and PDD [Bak et al., 2005], supporting previous studies in these conditions, where an alternative instrument like the Q*mci* may be used. The study suggests that comorbid depression affects the scores (total and subtests) and accuracy of instruments and their cognitive domains in patients with MCI. It suggests that comorbid depression likely made those with MCI perform less well on cognitive screening as suggested by the fact that both instruments were better able to detect patients with a history of comorbid depression than those without a history of depression.

The strength of this study is derived from its large sample size and careful pooling of data derived from similar data sets collected by the same principle investigator. This study also has limitations. As with the analysis of cut-off scores, pooling data from discreet, albeit related, data sets may create bias. Some data on gender were missing. The number of patients with atypical or less common dementia subypes was small and may be unrepresentative of the true performance of the instruments in that subtype, leading to bias. The data collection began in 1999 when the awareness of LBD was low. Likewise only patients with AD or those with AD,VaD and mixed dementia were included in the DARAD and Q*mci* validation databases respectively. Further, this study was a retrospective review of patients with

no detailed information available regarding the presence of active depressive symptoms. That said, those patients with normal cognition, with depression as the primary or only symptom, were excluded from the analysis. Similarly, it was not possible to assess MCI subtypes in this study, though the majority of patients in the GAT database reported amnestic type symptoms suggesting that most had aMCI.

In summary, this study confirms the accuracy of the Q*mci* in MCI. It also reaffirms that both the Q*mci* and SMMSE are useful in patients with dementia. It shows that different short screens have significantly different accuracy in different dementia subtypes, suggesting that pre-screen/pre-test suspicion of a possible diagnosis (MCI or specific dementia subtype) based upon history and examination should direct the choice of instrument. The results also suggest that a history of depression may effect the accuracy of cognitive screening, particularly in those with MCI. The effect of comorbid depression on cognitive screening scores merits further investigation. Further study as part of this PhD will investigate the accuracy of the Q*mci* and its subtests in an Irish setting against the SMMSE by way of comparison but also against more sensitive instruments such as the MoCA.

Section 3

External Validation of the Q*mci*

Chapter 7

Diagnostic utility of the Q*mci*: Comparison to the Montreal Cognitive Assessment (MoCA); Comparison to the 6-Item Cognitive Impairment Test (6CIT).

7.1 Introduction

As described in Chapter 2, memory loss is a spectrum from SMC but normal cognition on neuropsychological testing to MCI and dementia. Sensitivity and specificity are the most important psychometric properties of short cognitive screens, with high sensitivity preferable to exclude false negatives [Alberg et al., 2004]. The MoCA is highly sensitive at differentiating MCI from normal cognition and dementia [Nasreddine et al., 2005] and is widely validated against the most commonly used cognitive screen, the MMSE [Folstein et al., 1975],[Shulman et al., 2006],[Ismail et al., 2010], in multiple settings [Luis et al., 2008],[Olson et al., 2011],[Smith et al., 2007], disorders [Hoops et al., 2009],[Videnovic et al., 2010][Godefroy et al., 2011], and languages [Thissen et al., 2010],[Selekler et al., 2011],[Lee et al., 2008],[Fujiwara et al., 2010]. Normative population data are also increasingly available [Rossetti et al., 2011]. The MoCA overcomes the high ceiling effects and educational bias associated with the MMSE [Damian et al., 2011], has fewer practice effects and is available in multiple formats [Damian et al., 2011].

The MoCA has challenges; it is long, taking at least 10 minutes to complete [Nasreddine et al., 2005] and its specificity at its recommended cut-off (<26) is low [McLennan et al., 2011], considerably different from the 87% reported in the original validation cohort [Nasreddine et al., 2005]. Recently, different more specific cut-offs

have been published [Freitas et al., 2013]. In addition, the MoCA subtest scores are criticized for having low accuracy when predicting impairment in their respective cognitive domains [Moafmashhadi et al., 2013]. The 6CIT [Katzman et al., 1983], described and presented in Chapter 2, is another commonly used cognitive screening instrument. It identifies dementia with high accuracy though its accuracy in those with MCI is less established. A recent validation in a memory clinic population showed a sensitivity of only 66% [Abdel-Aziz & Larner 2015]. To date, no study has compared the effects to the MoCA and 6CIT.

Neither the MoCA nor Q*mci* are usually compared to short screens designed to detect MCI as well as dementia. Furthermore, little is known about the optimal cut-off scores for either instrument in patients referred to clinic. Given this, the primary objective of this study was to externally validate the Q*mci* by comparing it to the widely used MoCA in a memory clinic population. The 6CIT is also scored in clinic but was not originally part of the data collection. Given that the 6CIT has only one recent validation in patients with MCI, the secondary objective was to compare it with the Q*mci* in the same population. As this was a secondary outcome, the results of this subanalysis are discussed separately at the end of this chapter. Further, the MoCA was also compared with the 6CIT. Inter-rater reliability of the clock drawing test was also determined as part of this study.

7.2 Methods

Participants

Patients referred for investigation of memory loss were recruited from a university hospital memory clinic in Cork City, Ireland. Alzheimer's type and vascular dementia was classified using the DSM-R (4th-edition) [APA 2000]. Severity was correlated

with the Reisberg FAST scale [Reisberg 1988]. Amnestic type MCI was diagnosed using Petersens' criteria [Petersen et al., 1999] according to the National Institute on Aging-Alzheimer's Association workgroup diagnostic guidelines [Albert et al., 2011]. FTD was diagnosed using the Lund-Manchester Criteria [Brun et al., 1994]. FTD MCI was diagnosed clinically with reference to proposed criteria [de Mendonça et al., 2004]. PDD and MCI was defined by the Movement Disorder Society Task Force Guidelines [Emre et al., 2007],[Litvan et al., 2012], LBD and MCI using the third report of the LBD Consortium [McKeith et al., 2005]. SMC was defined as subjective non-progressive memory loss in patients without objective cognitive deficits or functional decline, scoring 'poor' or 'fair' on a five-point Likert scale in response to the question "how is your memory?" [Paradise et al., 2011]. Normal controls were recruited by convenience sampling from healthy participants, usually caregivers, without cognitive problems, accompanying the patients. Those with active depression (n=23) or delirium (n=2), aged <45 years (n=22), declining consent (n=3), with an unclear diagnosis (n=21) or unable to communicate in English (n=2) were excluded. Depression was excluded clinically and screened with the GDS short-form [Yesavage 1988] using a cut-off of ≥7 to optimize specificity [Marc et al., 2008]. Functional level was based upon clinical history and examination. To support the decision the Barthel Index [Collin et al., 1988] and Quick Activities of Daily Living (Q*adl*) scale were collected. Unless there was co-existing physical disability The Barthel Index measure basic ADL and is scored from functional independence 20/20 to full dependence 0/20 and is presented in Table 7.1. Even though this instrument is not validated in dementia, it is a well established instrument to measure ADL and is collected routinely in clinic. The Q*adl* is a shortened version of the Lawton-Brody ADL scale and includes both instrumental and basic ADL. It has 10 subtests, scored

by informants: medications, finances, telephone use, food preparation, grooming, bathing, walking, toileting (urine/feces), transfering and feeding themselves. Each subtest has two questions: what is the level of care required, and how much of a problem is this. Each subtest is scored from zero to four, with higher scores suggesting greater dependency. The Q*adl* has excellent inter-rater reliability [O'Caoimh, Trawley & Molloy, 2012] and is presented in Appendix 2.6. All patients diagnosed with SMC or MCI had a normal Barthel Index score of 20 or Q*adl* score of 40.

Table 7.1. The Barthel Index (BI) scoring sheet.

Item	**Range**	**Score**
Feeding	0 Unable 1 Needs help cutting, spreading butter etc, or needs modified diet 2 Independent	
Bathing	0 Dependent 1 Independent (or in shower)	
Grooming	0 Needs help with personal care 1 Independent face/hair/teeth/shaving (implements provided)	
Dressing	0 Dependent 1 Needs help but can do about half unaided 2 Independent (including buttons, zips, laces, etc.)	
Bowels	0 Incontinent (or needs to be given enemas) 1 Occasional accident 2 Continent	
Bladder	0 Incontinent or catherized and unable to manage alone 1 Occasional accident 2 Continent	
Toilet Use	0 Dependent 1 Needs some help but can do something alone 2 Independent (on and off, dressing, wiping)	
Transfers (bed to chair and back)	0 Unable, no sitting balance 1 Major help (one or two people, physical), can sit 2 Minor help (verbal or physical) 3 Independent	
Mobility (on level surface)	0 Immobile or < 50 metres 1 Wheelchair independent, including corners, > 50 metres 2 Walks with help of one person (verbal or physical) > 50 metres 3 Independent (but may use any aid; for example, stick)	
Stairs	0 Unable 1 Needs help (verbal, physical, carrying aid) 2 Independent	
Total Score		**/20**

Outcome measures

The optimal Q*mci* cut-off score for CI (MCI or dementia), based upon the cut-off analysis in Chapter 5, used was <60. For screening in primary care, where high

sensitivity is required, the established MoCA threshold of <26 is suggested [Nasreddine et al., 2005]. For testing in memory clinics, a lower threshold (<24) may have better predictive value [Damian et al., 2011]. A cut-off of ≥8/28 for dementia was used for the 6CIT. It does not have established cut-off scores for cognitive impairment.

Data Collection

Consecutive referrals underwent a comprehensive work-up for memory loss including history, physical examination, laboratory testing and neuroimaging. A short neuropsychological battery (the SMMSE [Molloy et al., 1991],[Molloy et al 1997] and two informant-rated assessments (the AD8 questionnaire [Galvin et al., 2005],[Razavi et al., 2014] and IQCODE Short Form [Jorm 1994]) were conducted by a consultant geriatrician to inform the diagnosis. Cognitive screening was performed in a random counterbalanced order, approximately one hour before consultant review, by two independent trained raters, blind to each other and the final diagnosis. Alternate validated versions of VF and LM were used for the Q*mci* to reduce learning effects [Cunje et al., 2007]. Normal controls underwent the same comprehensive review. The study adhered to the tenets of the Declaration of Helsinki. Ethics approval was obtained and subjects provided verbal consent. Assent was obtained from individuals who were felt to lack capacity.

Analysis

Data were analyzed using SPSS 20.0. The Shapiro–Wilk test was used to test normality and found that the majority of data were non-parametric. These were compared using the Mann–Whitney U test. Accuracy was assessed with ROC curves,

compared with the Hanley method [Hanley et al., 1983]. Sensitivity, specificity, PPV and NPV were calculated for all tests at different cut-off points and by age (≤75 and >75 to balance numbers between groups) and education (<12 and ≥12, mean education in the United Kingdom and Ireland [United Nations: http://hdr.undp.org/en/content/mean-years-schooling-adults-years]).

7.3 Results

Characteristics

In total, 551 participant assessments were included: 73 with SMC, 103 with MCI, 274 with dementia and 101 normal controls. Recruitment is presented in Figure 7.1. The majority of participants were female (n=363, 66%). The median age of participants was 76 years (interquartile range, IQR +/-12). Patients with dementia (median age of 77 +/-10 years) were significantly older than those with SMC (72 +/-11, p <0.001), MCI (76+/-13, p =0.03) and normal controls (74 +/-14, p <0.001). The median time in education was 12 +/-4 years. Those with dementia had spent less time in education (11+/-3 years), compared to those with SMC (12+/-4, p =0.07), MCI (13+/-5, p <0.001), or controls (13+/-4, p <0.001). There was no significant difference in age (p =0.82) or education (p =0.16) between those with SMC and controls. The majority of patients with dementia were classified as early to mild stage (n=201, 73%). Participant characteristics, median test scores according to diagnosis and the prevalence of MCI and dementia subtypes are presented in Table 7.2. Median administration time for the Q*mci* was 4.5 (+/-1.3) minutes, compared to 9.5 (+/-2.8) for the MoCA. IRR, measured using Pearson's correlation coefficient for a small sample of patients (n=14), choosen at random, was strong (r =0.97).

Figure 7.1. Flow chart of patients including number of assessments.

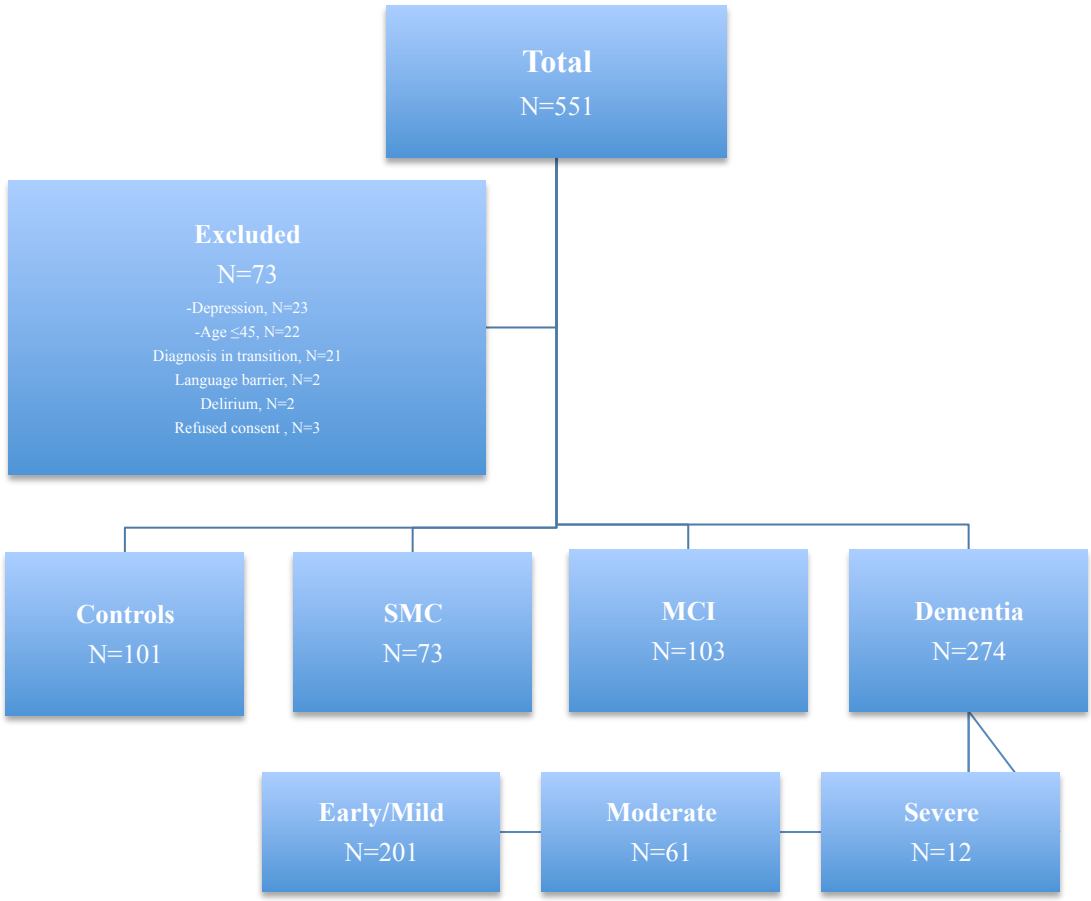


Table 7.2. Baseline characteristics including dementia and mild cognitive impairment subtypes and median Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) scores, with inter-quartile range (IQR) values, for normal controls and patients with subjective memory complaints (SMC), MCI and dementia.

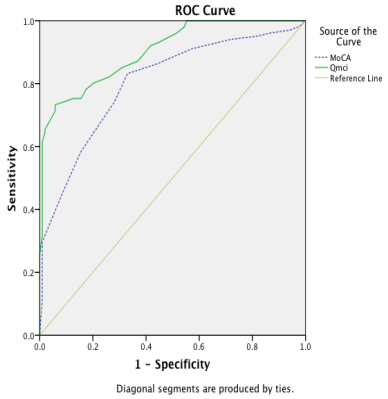
Group		**Total Included**	**Normal Controls**	**SMC**	**MCI**	**Dementia (Total)**	**Early-Mild**	**Moderate**	**Severe**
Participants		551	101	73	103	274	201	61	12
Age (Years)	**Median** (+/-IQR) (Q3-Q1)	76 +/-12 (81-69)	74 +/-14 (78-64)	72 +/-11 (78-67)	76 +/-13 (81-68)	77 +/-10 (82-72)	77 +/- (82-73)	79 +/-15 (84-69)	77 +/-11 (79-68)
Education (Years)	**Median** (+/-IQR) (Q3-Q1)	12 +/-4 (14-10)	13 +/-4 (15-11)	12 +/-4 (14-10)	13 +/-5 (16-11)	11 +/-3 (13-10)	11 +/-3 (13-10)	10 +/-2 (11-9)	13 +/-3 (13-10)
Q*mci* (Median +/- IQR) (Q3-Q1)		51 +/-29 (66-37)	86 +/-13 (81-68)	68 +/-9 (73-64)	56 +/-12 (64-52)	37 +/-23 (45-22)	41 +/-14 (46-32)	18 +/-17 (26-9)	7 +/-6 (9-3)
MoCA (Median +/- IQR) (Q3-Q1)		20 +/-12 (25-13)	26 +/-4 (28-24)	25 +/-4 (27-23)	22+/-5 (25-20)	13 +/-9 (17-8)	16 +/-7 (19-12)	6 +/-5 (9-4)	2 +/-3.5 (3.5-0)

Subtype	**Alzheimer's (possible/probable)**	**Vascular**	**Mixed**	**Frontotemporal**	**Lewy Body**	**Parkinson's disease**	**Other/ unknown**
Dementia (%)	176 (64%)	40 (15%)	24 (9%)	8 (3%)	12 (4%)	3 (1%)	11 (4%)
MCI (%)	Amnestic type 72 (70%)	14 (13.5%)	8 (8%)	5 (5%)	3 (3%)	1 (0.5%)	-
SMC	-	-	-	-	-	1	-

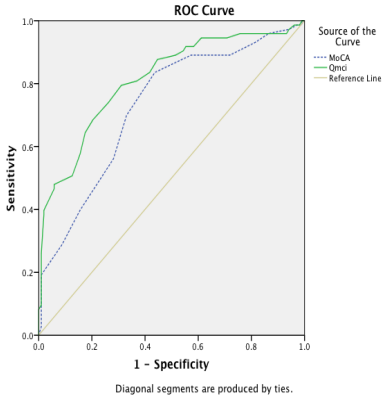
Accuracy of Q*mci* Versus MoCA

Comparing the accuracy of the tests at differentiating normal controls from MCI showed that the Q*mci* had significantly greater accuracy, AUC of 0.90 (95% confidence interval: 0.86-0.94) than the MoCA, AUC of 0.80 (95% confidence interval: 0.74-0.86), p =0.009. In their ability to discriminate SMC from MCI, the Q*mci* had better (AUC 0.81) accuracy than the MoCA (AUC 0.73), p =0.09, albeit a non-significant difference. The Q*mci* and MoCA had similar excellent accuracy at differentiating MCI from dementia (p =0.2), normal controls from cognitive impairment (p =0.04) and patients with SMC from cognitive impairment, (p =0.23). Both tests were poor at discriminating normal controls from SMC, (p =0.28). ROC curves are presented in Figure 7.2.

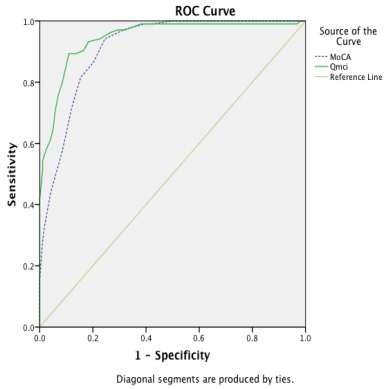
Figure 7.2. Receiver Operating Characteristic curves demonstrating the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen, and Montreal Cognitive Assessment (MoCA) in differentiating (a) mild cognitive impairment (MCI) from normal controls, (b) MCI from subjective memory complaints (SMC), (c) MCI and dementia, (d) normal controls from cognitive impairment (MCI and dementia), (e) SMC from cognitive impairment and (f) SMC from normal controls.



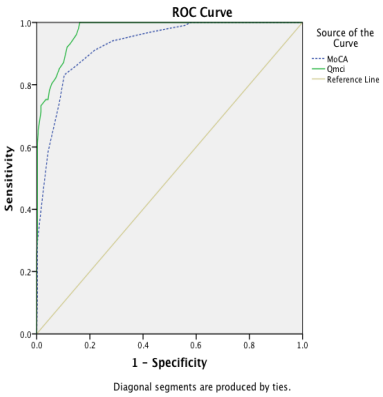
a.



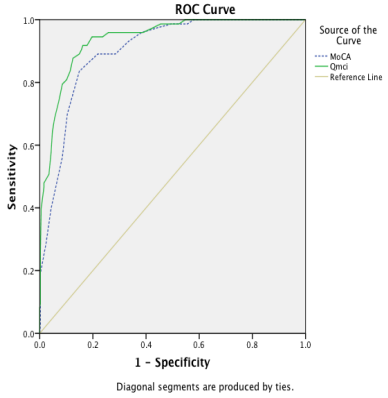
b.



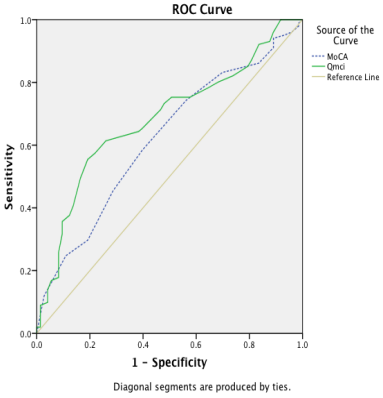
c.



d.



e.



.f

Figure	MoCA	Q*mci*
	Area Under the Curve (95% Confidence Intervals)	
a	0.80 (0.74-0.86)	0.90 (0.86-0.94)
b	0.73 (0.65-0.81)	0.81 (0.75-0.88)
c	0.91 (0.87-0.94)	0.95 (0.92-0.97)
d	0.90 (0.87-0.93)	0.94 (0.91-0.97)
e	0.93 (0.90-0.95)	0.97 (0.96-0.99)
f	0.62 (0.54-0.70)	0.68 (0.60-0.76)

The ability of both instruments to separate normal controls from cognitive impairment (MCI and dementia) was then assessed using different cut-off scores. Patients with SMC were analysed separately. At their established cut-offs, <62 for the Q*mci* and <26 for the MoCA, the Q*mci* had a sensitivity of 90% and specificity of 87% (PPV of 0.92, NPV 0.70) for cognitive impairment, compared to 96% sensitivity and 58% specificity (PPV of 0.89, NPV 0.80) for the MoCA. At these cut-offs, the MoCA had a false positive rate of 11% compared to 4% for the Q*mci*. The MoCA misclassified 42/101 (42%) of controls as having cognitive impairment compared to 7/101 (7%) with the Q*mci*. Increasing the Q*mci* cut-off to <65 improved the sensitivity (94%) but reduced the specificity (80%). Reducing the MoCA cut-off for cognitive impairment to <24 yielded an optimum sensitivity and specificity for the test, 89% and 83% respectively, and reduced the false positive rate to 5%. Sensitivity, specificity, PPV and NPVs are presented in Table 7.3. Adjusting the Q*mci* cut-off scores for age and education showed that the Q*mci* using a cut-off of <62 had an optimal sensitivity and specificity for cognitive impairment in younger patients with less education (<12 years), with a sensitivity of 99% and specificity of 85%. Lowering the cut-off to <60 improved the specificity (88%) for older people (>75), giving an arguably better balance between sensitivity and specificity, suggesting that this maybe the optimal cut-off in a geriatric clinic or GP setting. Sensitivity was lowest for younger patients aged <75 with >12 years in formal education (74%). The MoCA had better sensitivity (99%) for older patients (>75) with less education (<12) but very low specificity (37.5%). The MoCA had greater sensitivity for those with more education. These values, adjusted for age and education, are presented in Table 7.4. Re-analysis of the data comparing the ability of the tests at their established cut-offs to differentiate SMC from MCI and dementia showed similar results, see Table 7.5.

Table 7.3. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), with 95% confidence intervals (CI), for different Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) cut-off scores for cognitive impairment (mild cognitive impairment and dementia), without adjustment for age or education, compared with normal controls.

Cognitive Screen Cut-off score	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**False Positive (95% CI)**	**False Negative (95% CI)**
			Prevalence of cognitive impairment of 79%			
Q*mci*						
<65	94% (91-96)	80% (71-87)	94% (91-96)	80% (71-87)	6% (4-7)	20% (13-29)
<64	93% (89-95)	82% (73-89)	95% (92-97)	76% (69-84)	5% (3-8)	24% (16-33)
<63	91% (88-94)	85% (76-91)	96% (93-97)	74% (64-81)	4% (3-7)	26% (19-36)
<62†	90% (86-93)	87% (79-93)	96% (93-98)	70% (61-78)	4% (2-7)	30% (22-39)
<61	88% (84-91)	92% (85-96)	98% (95-99)	69% (60-76)	2% (1-5)	31% (24-40)
<60	87% (83-90)	93% (86-97)	98% (95-99)	67% (59-75)	2% (1-5)	33% (25-41)
<59	85% (81-89)	96% (90-99)	99% (96-100)	65% (56-72)	1% (0-4)	35% (28-44)
<58	84% (80-88)	98% (92-100)	99% (97-100)	64% (56-71)	1% (0-3)	36% (29-44)
<57	84% (79-87)	100% (95-100)	100% (98-100)	64% (55-71)	0% (0-2)	36% (29-45)
<56	82% (78-86)	100% (95-100)	100% (98-100)	61% (53-69)	0% (0-2)	39% (31-47)
<55	81% (76-85)	100% (95-100)	100% (98-100)	59% (52-67)	0% (0-2)	41% (33-48)
MoCA						
<26*	96% (93-98)	58% (48-68)	89% (85-92)	80% (68-88)	11% (8-15)	20% (12-32)
<24**	89% (86-92)	83% (74-90)	95% (92-97)	69% (60-77)	5% (3-8)	31% (23-40)
<23***	85% (81-88)	86% (77-92)	96% (93-97)	62% (53-70)	4% (3-7)	38% (30-47)
<22****	78% (74-82)	91% (83-96)	97% (94-98)	54% (46-62)	3% (2-6)	46% (38-54)

† Cut-off for cognitive impairment selected from O'Caoimh et al., 2014
* Cut-off for cognitive impairment selected from Nasreddine et al., 2005
** Cut-off for cognitive impairment selected from Damian et al., 2012
*** Cut-off for cognitive impairment selected from Luis et al., 2008
**** Cut-off for mild cognitive impairment selected from Freitas et al., 2013

Table 7.4. Sensitivity, specificity, positive predicative value (PPV), negative predicative value (NPV), and false positive and negative values for the Quick Mild Cognitive Impairment (Q*mci*) screen (using two different cut-off points) and Montreal Cognitive Assessment (MoCA), based upon cut-off scores for cognitive impairment (MCI and dementia), adjusted for age and education for the Q*mci* (CI= 95% Confidence Interval).

Cognitive Screen	**Age**	**Edu**	**Median Score (IQR)** Cognitive Impairment Controls	**N=X**	**Cut-off score**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**False Positive (95% CI)**	**False Negative (95% CI)**
Q*mci*	> 75	< 12	42 (50-26=24) 70 (75-63=12)	146/170 (86%)	<60	94% (88-97)	88% (66-97)	98% (93-99)	70% (50-85)	2% (1-7)	30% (15-50)
	> 75	≥ 12	47 (58-37=21) 78 (81-71=10)	59/76 (78%)		78% (65-87)	100% (77-100)	100% (90-100)	57% (38-74)	0% (0-10)	43% (26-62)
	≤ 75	≥ 12	47 (62-33=29) 79 (84-75=9)	73/110 (66%)		73% (61-82)	97% (84-100)	98% (89-100)	64% (50-76)	2% (0-11)	36% (24-50)
	≤ 75	< 12	41 (48-22=26) 74.5 (82-65=17)	77/97 (79%)		95% (87-98)	90% (67-98)	97% (90-100)	82% (59-94)	3% (0-10)	18% (6-41)
Q*mci* (based upon Youden's Index)	> 75	< 12	42 (50-26=24) 70 (75-63=12)	146/170 (86%)	<62	97% (92-99)	75% (53-89)	96% (91-98)	78% (56-92)	4% (2-7)	22% (8-44)
	> 75	≥ 12	47 (58-37=21) 78 (81-71=10)	59/76 (78%)		80% (68-89)	94% (69-100)	98% (89-100)	55% (36-73)	2% (0-11)	49% (27-64)
	≤ 75	≥ 12	47 (62-33=29) 79 (84-75=9)	73/110 (66%)		74% (63-83)	95% (80-99)	97% (87-99)	64% (50-76)	3% (1-13)	36% (24-50)
	≤ 75	< 12	41 (48-22=26) 74.5 (82-65=17)	77/97 (79%)		99% (92-100)	85% (61-96)	96% (89-99)	94% (71-100)	4% (1-11)	6% (0-29)
MoCA	> 75	< 12	14.5 (19-10=9) 25 (26-23=3)	146/170 (86%)	<26	99% (95-100)	37.5% (20-59)	91% (85-94)	82% (48-97)	9% (6-15)	18% (3-52)
	> 75	≥ 12	19 (22-13=9) 27 (29-25=4)	59/76 (78%)		91.5% (81-97)	71% (44-89)	91.5% (81-97)	71% (44-89)	8% (3-19)	29% (11-56)
	≤ 75	≥ 12	18 (23-12=11) 27 (30-25=6)	73/110 (66%)		90% (81-96)	73% (56-86)	87% (77-93)	79% (62-91)	13% (7-23)	21% (9-38)
	≤ 75	< 12	16 (20-7=13) 25.5 (27-24=3)	77/97 (79%)		99% (92-100)	50% (28-72)	88% (79-94)	91% (57-100)	12% (6-21)	9% (1-43)

Table 7.5. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), with 95% confidence intervals (CI), for different Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) cut-off scores for cognitive impairment (mild cognitive impairment and dementia), without adjustment for age or education, compared with patients diagnosed with subjective memory complaints.

Cognitive Screen Cut-off score	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**False Positive (95% CI)**	**False Negative (95% CI)**
			Prevalence of cognitive impairment of 84%			
Q*mci*						
<65	95% (92-97)	67% (55-77)	93% (89-95)	74% (62-84)	7% (5-11)	26% (16-38)
<63	92% (88-94)	77% (66-85)	95% (91-97)	67% (57-77)	5% (3-8)	35% (26-46)
<62†	90% (86-93)	80% (69-87)	95% (92-97)	65% (54-74)	5% (3-8)	36% (27-47)
<60	88% (84-91)	88% (79-94)	97% (94-99)	63% (53-72)	3% (1-6)	37% (28-47)
<58	85% (81-89)	92% (83-97)	98% (95-99)	59% (49-67)	2% (1-5)	41% (33-51)
<56	82% (78-86)	94% (85-98)	98% (96-99)	55% (46-63)	2% (1-4)	45% (37-54)
MoCA						
<26*	96% (93-98)	41% (31-54)	88% (84-91)	72% (56-84)	12% (9-16)	28% (16-44)
<24**	90% (86-93)	72% (60-81)	93% (90-96)	63% (52-73)	7% (4-10)	37% (27-48)
<23***	85% (81-88)	82% (71-89)	95% (92-97)	56% (46-65)	5% (3-8)	44% (35-54)
<22****	78% (73-82)	87% (77-93)	96% (93-98)	48% (39-56)	4% (2-7)	52% (44-61)

† Cut-off for cognitive impairment selected from O'Caoimh et al 2014
* Cut-off for cognitive impairment selected from Nasreddine et al 2005
** Cut-off for cognitive impairment selected from Damian et al 2012
*** Cut-off for cognitive impairment selected from Luis et al 2008
**** Cut-off for mild cognitive impairment selected from Freitas et al 2013

Inter-rater reliability of the clock drawing test

IRR of the clock drawing test was determined by asking two trained and one untrained raters (given the administration and scoring guidelines, including the clock drawing scoring template prior to testing) to score a random sample of clocks, n=20. Pearsons correlation coefficient demonstrated a strong correlation, r =0.99, p <0.001, between trained raters. A strong correlation was also demonstrated between trained and untrained raters, r =0.96, p <0.001. Cohen's Kappa (K, Weighted) also showed strong to near perfect agreement between trained raters (K =0.8909, SE = 0.0297, 95%CI = 0.8327 to 0.9490) and trained versus untrained raters (K =0.7925, SE =0.0494, 95%CI = 0.6957 to 0.8892). There was also an overall fair level of agreement between the three (trained and untrained) raters, (Fleiss's K =0.3754, SE = 0.0483, 95%CI = 0.2807 to 0.470).

7.4 Discussion

This study compares the ability of Q*mci* and MoCA to detect cognitive impairment and differentiate NC from MCI and dementia. Overall, the results suggest that the Q*mci* is the shorter, more accurate and useful screen for detecting cognitive impairment, producing the best balance between sensitivity and specificity at its established cut-off score. Comparing the ability of the two tests to differentiate NC from MCI, the Q*mci* demonstrated statistically significantly greater accuracy, an AUC of 0.82 compared to 0.74 for the MoCA. At the widely used cut-off of <26, the MoCA had 96% sensitivity but only 41% specificity for detecting cognitive impairment compared to 88% and 88% respectively for the Q*mci* at a cut-off of <60. The poor specificity of the MoCA at this cut-off is similar to results published elsewhere of between 35% [Luis et al., 2008] and 52% [Damian et al., 2011] for

detecting cognitive impairment. The specificity of the MoCA improved when the cut-off was lowered and from this data, the optimal cut-off appears to be that suggested by Luis et al at <23 [Luis et al., 2008], which produced a sensitivity of 85% and specificity of 82% for cognitive impairment. Although reducing the cut-off threshold improved its specificity, this was at the cost of sensitivity, the main advantage of using the MoCA. The Q*mci* and MoCA had similar good to excellent accuracy (non-significantly different) in separating patients presenting with SMC but found to have normal cognition and those with cognitive impairment (MCI or dementia). This suggests that the instruments are both appropriate in this setting, but given the Q*mci*'s short administration time it may be the more useful particularly where time is short. The Q*mci* is more efficient because it takes half the time to complete compared to the MoCA. In this study, the median length of time to score the Q*mci* was 4.5 minutes, half the time of the MoCA.

This study demonstrates several other advantages of the Q*mci* over the MoCA. The Q*mci* was associated with fewer false positive results for cognitive impairment, 4% at <62, compared to 12% for the MoCA at <26. At this cut-off the majority of subjects with controls (54%) screened positive using the MoCA. While this questions the tests' utility at this cut-off, it also questions the broader utility and ability of the test to differentiate normal controls from MCI, because the majority with normal age associated memory loss test positive for cognitive impairment necessitating more detailed assessment and negating the purpose of the test. The suboptimal specificity of the MoCA has been reported previously for cognitive impairment associated with PD [Hoops et al., 2009] and stroke [Godefroy et al., 2011]. To our knowledge, this is the first time this has been demonstrated among subjects, predominantly diagnosed with AD, in an outpatient memory clinic setting. The cut-off scores for the MoCA are less

clearly defined than those of the Q*mci*. Several studies have demonstrated that established cut-offs for the MoCA lack accuracy, particularly specificity, among older adults and those with less time in formal education [Rossetti et al., 2011]. This might be related to the fact that the MoCA and its established cut-off score of <26 were originally validated exclusively among subjects with AD. In contrast, the original Q*mci* validation sample included those with AD, vascular dementia and mixed AD-vascular subtypes [O'Caoimh et al., 2012]. While the MoCA is validated in different conditions, the same cut-offs are often applied although recent evidence suggests that the original cut-off requires adjustment for both MCI and dementia [Freitas et al., 2013] as well as for specific types of cognitive impairment [Hoops et al., 2010],[Godefroy et al., 2011].

The Q*mci* is the more useful test in clinical practice with wider and more clinically significant percentage difference in median scores that can better discriminate MCI from normal controls and dementia. The MoCA, like the SMMSE is scored out of 30 points giving it a narrow scoring range and reducing its utility in clinical practice. In addition, with this limited scoring, much of the detail and richness of the assessment is lost. This is exemplified by the scoring of the Clock. Although requiring more interpretation, the scoring of the Q*mci*-Clock, provides more information and contributes more to the final score of the test, particularly in those with established cognitive impairment. The MoCA also had significant floor effects, with a median score of two points, making it particularly difficult for those with moderate to severe dementia to complete and therefore limiting its utility in severe dementia.

The Q*mci* incorporates fewer subtests that require normal vision than the MoCA. Visual impairment affects the performance of subjects on cognitive testing,

particularly in older adults [Killen et al., 2013]. Visual tasks account for 27% of the MoCA's (Visuospatial/Executive and Naming) overall score compared to 15% for the Q*mci* (clock drawing). This said, both tests can be corrected to account for incomplete data and recently a modified version of the MoCA for the visually impaired has been validated [Wittich et al., 2010]. However, the elimination of subtests that require vision (naming, visuospatial and executive function) reduces the discriminating function of the 'MoCA-BLIND', particularly its ability to differentiate MCI from NC [Wittich et al., 2010]. Given that this is the principal advantage of the MoCA over other cognitive screens, this suggests that the MoCA is overly weighted towards tests that require normal vision, an especially important component when assessing older adults [Killen et al., 2013]. The Q*mci* on the other hand derives its accuracy for identifying MCI from its delayed recall, verbal fluency and logical memory subtests [O'Caoimh et al., 2013]. At present, no accepted population norms for age, culture or education have been published for the MoCA [Rossetti et al., 2011], although the ACE trial is currently planned to develop these specific cut-offs. Similarly, no cut-offs, adjusted for age or education, exist for those presenting with memory loss. Finally, the Q*mci* is arguably easier to use than the MoCA, requiring less training, thereby increasing its generalizability.

The MoCA may however be more sensitive and specific for younger subjects with more education. In older adults the MoCA may perform with more accuracy using a lower cut-off than the established score. The MoCA is less weighted towards language, with 73% of the test requiring verbal skills versus 85% for the Qmci. That said, the MoCA subtests are subject to greater educational bias, than the Qmci. Although the Q*mci* is easier to score, its Clock subtest, scored out of 15 points, requires greater interpretation. That said, the Q*mci*-Clock scoring method is validated

against and is superior to other forms of Clock drawing [Kanji et al., 2006] and showed good IRR in this study, consistent with research showing excellent IRR for clock drawing for specialists in dementia [Nair et al., 2010].

The MoCA is validated widely, in different languages [Thissen et al., 2010],[Fujiwara et al., 2010] and in different clinical settings. Validation of the Q*mci* in other countries, languages and cultures is now underway. Future validation should also include comparison with the MoCA and other standardized neuropsychological tests in different clinical populations.

This study has a number of limitations. The diagnosis of MCI is contentious and the criteria used here are not a gold standard. In particular, no formal neuropsychological testing was routinely performed. That said, at present no single screening instrument is recommended for MCI, no standardized criteria are accepted [Bischkopf et al., 2002] with definitions differing between studies [Stephan et al., 2013]. The protocol was developed and data collection begun before the publication of DSM-5. For these reasons MCI was defined according to its fundamental characteristics: the presence of subjective and corroborated memory loss, in the absence of impairment in ADLs. Possible learning effects due to repetition of VF and LM may have been present although different versions were used in an attempt to minimize this. No specific screening test such as the MAC-Q was used for SMC [Crook et al., 1992]. This said, a short Likert scale in response to a single question has been used in previous studies assessing SMC [Paradise et al., 2011].

This is the first study to compare a short cognitive screen, designed specifically to differentiate MCI from normal cognition and dementia with the MoCA. While the MoCA overcomes many of the difficulties associated with the MMSE, particularly in those with high levels of education, this study suggests that the

MoCA is too challenging and overly sensitive among older adults attending a memory clinic. This study also confirms the growing concern that the established MoCA cut-off (<26), while sensitive to cognitive impairment, has poor specificity and produces an unacceptably high false positive rate. As older adults represent the majority of patients who have cognitive screening performed for symptoms of memory loss, the Q*mci* is likely to be a shorter and more accurate alternative. Further research is required to confirm these findings and compare the Q*mci* and MoCA in different clinical settings, particularly in primary care, where the brevity and usability of the Q*mci* is likely to be of most benefit. The MoCA may be better with a lower cut-off than the established score, particularly for older adults. The Q*mci*, with a cut-off of <60 for CI, has superior sensitivity and specificity and should be considered as a shorter alternative to the MoCA for use in everyday practice.

7.5 Subanalysis: comparison of the Q*mci* to the 6-Item Cognitive Impairment Test (6CIT) and MoCA.

Results

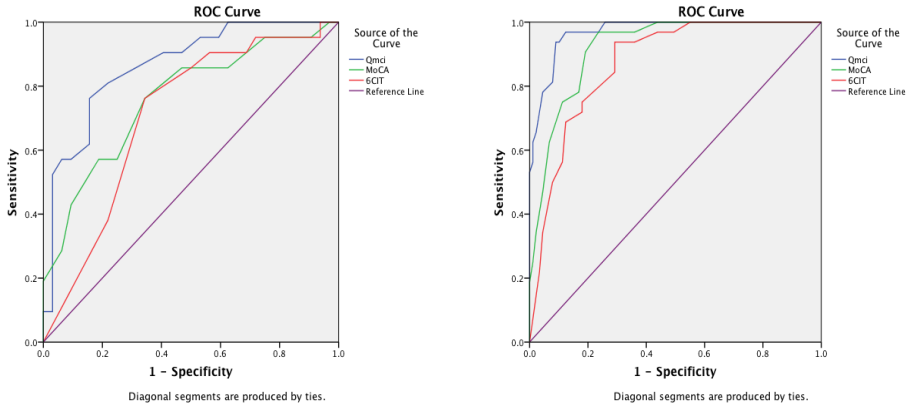
As described in the introduction to Chapter 7, the 6CIT was scored in clinic in addition to the requirements of this study. The results of the 6CIT scoring were blinded to the attending consultant and they did not influence the diagnosis. In all, 142 6CIT assessments were available (21 with SMC, 32 MCI and 89 with dementia). No normal controls were available. The median age of patients included was 76 years (interquartile range: 81-70= +/-11). In all, 68% were female. The median Q*mci* score was 44 (+/-33) compared to 10/28 (18-4= +/-14) for the 6CIT. The median Q*mci* score for SMC, MCI and dementia was 69 (73-63= +/-10), 57 (62-52 +/-10) and 32.5/100 (42-20= +/-22) respectively compared to 2/28 (4-0= +/-4), 5/28 (9-2= +/-7) and 17/28 (21-10= +/-11) respectively for the 6CIT. Characteristics of patients

included in this subanalysis are presented in Table 7.6. The Q*mci* had excellent accuracy for identifying cognitive impairment (either MCI or dementia) with an AUC of 0.96 (95% CI: 0.94-0.99). It performed significantly better than the 6CIT, AUC 0.88 (95% CI: 0.82-0.94), z=2.4, p =0.02, but not the MoCA in this data set 0.92 (0.87-0.97), z=1, p= 0.32. The MoCA had similar accuracy to the 6CIT (z=-0.54, p =0.59). The Q*mci* had greater accuracy than the 6CIT in differentiating MCI from those with SMC, AUC of 0.91 versus 0.71,although this did not reach statistical significance, z=1.7, p =0.09. It did however, have significantly better accuracy in differentiating MCI from dementia, AUC of 0.97 versus 0.87, z=2.1, p =0.04. Median administration times were 4.38 minutes for the Q*mci* versus 2.05 for the 6CIT. ROC curves demonstrating the accuracy of the Q*mci*, MoCA and 6CIT in differentiating MCI from SMC and dementia are shown in Figure 7.3.

Table 7.6. Characteristics of patients included in the subanalysis of 6-item Cognitive Impairment Test (6CIT) in patients with subjective memory complaints (normal), mild cognitive impairment (MCI) and dementia.

Group		**Total**	**SMC**	**MCI**	**Dementia**
Number of Assessments		142	21	32	89
Gender (% female)		68%	43%	75%	72%
Age					
(years)	**Median**	76	71	77	77
	Interquartile range (IQR)	(81-70=11)	(75-66=9)	(80-71=9)	(82-71=11)
	range	49-91	54-89	61-91	49-91
Education					
(years)	**Median**	12	11	12	11
	Interquartile range (IQR)	(14-10=4)	(13-10=3)	(16-11=5)	(13-10=3)
	range	7-18	9-17	9-18	7-18
Q*mci* (median score with IQR)		44 (60-27=33)	72 (73-65=8)	60 (63-52=9)	33 (42-20=22)
MoCA (median score with IQR)		17 (22-10=12)	25 (27-23=4)	22 (24-19=5)	14 (18-8=10)
6CIT (median score with IQR)		10 (18-4=14)	2 (4-0=4)	5 (9-2=7)	17 (21-10=11)

Figure 7.3. Receiver Operating Characteristic curves demonstrating the accuracy of the Q*mci*, MoCA & 6CIT in differentiating (a) MCI from subjective memory complaints (SMC) and (b) MCI from dementia.



a. b.

Screen	Area Under the Curve	Area Under the Curve
Diagnosis	a) SMC from MCI (95% confidence intervals)	b) MCI from dementia (95% confidence intervals)
Q*mci*	0.87 (0.77-0.96)	0.97 (0.95-1.00)
6CIT	0.71 (0.57-0.85)	0.87 (0.81-0.94)
MoCA	0.76 (0.63-0.90)	0.92 (0.87-0.97)

Discussion

This subanalysis presents the results of comparison between three short cognitive screens, the Q*mci*, MoCA and 6CIT, in a geriatric memory clinic. The results show that the Q*mci* was more accurate than the 6CIT, in identifying cognitive impairment. Although all three instruments had statistically similar accuracy in separating MCI from SMC, the Q*mci* had the larger AUC suggesting greater accuracy. All three instruments were equally able to identify dementia suggesting that the 6CIT with its shorter administration time, may be useful as a short screen when assessing patients with a high index of suspicion for dementia or monitoring progression of dementia over time. Designed for primary care, the 6CIT is more weighted towards verbal skills (100%) compared to the Q*mci* (85%) and lacks tests of higher cognitive function. In conclusion, though the sample size was small, this study suggests that the 6CIT is not useful in differentiating CI from SMC in clinic settings and may be more useful as a quick screen to confirm dementia particularly in settings such as hospitals.

Chapter 8

Measuring cognitive change over time; Comparison of the Q*mci* to instruments in a clinical trial

8.1 Introduction

A number of cognitive screening instruments are used in clinical care and research. To standardise assessments and allow comparison between settings, there is a need for valid and reliable cognitive assessment tools. No single cognitive screening instrument is ideal, and to date, none have become established as the standard [Gifford et al., 1999]. Several are limited by their inability to detect significant variations between patients with respect to age and or educational status [Crum et al 1993]. Researchers and clinicians require short instruments that are reliable, valid and responsive to change across a wide range of cognitive function. They need multiple, standardised scoring formats that measure changes early (high ceiling) and in the later stages of dementia (low floor). The existing accepted standard for measuring cognitive function in clinical trials in dementia, is the ADAS-cog [Rosen et al., 1984],[O'Halloran et al., 2011],[Weyer et al., 1997] and its standardised version, the SADAS-cog. The hypothesis tested in this study within the PhD is whether the short Q*mci* screen could be used in clinical trials instead of the longer SADAS-cog. In order to test this we performed an analysis of data from the Doxycycline and Rifampicin for Alzheimer's Disease (DARAD) trial comparing the Q*mci* with the SADAS-cog, to investigate the extent to which the two tests were correlated and to determine each instruments` sensitivity to change (responsiveness) in this setting.

8.2 Methods

Study Sample

The DARAD trial investigated the use of two antibiotics, doxycycline and rifampicin, in 406 patients with mild to moderate Alzheimer's dementia. Subjects were randomised into four arms: doxycycline 100 mg twice daily with rifampin 300 mg daily, or doxycycline 100 mg twice daily with placebo-rifampin daily, or rifampin 300 mg daily with placebo-doxycycline twice daily or placebo-doxycycline twice daily, with placebo-rifampin daily [Loeb et al., 2004],[Molloy et al., 2012]. Patients, were recruited from 14 Canadian geriatric clinics, between 2006 and 2010. The DARAD database contains data for a range of variables at one, three, six, nine and twelve months. Patient's aged ≥50 years, meeting the NINCDS criteria for Alzheimer's disease [McKhann et al., 1994], with SMMSE scores between 14 and 26, were included. Patients were excluded if they were unable to communicate verbally in English.

Measures

The co-primary outcomes in the DARAD trial were the SADAS-cog and the Clinical Dementia Rating scale (CDR) using the Sum of the Boxes technique [Morris 1993],[Schafer et al., 2004]. Secondary outcomes included the Q*mci* and Lawton-Brody ADL scale [Lawton & Brody, 1969]. A trained rater administered the SADAS-cog, Q*mci*, and CDR in a random sequence, blinded to each study arm.

The Standardised Alzheimer`s Disease Assessment Scale-cognitive section (SADAS-cog)

The SADAS-cog is described in detail in Chapter one and is presented in Appendix 2.5.

The Clinical Dementia Rating scale (CDR)

The CDR is a global assessment scale measuring cognitive impairment in six areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care [Morris 1993],[Schafer et al., 2004]. The CDR is scored from zero to three and is presented in Table 8.1.

Table 8.1. Clinical Dementia Rating (CDR) Scale score.

Clinical Dementia Rating (CDR) Scale score	Stage	Description
CDR-0	Normal	-
CDR-0.5	MCI	Memory problems are slight but consistent; some difficulties with time and problem solving; daily life slightly impaired
CDR-1	Mild	Memory loss moderate, especially for recent events, and interferes with daily activities. Moderate difficulty with solving problems; cannot function independently at community affairs; difficulty with daily activities and hobbies, especially complex ones.
CDR-2	Moderate	More profound memory loss, only retaining highly learned material; disoriented with respect to time and place; lacking good judgment and difficulty handling problems; little or no independent function at home; can only do simple chores and has few interests.
CDR-3	Severe	Severe memory loss; not oriented with respect to time or place; no judgment or problem solving abilities; cannot participate in community affairs outside the home; requires help with all tasks of daily living and requires help with most personal care. Often incontinent.

Lawton-Brody Activities of Daily Living Scale

The Lawton-Brody ADL scale is an established instrument for measuring instrumental and basic ADLs [Lawton & Brody, 1969]. It includes 14 subtests, scored from 14 to 65 points, with higher scores suggesting greater independence. Basic ADL include: the ability to toilet, feed themselves, dress, groom, bath and walk. Instrumental include the ability to shop, prepare food, perform housekeeping, laundry, arrange transportation, administer medication, use the telephone and manage finances). The scale can be self-reported or completed by an informant. It has high IRR (0.85) [Lawton & Brody, 1969].

Data Analysis

Data from the DARAD database were analysed using SPSS, version 20.0 The Shapiro-Wilk test was used to test normality and found that most data were approximately symmetrical, having a small deviation from normality. The median and IQR were reported for skewed continuous data (age and SMMSE). This analysis included only those patients who had complete data. The correlations between the Q*mci* and the SADAS-cog, were calculated using the data collected at one, three, six, nine and twelve months. The original values were standardized, to remove within subject variations, and simple regression analyses were run to estimate correlation coefficients. To address the validity of the two instruments, the relationship between both the SADAS-cog and the Q*mci* and two other variables (Lawton-Brody ADL scale and CDR), were analysed using different analytic approaches. Correlations were analysed at each time point, then for all time points together and finally for mean values across time. Fishers Z test was used to determine differences in correlations between tests. To compare the responsiveness of the two instruments, at each time point, the standardized response mean (SRM), the mean score change

divided by the standard deviation of the score change using baseline as the initial score, were calculated for the SADAS-cog and Q*mci*. Paired-samples t-tests were performed to detect if a statistically significant difference existed in the SRM between the SADAS-cog and Qmci.

8.3 Results

Overall, 365 of the 406 patients who entered the DARAD study completed one year. Median age of the total population was 79 years, IQR 10. The median SMMSE score at baseline was 23, IQR 5. Over 90% were taking a cholinesterase inhibitor and 13%, the N-Methyl-D-Aspartate receptor antagonist, memantine. In total, 360 patients had complete data for the Q*mci* and 363 for the SADAS-cog, 364 for the Lawton-Brody ADL scale and 360 for the CDR. 358 patients had complete data for the Q*mci* and SADAS-cog, at each time point, over the year. Correlation coefficients between the outcome measures along with their 95% CI, at each time point, at all time points and using mean values across time are reported in Table 8.1.The correlation coefficients demonstrated significant, strong correlation between the Q*mci* and the SADAS-cog, at each time point, r =-0.69 (95% CI, -0.62 to -0.78) p=<0.001, for the first month and -0.76, (95% CI, -0.70 to -0.83), p <0.001 for the last month. The data most closely correlated at nine months, r =-0.78, p <0.001. Each patient was included five times (corresponding to each time point) in the calculation, which would be expected to inflate the value of the correlation coefficient. However, estimating correlations between measures overall, at all time points, pooled together, showed that the correlations between the SADAS-cog and Q*mci* remained strong and significant r = -0.75 (95% CI, 0.72 to 0.78), p <0.001. Correlations increased to -0.8 using mean values across time.

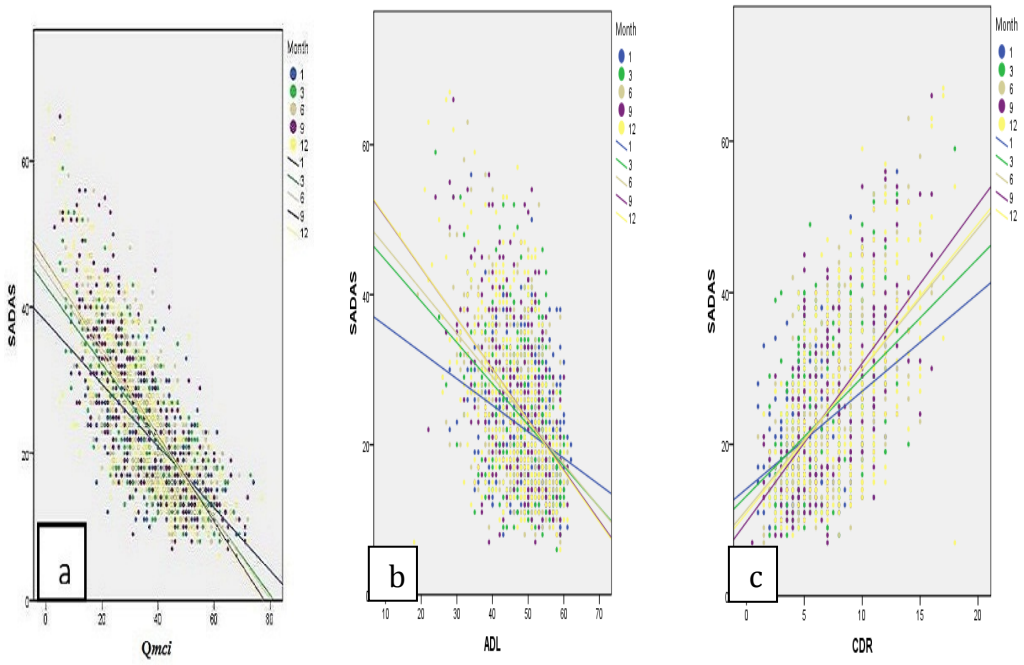
Table 8.2. Demonstrating correlation coefficients, with 95% Confidence Intervals (CI), between the Standardised Alzheimer`s Disease Assessment Scale-Cognitive section (SADAS-cog) and Quick Mild Cognitive Impairment (Q*mci*), Lawton-Brody Activities of Daily Living (ADL) scale and Clinical Dementia Rating scale (CDR) using different analysis methods.

Analysis Method	**Month**	**SADAS-cog to Q*mci*** (Correlation Coefficient [95% CI])	**SADAS-cog to ADL** (Correlation Coefficient [95% CI])	**Q*mci* to ADL** (Correlation Coefficient [95% CI])	**Fisher Z test for difference in correlations with ADL**	**SADAS-cog to CDR** (Correlation Coefficient [95% CI])	**Q*mci* to CDR** (Correlation Coefficient [95% CI])	**Fisher Z test for difference in correlations with CDR**
Correlations at each time point	1	-0.69 [-0.62 to -0.76]	-0.31 [-0.21 to -0.40]	0.26 [0.17 to 0.36]	$z = .66$ $p = .51$	0.41 [0.32 to 0.50]	-0.38 [-0.29 to -0.47]	$z = .44$ $p = .66$
	3	-0.75 [-0.69 to -0.82]	-0.41 [-0.32 to -0.50]	0.32 [0.22 to 0.42]	$z = 1.39$ $p = .17$	0.45 [0.36 to 0.54]	-0.48 [-0.39 to -0.57]	$z = -.52$ $p = .60$
	6	-0.76 [-0.69 to -0.83]	-0.44 [-0.34 to -0.53]	0.34 [0.24 to 0.44]	$z = 1.45$ $p = .15$	0.56 [0.48 to 0.65]	-0.55 [-0.46 to -0.64]	$z = .28$ $p = .78$
	9	-0.78 [-0.71 to -0.85]	-0.46 [-0.36 to -0.56]	0.39 [0.29 to 0.49]	$z = 1.14$ $p = .25$	0.59 [0.50 to 0.68]	-0.56 [-0.46 to -0.65]	$z = .70$ $p = .48$
	12	-0.76 [-0.70 to -0.83]	-0.49 [-0.40 to -0.58]	0.45 [0.36 to 0.55]	$z = .65$ $p = .51$	0.57 [0.49 to 0.66]	-0.55 [-0.46 to -0.64]	$z = .42$ $p = .67$
Unadjusted correlations using all time points together		-0.75 [-0.72 to -0.78]	-0.42 [-0.37 to -0.46]	0.37 [0.33 to 0.42]	$z = 1.67$ $p = .09$	0.51 [0.47 to 0.55]	-0.52 [-0.48 to -0.56]	$z = -.28$ $p = .78$
Unadjusted correlations using mean values across time		-0.80 [-0.74 to -0.86]	-0.43 [-0.34 to -0.52]	0.38 [0.29 to 0.47]	$z = .75$ $p = .45$	0.54 [0.46 to 0.62]	-0.54 [-0.46 to -0.62]	$z = -.02$ $p = .98$

The relationship between the SADAS-cog and Q*mci*, and the other measures, Lawton-Brody ADL scale and CDR, at each of the five time points, showed modest to strong, significant correlations. Correlations between the CDR and SADAS-cog (range from 0.41 to 0.59) were stronger than between the Lawton-Brody ADL scale and SADAS-cog (range from -0.31 to -0.49). Figure 8.1 provides the correlations between the SADAS-cog and Q*mci*, and between the Q*mci* and SADAS-cog and the other variables, Lawton-Brody ADL scale and CDR, at each time point. Confidence intervals for correlations between the outcome measures at different time points overlap, indicating no difference between them. Fishers Z test confirmed that there was no statistically significant difference in correlations between the SADAS-cog and Q*mci* with either Lawton-Brody ADL scale, z=1.67, p =0.09 or CDR scores, z =-0.28, p= 0.78. Responsiveness of the SADAS-cog and Q*mci*, determined using the SRM, demonstrated that the mean change in SADAS-cog scores, between months one and twelve, calculated for each patient, was approximately five points, with a standard

deviation (SD) of 7.56.The estimated mean difference in scores, repeated for the Q*mci*, was 5.41 points, SD of 10.02 .Paired-samples t-test, showed there was no statistically significant difference in the SRMs for SADAS-cog and Q*mci*, t(357) = -0.32, p =0.75. This means that the change in Q*mci* scores are very similar to changes in SADAS-cog scores, between months one to twelve. There was a statistically significant increase in SADAS-cog scores, mean of 21.56, SD of 7.89 at month one, to a mean of 26.56, SD 12.01, at month twelve, t(362) = 12.60, $p < 0.001$. There was a statistically significant decrease in Q*mci* scores from month one, mean 38.58, SD = 12.83, to month twelve, mean = 32.76, SD = 15.593, t(359) = -10.23, p <0.001.

Figure 8.1. Scatter plot depicting correlations between a) Standardised Alzheimer`s Disease Assessment Scale-Cognitive section (SADAS-cog) and Quick Mild Cognitive Impairment (Q*mci*), b) SADAS-cog and Lawton-Brody Activities of Daily Living (ADL) scale and c) SADAS-cog and Clinical Dementia Rating (CDR), at each time point, (1,3,6,9,12 months).



Internal Consistency of the Q*mci*

Internal consistency of the Q*mci* was assessed using Cronbach's Alpha and by calculating the correlation between Q*mci* scores over time (five data points in the DARAD trial: Months 1,3,6,9 and 12). Internal consistency of the Qmci measure measured using Cronbach's Alpha for five data points was exceptionally strong $\alpha = 0.95$. Strong significant correlation was seen between the Q*mci* and itself over time, correlations ranging between r= 0.73 and 0.83. These are presented in Table 8.3.

Table 8.3. Correlation of a) the Standardised Alzheimer`s Disease Assessment Scale-Cognitive section (SADAS-Cog) to itself and b) the Quick Mild Cognitive Impairment (Q*mci*) to itself, over each time point (1,3,6,9,12 months).

a

	(1)	(2)	(3)	(4)
(1) SADAS-cog at 1 month	-			
(2) SADAS-cog at 3 months	.86**	-		
(3) SADAS-cog at 6 months	.86**	.89**	-	
(4) SADAS-cog at 9 months	.83**	.88**	.90**	-
(5) SADAS-cog at 12 months	.79**	.84**	.87**	.91**

b

	(1)	(2)	(3)	(4)
(1) Q*mci* at 1 month	-			
(2) Q*mci* at 3 months	0.80**	-		
(3) Q*mci* at 6 months	0.79**	.83**	-	
(4) Q*mci* at 9 months	0.77**	0.81**	.83**	-
(5) Q*mci* at 12 months	0.73**	0.76**	.78**	.82**

**. Correlation is significant at the 0.001 level

8.4 Discussion

This study compared the SADAS-cog to the Q*mci*, Lawton-Brody ADL scale and CDR, by comparing observations at multiple time points, from data collected in the DARAD trial, over one year. The SADAS-cog correlated closely with the Q*mci*, irrespective of the method of analysis.The SADAS-cog and ADL also correlated with both the Lawton-Brody ADL scale and CDR. The confidence intervals for correlation coefficient estimates for the Q*mci* and SADAS-cog and intervals for correlations between the SADAS-cog and ADL or CDR, did not overlap, indicating a significantly

stronger relationship between the Q*mci* and SADAS-cog than between the ADL or CDR and SADAS-cog and Q*mci* scores. In other words, the Q*mci* and SADAS-cog are better predictors of each other than of the other two measures (ADL and CDR). This is expected given that the SADAS-cog and Q*mci* are measures of cognitive function, although the SADAS-cog also correlated to functional status [Caro et al., 2002]. Both the Q*mci* and the SADAS-cog are equally sensitive to change, and have similar responsiveness. Both had weak correlations with ADL, particularly at the outset. Correlation between the Q*mci* and the Lawton-Brody ADL scale was especially weak at month one (r=0.26) but improved towards moderate at one year. This weak correlation with ADLs at the entry point to the study was also found for the more detailed neuropsychological test, the ADAS-cog. This is not unexpected as ADL are a poor surrogate marker for cognitive scores and vice versa. ADL strongly reflect the stage of cognitive impairment but can be confounded by medical conditions and physical disability. Cognitive screening instruments such as the Q*mci*, like more detailed neuropsychological testing, are often confounded by baseline IQ, age and education. The CDR, a global marker of dementia incorporating function and cognition, had weak correlation to the Q*mci*, which again became moderate as the study progressed. There was no statistically significant difference with the SADAS-cog showing that the performance of both the longer neuropsychological battery and short screening instrument were similar. The reasons for the improvement in the correlation coefficients over time are unclear. It might reflect improved inter-rater or test-re-test reliability as the study progressed, a therapeutic effect or convergence as cognitive function and ADL function declined over time. It may also reflect the poor content validity of the Lawton-Brody ADL scale. The strength of this paper lies in its methodology. Correlation between the SADAS-cog and each of the measures was

demonstrated using different statistical methods. Each consistently confirmed strong correlation between the SADAS-cog and Q*mci* and moderate to strong correlation between the SADAS-cog and Q*mci*, Lawton-Brody ADL scale and CDR. The correlations demonstrated at each of the five time points, were similar to the pooled correlation coefficients. Another strength, is that this data, a post hoc analysis of the DARAD trial database, represents the "real life" performance of the Q*mci*, compared to the accepted standard, in a previously conducted, multi-centre, blinded, randomised control trial. Given that a four-point change at six months in the ADAS or SADAS-cog is widely recognised as a clinically significant difference [Matthews et al., 2000],[Aisen et al., 2003], the similar responsiveness of the Q*mci* and SADAS-cog suggests that a comparable change in the Q*mci* is equivalent to a significant change in the SADAS-cog. Given that the Q*mci* is shorter and easier to score, this data supports the use of the Q*mci* as an alternative to the SADAS-cog in clinical trials. While a small change and only relevant if associated with clinical improvement, it is required by the Food and Drug Administration in the United States before a drug can be licensed in dementia.

This study has several limitations. Although a four-point change in the SADAS-cog is traditionally accepted as significant, it is not an ideal test. Comparing the Q*mci* to the SADAS-cog only suggests that the Q*mci* has similar sensitivity and responsiveness, not that it is a "gold standard". Although useful, the Q*mci* is less comprehensive than the SADAS-cog and not all neuropsychological domains are accounted for. That said, in contrast to the SADAS-cog the Q*mci* is shorter and easier to apply, covering many relevant cognitive domains including orientation, working memory, visuospatial, executive function, semantic memory and episodic memory. In contrast, the SADAS-cog is overly long and heavily weighted towards language. The

SADAS-cog, because of ceiling effects, is less responsive to detecting MCI [Skinner et al., 2012], possibly limiting its usefulness. The Q*mci,* in contrast, is accurate at differentiating MCI from normal cognition and dementia [O'Caoimh et al., 2012] suggesting that where this is the outcome measure of interest the Q*mci* could be used in preference. The ADL measure used in this study, the Lawton-Brody ADL scale, has limitations. Although it is widely validated, it measures instrumental ADLs and like any measure of ADL is self-reported, potentially over or under-estimating functional impairment and is not a recognised standard for measuring ADLs. This said, no gold standard of measure of ADL is available.

In summary, the ADAS-cog and its standardised form the SADAS-cog, are valid, reliable and widely used cognitive measures in clinical trials [Rockwood et al., 2006],[Molloy et al., 2012],[Chen et al., 2011],[Sano et al., 2011]. They have been validated internationally from Iceland [Hannesdóttir et al., 2002] to Turkey [Mavioglu et al., 2006] and Hong-Kong [Chu et al., 2000] and despite flaws, remain the standard. This data demonstrates that the Q*mci* correlates strongly, significantly and correspondingly over time to the SADAS-cog and that both are equally sensitive with similar responsiveness to deterioration over time. Although the correlation with each other was stronger, the SADAS-cog and Q*mci* had moderate to strong correlations with both functional (Lawton-Brody ADL scale) and global assessments (CDR), confirming their utility in clinical practice as well as in drug trials. Although further external validation of the instrument in other clinical settings, trials and languages is required, this study provides a rationale for using the shorter Q*mci*, as a cognitive outcome measure in clinical drug trials, particularly where differentiating MCI from normal cognition and dementia is important. It also shows that the Q*mci* had high internal consistancy.

Chapter 9

Clinical utility of the Q*mci* outside of a memory clinic; Use of the Q*mci* in a movement disorder clinic.

9.1 Introduction

The prevalence of movement disorders is also increasing as society ages with the number of persons with PD worldwide expected to nearly double by 2030 [Tanner 2013]. The most prevalent movement disorder worldwide is PD [Dorsey et al., 2007]. With this will come an increase in the prevalence of cognitive impairment associated with PD. Cognitive impairment is common in PD and is the most common non-motor symptom of PD [Sitek et al., 2014]. Prevalence rates approach 80% [Aarsland et al., 2003], while the lifetime incidence of PDD lies between 40% and 100% [Aarsland et al., 2003]. Many patients with PD have CI from the time of diagnosis. PD with mild cognitive impairment (PD-MCI) is common [Litvan et al., 2011] and is associated with an increased chance of developing dementia, particularly when already present at diagnosis [Pederson et al., 2013].

Cognitive impairment impacts upon life expectancy [Marder et al., 1991], quality of life [Schrag et al., 2000], and ADL even among those without PDD [Aarsland et al., 2003]. Early diagnosis of cognitive decline is important to facilitate prompt treatment, identify reversible or compounding factors and plan for the future [Boise et al., 1999]. Monitoring change over time is important and screening with short cognitive instruments and repeated neuropsychological testing [Pederson et al., 2013] is recommended to increase prognostic accuracy, particularly conversion from PD-MCI to PDD. PD-MCI in particular is challenging to diagnose. It differs from MCI associated with Alzheimers disease [Caviness et al., 2007] and typically presents

with exaggerated attention and executive function deficits [Petrova et al., 2010]. Other movement disorders such as LBD [Molano et al., 2010],[Ferman et al., 2013] and vascular PD [APA 2013] are also associated with a MCI phase, that differs from those seen in other neuro-degenerative disorders.

The MMSE [Folstein et al., 1975] and its standardised form, the SMMSE [Molloy et al., 1997], is widely used in the detection of cognitive impairment associated with PD [Lyness et al., 2014]. The MoCA [Nasreddine et al., 2005] has been recommended, by the Movement Disorder Society, as the cognitive screen of choice in PD [Emre et al., 2007],[Barton et al., 2012]. The MoCA is more sensitive than the MMSE for detecting mild cognitive deficits in PD [Gill et al., 2008] and has several advantages over the MMSE. The MoCA lacks a ceiling effect [Zadikoff et al., 2008] making it more useful in younger and more educated subjects and it is weighted more towards attention, visospatial and executive functioning and less towards orientation and language, which are relatively well preserved in PD [Petrova et al., 2010],[Caviness et al., 2007]. Despite these advantages some challenges remain with using the MoCA in routine clinical practice as described above in Chapter 7. In particular, it takes time (10-12 mins), it is has low specifcity [McLennan et al., 2011] and a high false positive rate in older adults at its recommended cut-off score (≥26 for normal cognition). Given this we sought to investigate if the Q*mci* screen, designed to detect MCI and validated in patients without PD, could be used to detect cognitive impairment in a movement disorder clinic and how it compared to two of the most widely used instruments in this setting, the MMSE and MoCA.

9.2 Methods

Patients

Patients, referred to a university hospital movement disorder clinic were classified as having normal cognition, MCI or dementia by a consultant physician, specialised in the diagnosis and management of cognitive impairment associated with movement disorders. A diagnosis of PD-MCI was made by a consultant geriatrician using level I diagnostic criteria according to the Movement Disorder Society Task Force Guidelines [Litvan et al., 2012], defined as recent, subjective but corroborated memory loss without obvious loss of social or occupational function, with evidence of deficits on a global cognitive scale: the Unified Parkinson's Disease Rating Scale (UPDRS) part I, in those with established PD. A diagnosis of LBD-MCI was made using the third report of the LBD Consortium [McKeith et al., 2005]. Subjects were excluded if they were under 55 years of age, unable to communicate verbally in English, if they had active depression, diagnosed clinically and supported by the GDS-Short Form, using a cut-off greater than seven to increase specificity [Marc et al., 2008], or if a reliable collateral was not available. The GDS Short Form, scored out of 15 points, is validated in older adults with PD [Weintraub et al., 2006] and has been used in other movement disorders including LBD [Kao et al., 2009]. Patients presenting with essential tremor (n=3) were also excluded.

Data Collection

Patients attending a movement disorder clinic in Cork City, Ireland, between July 2013 and July 2014 underwent comprehensive clinical assessment and were screened for cognitive impairment. An attempt was made to screen patients consecutively but because of time restraints and practical reasons sampling was by convenience. The

Q*mci* and MoCA were scored in random order, by two trained raters, prior to the clinic and blind to the diagnosis, one of whom was a trained Parkinson's nurse specialist. The SMMSE is collected routinely by clinic nursing staff. The presence and severity of any extrapyramidal symptoms were graded using the motor component of the UPDRS. All patients provided verbal consent; assent was obtained from individuals who were felt to lack capacity. Diagnosis was made by the attending consultant Geriatrician, Dr Suzanne Timmons using clinical history and examination, supported by the UPDRS.

Measures

The MoCA and Q*mci* were compared in this study. The Q*mci* was used with an initial cut-off score of <62 as described above in Chapter 5. A score of <26 was used as the MoCA cut-off for cognitive impairment [Nasreddine et al., 2005]. The severity of PD was determined using the UPDRS [Fahn et al., 1987]. The UPDRS total score consists of the sum of parts I (mentation, behaviour and mood), II (ADL) and III (motor examination), with scores ranging from 0 (not affected) to 176 (most severey affected). A score of one or more on item one (intellectual impairment) of part I was taken as suggestive of cognitive impairment. Type of medications including the use of dopaminergic agents, anti-cholinergics and cholinesterase inhibitors was also included.

Analysis

Accuracy was determined from analysis of the AUC generated by receiver ROC curves. Sensitivity, specificity, PPV and NPV were also determined. The majority of the data were non-parametric. The Mann –Whitney U test compared two variables; the Kruskal-Wallis Test was used to compare more than two variables.

9.3 Results

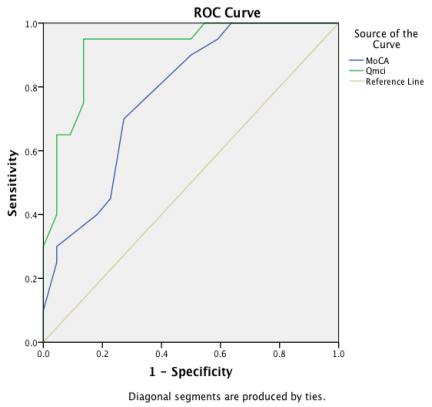
In total, 84 paired assessments (from 66 individual patients) were available. The majority of patients had PD (n=57); nine had LBD. The characteristics of patients including their time since diagnosis, UPDRS scores and cognitive screen scores are presented in Table 9.1. The median age of patients was 75 years and there were no significant differences in ages profile between those with normal cognition, MCI or dementia, z =5.1, p =0.08. Patients with normal cognition reported having spent more time in education than those with MCI or dementia. Where available, median time since diagnosis of a movement disorder (predominantly PD) was 7.5 years +/-8. Patients with MCI and dementia had similar disease duration, (median 9.5 years, z =-0.2, p = 0.86). As would be expected patients with dementia had greater median UPDRS total scores though no difference in scores were found for those with MCI or normal cognition (median 36). The median Q*mci* score for those with normal cognition was 70 +/-8 compared with a median of 55 +/-7 for those with MCI and a median of 36 +/-17 for patients diagnosed with dementia. There was only a small difference in median MoCA scores between normals and those with MCI, 23 versus 22 respectively, although this was statistically significantly different, z =-3.1, p =0.002. A statistically significant difference was also found for the Q*mci*, z =-4.7, p <0.001. Twelve patients were receiving an anti-cholinergic and only 11/29 individuals with dementia were receiving a cholinesterase inhibitor.

Table 9.1. Characteristics of patients with normal cognition, mild cognitive impairment (MCI) and dementia, recruited from the movement disorder clinic including demographics, Unified Parkinson's Disease Rating Scale (UPDRS), Standardised Mini-Mental State Examination (SMMSE), Quick Mild cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) scores.

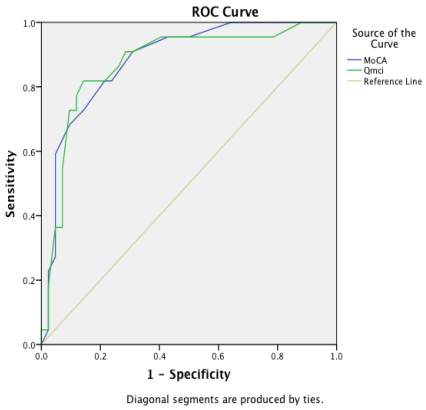
Group	**Included Individuals** (assessments)	**UPDRS**	**UPDRS-Cog**	**Years since Diagnosis**	**Gender (female)**	**Age (Median & IQR)**	**Education (Median & IQR)**	**SMMSE (Median & IQR)**	**Q*mci* (Median & IQR)**	**MoCA (Median & IQR)**
All	66 (84)	39 53-30=+/-23	3 5-1=4	7.5 11-3=+/-8	25/66 (38%)	75 80-72=+/-8	12 14-10=+/-4	26 28-22=+/6	51 63-35=+/-28	18 23-12=+/-11
Normal Cognition	16 (20)	36 52-23=+/-29	1 3-1=+/-2	5.5 7-2=+/-5	6/16 (37.5%)	75 79-71=+/-8	14.5 17-11=+/-6	29 30-28=+/-2	70 73-65=+/-8	23 26-22=+/-4
MCI	21 (22)	36 44-24=+/-20	4 5-3=+/-2	9.5 12.5-3=+/-9.5	6/21 (29%)	75 78-73=+/-5	12 14-10=+/-4	27 28-26=+/-2	55 59-52=+/-7	22 23-17=+/-6
Dementia **-Mild 33** **-Mod 8** **-Severe 1**	29 (42)	54 64-33=+/-31	4.5 5-3=+/-2	9.5 11-4.5=+/-6.5	13/29 (45%)	75 81-72=+/-9	11 13-10=+/-3	22 26-18=+/-8	36 45-28=+/-17	13 15-10=+/-5

ROC curves showing the accuracy of the Q*mci* and MoCA are presented in Figure 9.1. The Q*mci* had similar accuracy to the MoCA in differentiating MCI from SMC and dementia, with no statistically significant differences between either screen found in this sample. Examining the sensitivity and specificity of both instruments suggests that the best balance for the Q*mci* was produced at a cut-off score less than 60 (i.e. <61). At this cut-off its sensitivity was 94% and specificity 95%. At the cut-off presented in chapter 5, <62, the sensitivity was 94% and specificity 90%. The established MoCA cut-off score for cognitive impairment (<26) produced high sensitivity (97%) but markedly low specificity (30%). A cut-off of <23 provided the optimal balance for the MoCA (sensitivity of 88%, specificity of 70%). Sensitivities and specificities for a range of MoCA and Q*mci* cut-offs are presented in Table 9.2. The median administration time for the Q*mci* was 5.17 mins compared to 9.24 mins for the MoCA.

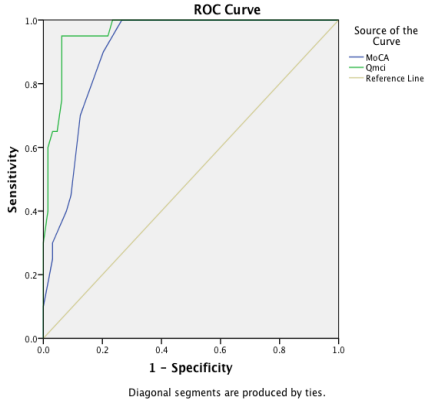
Figure 9.1. Receiver Operating Characteristic curves demonstrating the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) in differentiating patients with movement disorders (Parkinson's disease and Lewy Body Dementia) with (a) mild cognitive impairment (MCI) from normal cognition, (b) MCI and dementia, (c) normal from cognitive impairment (MCI and dementia), (d) Dementia from everything else.



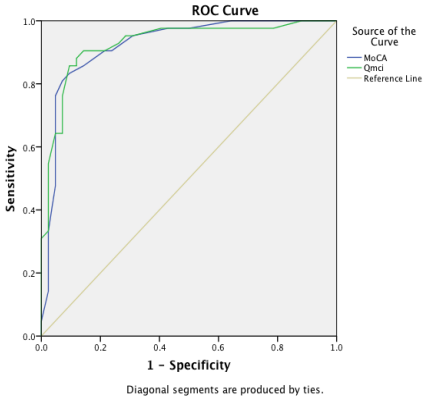
a.



b.



c.



d.

Figure	MoCA	Q*mci*	Comparison
	Area Under the Curve (95% Confidence Intervals)		(p=x)
a	0.78 (0.64-0.92)	0.92 (0.84-1.0)	z=-1.7 (p=0.09)
b	0. 88 (0.80-0.97)	0.87 (0.78-0.97)	z=0.14 (p=0.89)
c	0.90 (0.84-0.97)	0.97 (0.93-1.0)	z=-1.1 (p=0.26)
d	0.92 (0.86-0.98)	0.93 (0.87-0.97)	z=-0.1 (p=0.93)

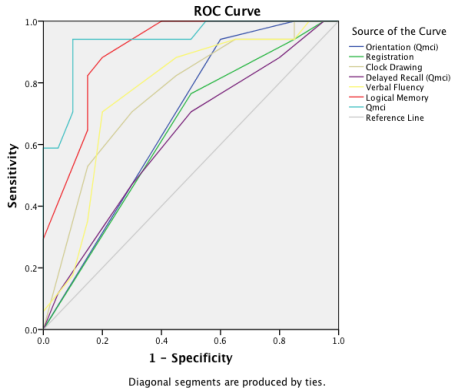
Table 9.2. Sensitivity, Specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV), with 95% confidence intervals (CI), for different Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) cut-off scores for cognitive impairment (mild cognitive impairment and dementia) versus those with normal cognition.

Cognitive Screen (reference)	**Cut-off score**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**PPV (95% CI)**	**NPV (95% CI)**	**False Positive (95% CI)**	**False Negative (95% CI)**
				Prevalence of cognitive impairment of 76%			
Q*mci*							
	<65	94% (84-98)	75% (51-90)	92% (82-97)	79% (54-93)	8% (3-18)	21% (7-46)
	<64	94% (84-98)	75% (51-90)	92% (82-97)	79% (54-93)	8% (3-18)	21% (7-46)
	<63	94% (84-98)	90% (67-98)	97% (88-99)	82% (59-94)	3% (0.5-12)	18% (6-41)
†	<62	94% (84-98)	90% (67-98)	97% (88-99)	82% (59-94)	3% (0-12)	18% (6-41)
	<61	94% (84-98)	95% (73-100)	98% (90-100)	83% (60-94)	2% (0-10)	17% (6-40)
	<60	92% (82-97)	95% (93-100)	98% (90-100)	79% (57-92)	2% (0-10)	21% (8-43)
	<59	84% (73-92)	95% (73-100)	98% (89-100)	66% (46-81)	2% (0-11)	34% (19-54)
	<58	84% (73-92)	95% (73-100)	98% (89-100)	66% (46-81)	2% (0-11)	34% (19-54)
	<57	83% (71-91)	95% (73-100)	98% (89-100)	63% (44-79)	2% (0-11)	37% (21-56)
	<56	81% (68-89)	95% (73-100)	98% (89-100)	61% (42-78)	2% (0-12)	39% (22-58)
	<55	78% (66-87)	95% (73-100)	98% (88-100)	58% (39-74)	2% (0-12)	42% (26-61)
MoCA							
	<26	97% (88-99)	30% (13-54)	82% (71-89)	75% (36-96)	18% (11-29)	25% (4-64)
	<25	92% (82-97)	40% (20-64)	83% (72-91)	62% (32-85)	17% (9-28)	38% (15-68)
	<24	91% (80-96)	45% (24-68)	84% (73-91)	60% (33-83)	16% (9-27)	40% (17-67)
	<23	88% (76-94)	70% (46-87)	90% (79-96)	64% (41-82)	10% (4-21)	36% (18-59)
	<22	80% (67-88)	90% (67-98)	96% (86-99)	58% (39-75)	4% (1-14)	42% (25-61)

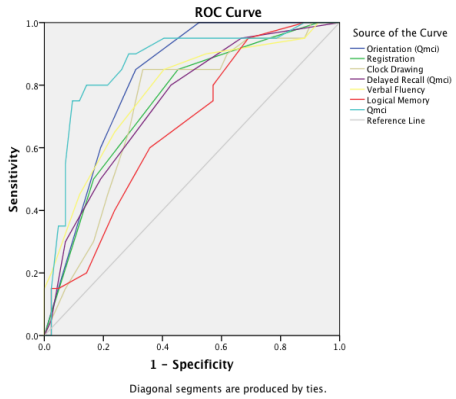
† O'Caoimh et al IJMS 2014

Figure 9.2 presents ROC curves for the Q*mci* subtests; Figure 9.3 presents the curves for the MoCA subtests. The results suggest that the most accurate Q*mci* subtest for differentiating MCI from normal cognition is LM (AUC 0.90), while the most accurate MoCA subtest were the visuospatial tasks (AUC 0.79). The DR (five word recall) subtests were both poor in separating those with MCI form normal cognition was poor (AUC 0.62 for the Q*mci* and 0.56 for the MoCA). Orientation was the best subtest for both instrument for differentiating MCI from dementia (AUC 0.82 for the Q*mci* and 0.84 for the MoCA). LM was less able to separate MCI from dementia in this population (AUC 0.66). Good to excellent accuracy for both instruments subtests were found for the ability to distinguish cognitive impairment (MCI and dementia) from normal and dementia from normal and MCI. ROC curves for patients with PD, excluding those with LBD, are presented in Figure 9.4. These show similar AUC values.

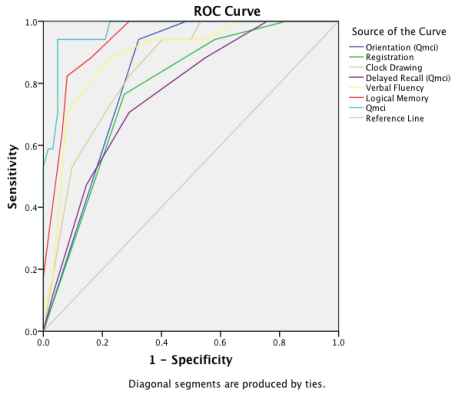
Figure 9.2. Receiver Operating Characteristic curves demonstrating the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen subtests in differentiating patients with movement disorders (Parkinson's disease and Lewy Body Dementia) with (a) mild cognitive impairment (MCI) from normal cognition, (b) MCI and dementia, (c) normal from cognitive impairment (MCI and dementia), (d) Dementia from everything else.



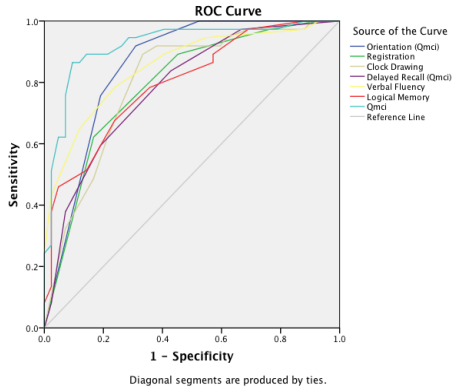
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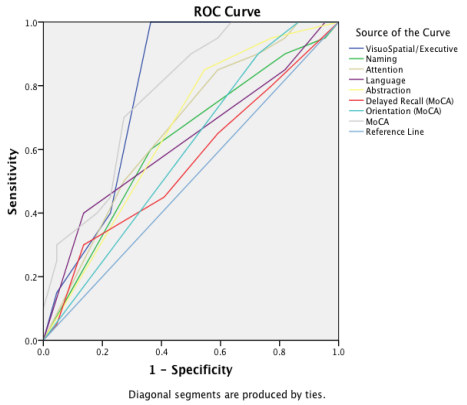
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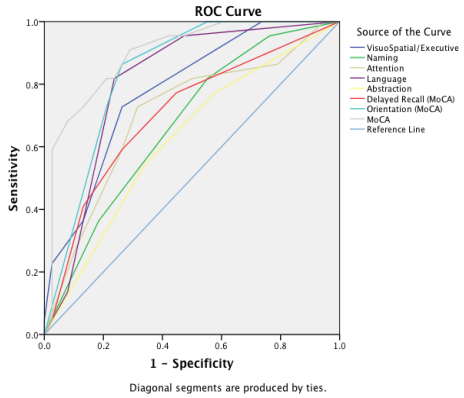
d.

Qmci	**a. Normal V MCI**	**b. MCI V Dementia**	**c. Normal V CI**	**d. Dementia V everything else**
Subtests	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)
Orientation	0. 68 (0.50-0.85)	0.82 (0.72-0.92)	0.82 (0.74-0.91)	0.85 (0.77-0.94)
Registration	0.64 (0.46-0.82)	0.75 (0.62-0.88)	0.78 (0.67-0.89)	0.79 (0.69-0.89)
Clock Drawing	0.76 (0.61-0.92)	0.73 (0.60-0.86)	0.85 (0.77-0.94)	0.80 (0.70-0.90)
Delayed Recall	0.62 (0.44-0.81)	0.75 (0.62-0.87)	0.77 (0.65-0.88)	0.79 (0.69-0.89)
Verbal Fluency	0.77 (0.61-0.93)	0.78 (0.65-0.90)	0.89 (0.80-0.97)	0.85 (0.77-0.94)
Logical Memory	0.90 (0.80-1.0)	0.66 (0.52-0.80)	0.94 (0.89-0.99)	0.80 (0.70-0.89)

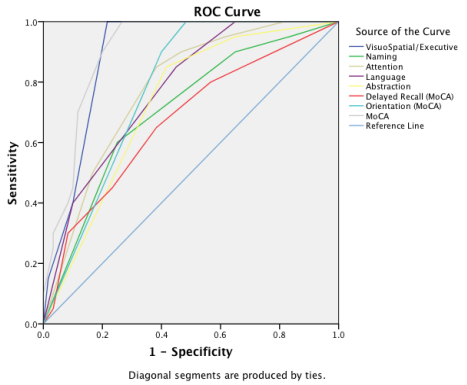
Figure 9.3. Receiver Operating Characteristic curves demonstrating the accuracy of the Montreal Cognitive Assessment (MoCA) subtests in differentiating patients with movement disorders (Parkinson's disease and Lewy Body Dementia) with (a) mild cognitive impairment (MCI) from normal cognition, (b) MCI and dementia, (c) normal from cognitive impairment (MCI and dementia), (d) Dementia from everything else.



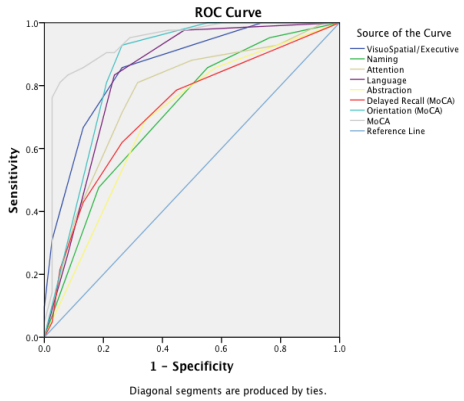
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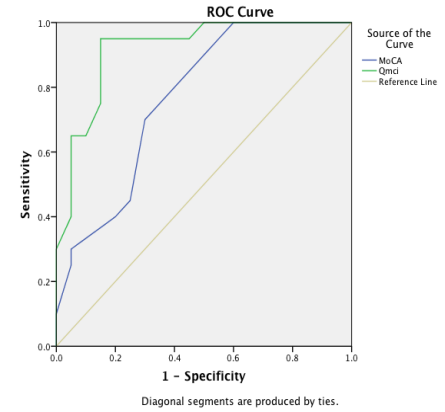
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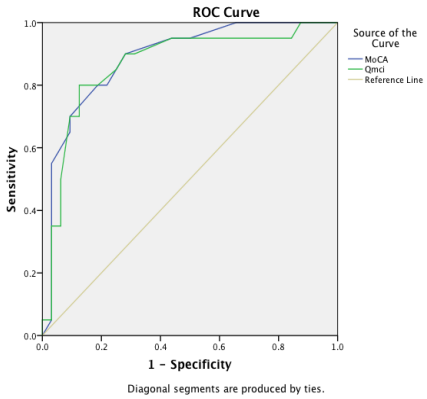
d.

MoCA	**a. Normal V MCI**	**b. MCI V Dementia**	**c. Normal V CI**	**d. Dementia V everything else**
Subtests	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)	**Area Under the Curve** (95% Confidence Intervals)
VisuoSpatial/ Executive	0.79 (0.64-0.93)	0.78 (0.66-0.90)	0.89 (0.82-0.96)	0.86 (0.78-0.94)
Naming	0.62 (0.45-0.79)	0.67 (0.53-0.81)	0.71 (0.58-0.84)	0.71 (0.60-0.83)
Attention	0.67 (0.50-0.83)	0.70 (0.56-0.84)	0.78 (0.67-0.88)	0.77 (0.66-0.88)
Language	0.63 (0.45-0.80)	0.81 (0.69-0.92)	0.77 (0.67-0.88)	0.83 (0.74-0.93)
Abstraction	0.66 (0.49-0.82)	0.62 (0.48-0.77)	0.73 (0.61-0.85)	0.69 (0.58-0.81)
Delayed Recall	0.56 (0.38-0.73)	0.71 (0.57-0.85)	0.67 (0.53-0.81)	0.72 (0.61-0.83)
Orientation	0.60 (0.42-0.77)	0.84 (0.74-0.94)	0.78 (0.68-0.88)	0.86 (0.77-0.95)

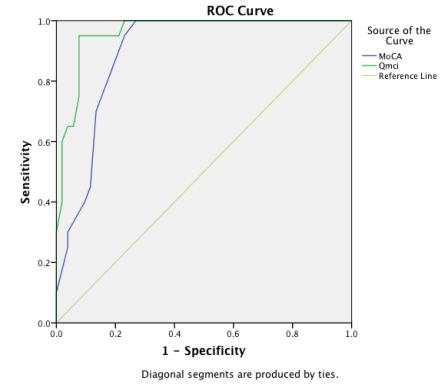
Figure 9.4. Receiver Operating Characteristic curves demonstrating the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) in differentiating patients with Parkinson's disease only with (a) mild cognitive impairment (MCI) from normal cognition, (b) MCI and dementia, (c) normal from cognitive impairment (MCI and dementia), (d) Dementia from everything else.



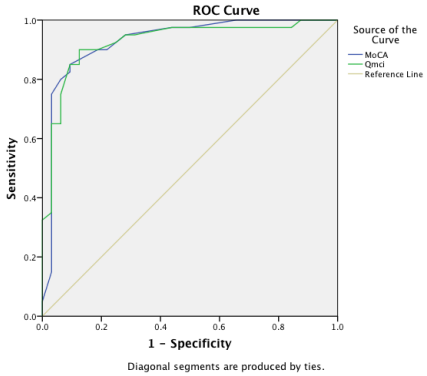
a.



b.



c.



d.

Figure	MoCA	Q*mci*	Comparison
	Area Under the Curve (95% Confidence Intervals)		(p=x)
a	0.77 (0.62-0.91)	0.92 (0.83-1.0)	z=-1.7 (p= 0.09)
b	0. 89 (0.79-0.98)	0. 87 (0.76-0.98)	z=0.26 (p= 0.8)
c	0.89 (0.82-0.97)	0.96 (0.92-1.0)	z=-1.1 (p= 0.25)
d	0.93 (0.86-1.0)	0.93 (0.86-0.99)	z=0.07 (p= 0.95)

9.4 Discussion

This study compares two short cognitive screening instruments, the Q*mci* and the MoCA, in their ability to differentiate normal cognition from MCI and dementia in a sample of patients attending a movement disorder clinic. It shows that the Q*mci* had greater accuracy than the MoCA in differentiating normal cognition from MCI, although this did not reach statistical significance. Both instruments had similar accuracy in detecting dementia. The study also explores the accuracy of both instruments' subtests and shows that visiospatial tasks and LM were the most useful in separating those with normal cognition from MCI. It also shows that orientation is the most accurate for identifying dementia.

A cut-off score of <61 for the presence of cognitive impairment for the Q*mci* provided the balance between sensitivity (94%) and specificity (95%). This cut-off is similar to that seen in the pooled Canadian database, presented in Chapter 5 and the external validation of the Q*mci* against the MoCA in Chapter 7. This study also reaffirms that the traditional MoCA cut-off of <26 is unsuitable in older adults including those attending a movement disorder clinic. At this widely used cut-off the MoCA had excellent sensitivity (97%) but a very poor specificity of 30%. Again, a lower cut-off, in this case <23, produced a better balance (sensitivity of 88% and specificity of 70%) though the specificity remained relatively low. This MoCA cut-off is the same as that seen in patients attending the memory clinic presented in Chapter 7. Further, the established cut-off produced a very high level of false positive results (18%), which reduced to 10% with a cut-off of <23, suggesting that the MoCA would be less useful in screening patients with movement disorders in general practice.

This study also shows that a relatively high proportion of this sample were currently receiving anti-cholingeric medications and few with dementia were treated with cholinesterase inhibitors. Though this study was not designed to examine the reasons for this, it suggests that poor recognition of cognitive status may lead to inappropriate prescribing. Given that even short term exposure to mild anti-cholinergics is associated with an increased incidence of MCI [Cai et al., 2012], this raises concern that inadequate screening and submaximal identification of those with cognitive impairment could result in an occult deterioration in cognition. Given that the presence of PD-MCI at diagnosis is highly predictive of early dementia [Pederson et al., 2013], patients with early cognitive impairment, including those with SMC but normal cognition should be monitored closely and re-screened at a suitable interval. As the median time since diagnosis of movement disorder for the total in this study was 7.5 years (IQR +/-8) and that the mean time from PD onset to PDD (the main movement disorder subtype in this study) is approximately 10 years [Aarsland et al., 2007], this may explain the high prevelance of cognitive impairment found in this sample. However, this study was not a prevalence study and although attempts to sample patients consecutively were made, no inference on prevalence can be drawn. The study also showed that the prevalence of cholinesterase inhibitor prescription in those with dementia was low.

The SMMSE, although not used as an outcome measure in this study, was less accurate than both the MoCA & Q*mci* in differentiating both normal cognition & dementia from MCI. The SMMSE, because of its low ceiling effect and selected cognitive domains, misses cognitive deficits in these patients. Given the high prevalence of cognitive impairment in patients with movement disorders a balance between sensitivity and specificity is required where specificity is also important. A

strength of this study is that patients with normal cognition, MCI and dementia were well matched.

Limitations

This study has a number of limitations. The diagnosis of PD-MCI remains contentious. In this study the diagnosis was made clinically in conjunction with the cognitive component of the UPDRS-cog, which while not a gold standard, is widely used to register cognitive impairment in patients with movement disorders. Despite this, it is not possible to confirm duration of movement disorders and this information was not available for all patients creating potential bias. Furthermore, the diagnosis of PD-MCI was sometimes based on a single cognitive assessment score which may have reduced accuracy. That said, it is argued that where clinical findings are consistent with screening scores, multiple repeated and or neuropsychological assessment may not be required [Sitek et al., 2014]. Likewise, the diagnosis of LBD including LBD-MCI is also poorly defined [Huang & Halliday, 2013]. That said, the study uses recognised criteria advocated by the Movement Disorder Society. Another limitation of this study is that there was again a high prevalence (76%) of cognitive impairment in the sample, in keeping with a sample of predominantly older adults with complex needs attending a movement disorder clinic under the care of a consultant geriatrician. Thus, the main benefit of using a short cognitive screen such as the Q*mci*, with its brief administration time (almost half that of the MoCA) may be in its ability to flag up subtle changes in cognition in high risk patietns like those with a known movement disorder. Finally, the sample size was again small, limiting the ability to say that one instrument was definitely more accurate than another in differentiating MCI from normal cognition. Likewise, not all patients were re-reviewed in this study. However, this study was not a longitudinal follow-up study

and patients that had a clear diagnosis of dementia at first assessment or who were under follow-up with an already established diagnosis of dementia, were only assessed and included once. Future studies, comparing the Q*mci* and MoCA in this subgroup of patients, require larger numbers to confirm superiority.

In summary, cognitive impairment is common among patients attending the movement disorder clinic and may be overlooked using commonly used but less accurate instruments like the MMSE and SMMSE. Failure to recognise cognitive impairment in a movement disorder clinic may result in failed opportunities to initiate early appropriate treatment and discontinue inappropriate medications like anti-cholinergics. As clinic is busy and cognitive impairment is not the sole focus of these appointments, unlike memory clinics, there is a need for brief and accurate screening instruments for use in this subpopulation of older patients. The results show that the Q*mci* had a better balance between sensitivity and specificity at their optimal cut-off scores (<61 for the Q*mci* and <23 for the MoCA) although no statistically significant difference in accuracy as determined by ROC curve analysis was found. This study suggests that the Q*mci* may be the more useful test particularly given its shorter administration time though further research is required to confirm this. The study also demonstrates that different cognitive domains are useful where there is suspicion for MCI or dementia confirming that a battery of subtests are required to allow instruments be useful across the cognitive spectrum.

Chapter 10

Reliability and validity of the Q*mci* in General Practice

10.1 Introduction

Establishing the presence of cognitive impairment in general practice is challenging and there is evidence that it often goes unrecognized [Brodaty et al., 1998], [Valcour et al., 2000],[Boustani et al., 2005], with more than half of patients diagnosed outside of GP surgeries [Knopman 2006]. The diagnosis of MCI, because it represents a heterogeneous group of memory disorders [Petersen et al., 2004] with subtle, cognitive changes and variable progression rates [Mitchell et al., 2009], is particularly difficult to diagnose in general practice [Kaduszkiewicz et al., 2010]. Distinguishing MCI is important as treatment choices and prognosis differ [Peterson 2005],[Tricco et al., 2013]. Specific barriers to GPs include poor recognition and response to symptoms of MCI and dementia [O'Connor 1996], perceived lack of benefit [Boise et al., 1999], patient and caregiver stigma [lliffe et al., 2003],[lliffe et al., 2005], and limited time, financial, and human resources [Boustani et al., 2003]. Compounding this, although patients and their caregivers are often open to early diagnosis [Luck et al., 2012], they frequently do not recognise or report cognitive difficulties [Watson et al., 2005]. As cognitive screening takes approximately 20 minutes per patient [Boustani et al., 2003], time in particular, constrains the use of formal neuropsychological testing, necessitating the use of short cognitive screens or informant questionnaires.

At present community screening for cognitive impairment is not recommended [Lin et al., 2013] and few screening programmes have been trialed in general practice [Boustani et al., 2005]. A major reason for this is the lack of suitable screening instruments [Winblad et al., 2004], [Boustani et al., 2005]. Features of

acceptable cognitive screens, for use in GP surgeries include brevity, ease of administration and sufficient sensitivity and specificity to differentiate between normal cognition, MCI and dementia. Sensitivity is particularly important in primary care to avoid false negatives. Although several cognitive screens are available, including those designed specifically for GPs, the most commonly used tests remain the abreviated mental test score and the MMSE [Ismail et al., 2010]. The GPCOG [Brodaty et al., 2002], Mini-cog [Borson et al., 2000], and Memory Impairment Screen are all recommended for use in primary care to screen for dementia [Brodaty et al., 2006]. While the MoCA is gaining acceptance as a cognitive screen of choice in multiple settings [Nasreddine et al., 2005], it does not appear to be validated in general practice. The GPCOG, described in Chapter 2 and presented in Appendix 2.3 is designed specifically for use by GPs, is short (5-6 mins) and acceptible to patients and physicians alike [Brodaty et al., 2002]. The GPCOG, which has a sensitivity of 85%, specificity of 86%, a misclassification rate of 14%, and a PPV of 71.4% [Brodaty et al 2006] has not been validated in MCI. It is also critised for having age and educational bias [Cullen et al., 2007],[Brodaty et al., 2004]. Given the brevity, accuracy and ease of use so far demonstrated in this PhD, the utility of the Q*mci* screen, including IRR and concurrent validity against the MoCA and GPCOG, was investigated in general practice.

10.2 Methods

Sample

Consecutive patients attending two large GP surgeries in Co Cork: Mallow Primary Healthcare Centre (MPHC) and Elmwood Medical Centre, Douglas, Cork City, were invited to participate in cognitive screening. Subjects were included if they

complained of symptomatic memory loss, were aged > 55 and were fluent in English. Subjects with active depression, screened using the 15-point GDS Short Form [Yesavage 1988] (score of seven or more), were excluded.

Data Collection

All subjects underwent a comprehensive clinical assessment including evaluation of baseline demographics (age, gender, number of years in education) and cardiovascular risk factors. Where a collateral history was possible, informant screening was performed using both the IQCODE-SF [Jorm 1994] and AD8 [Galvin et al., 2005], in person or by telephone. Each subject had the Q*mci*, MoCA and GPCOG administered sequentially, but randomly by two trained raters, who were blind to the eventual diagnosis. All subjects were subsequently reviewed by a consultant physician, specialised in the diagnosis of cognitive impairment, and diagnosed with either MCI, dementia or SMC but normal cognition. An "outreach" memory clinic was created in MPHC for the purposes of this study. A diagnosis of MCI was based upon a history of subjective and corroborated memory loss, without loss of social or occupational function using the results of an SMMSE and the informant reports to form the diagnosis. Dementia was diagnosed using DSM-IV-R criteria [APA 2000]. Persons with SMC but normal cognition were also included. These underwent the same work-up. Ethical approval was obtained and all subjects provided informed verbal consent. Assent was obtained from individuals with cognitive impairment.

Q*mci* inter-rater reliability in general practice

GPs were trained prior to the study on how to score the Q*mci*. Training involved a lecture on the Q*mci*. In addition, the Q*mci* has been filmed by the Health Service Executive for training and teaching purposes and was made available to all GP raters. Q*mci* IRR, between the GP and Memory clinic trained raters, was shown by comparing the results of the Q*mci* scored by the GP with the repeat in the memory clinic (n =57). Six were reviewed in clinic more than one month after the initial scoring by the GP and were therefore not included in the IRR analysis.

Analysis

Analyses were conducted using SPSS 20.0. The Shapiro–Wilk test was used to test normality and found most of the data were non-parametric. Simple descriptive statistics were performed. Data were also analysed using ROC curves.

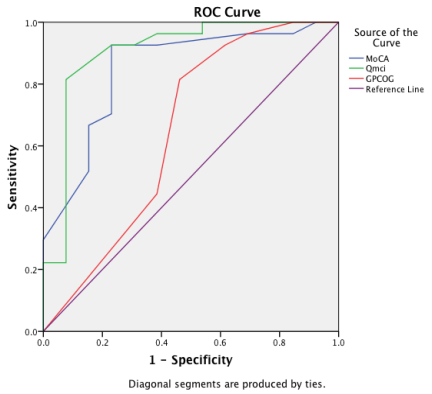
10.3 Results

In all, 63 patients (31 normals with SMC, 16 with MCI and 16 with dementia) were screened. Only 57% (n=36) of patients were accompanied by a caregiver or provided contact details for a collateral history, reducing the number of AD8 or IQCODE-SF scores that could be completed. Characteristics of patients included in this study are presented in Table 10.1. Pearson's correlation coefficient showed good IRR between the trained GPs and the clinic assessment, r =0.89, for the 57 subjects included in the IRR analysis. The median age of all patients was 73 years, (IQR +/-17). Patients with SMC were significantly younger than those with MCI or dementia, $p < 0.001$. Median Q*mci*, MoCA and GPCOG scores were 60/100 (+/-24), 22/30 (+/-8) and 8/9 (+/-5) respectively. Figure 10.1 presents ROC curves comparing the Q*mci*, MoCA and

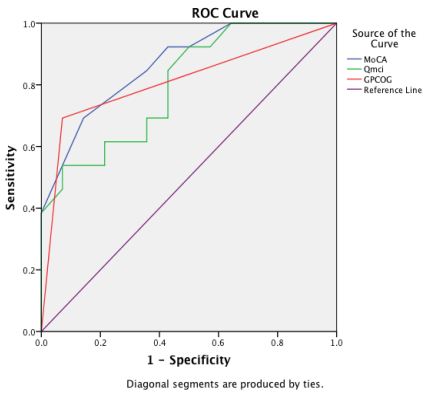
GPCOG in their ability (accuracy) to distinguish SMC from MCI and dementia. The Q*mci* was more accurate than the MoCA or GPCOG in differentiating MCI from those with SMC but normal cognition, AUC of 0.91 versus 0.85 and 0.65 respectively. There was no statistically significant difference in the accuracy of the Q*mci* and MoCA (p=0.46) in differentiating MCI from SMC. The Q*mci* (p=0.01) but not the MoCA (p=0.06) was significantly more accurate than the GPCOG. All had similar accuracy in differentiating those with SMC from those with cognitive impairment, AUC of 0.95 versus 0.92 and 0.80. The GPCOG classified 34% of patients as having cognitive impairment (including 93% of those with dementia) with only 3.6% of patients with SMC but normal cognition misclassified.

Median administration time was 4.4 (5-4= +/-1) minutes for the Q*mci* compared to 8.2 (10-7.5= +/-2.5) for the MoCA and 2.5 (3.5-2.5= +/-1) for the GPCOG.

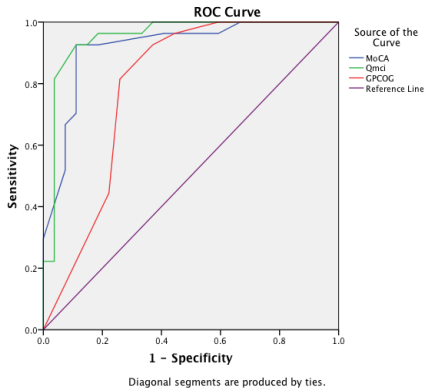
Figure 10.1. Receiver Operating Characteristic curves demonstrating the accuracy of the Quick Mild Cognitive Impairment (Q*mci*) screen and Montreal Cognitive Assessment (MoCA) and the General Practitioner Assessment of Cognition (GPCOG) in differentiating patients attending general practice with (a) mild cognitive impairment (MCI) from subjective memory complaints (SMC) but normal cognition, (b) MCI and dementia, (c) SMC from cognitive impairment (MCI and dementia), (d) Dementia from everything else.



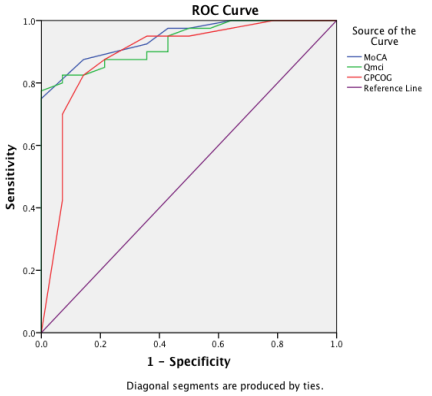
a.



b.



c.



d.

1Figure	MoCA	Q*mci*	GPCOG
	Area Under the Curve (95% Confidence Intervals)		
10a	0.85 (0.72-0.98)	0.91 (0.79-1.0)	0.65 (0.44-0.85)
10b	0. 87 (0.73-1.0)	0.80 (0.63-0.97)	0.81 (0.64-0.99)
10c	0.92 (0.84-1.0)	0.95 (0.89-1.0)	0.82 (0.69-0.94)
10d	0.94 (0.89-1.0)	0.93 (0.86-1.0)	0. 91 (0.82-1.0)

Table 10.1. Characteristics of patients reviewed in General Practice including AD8, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Standardised Mini-Mental State Examination (SMMSE), Quick Mild Cognitive Impairment (Q*mci*) screen, Montreal Cognitive Assessment (MoCA) and General Practitioner Assessment of Cognition (GPCOG).

Diagnosis	**Total**	**SMC**	**MCI**	**Dementia**
Age (Median & IQR)	73 (81-64 = ±17)	66 (74-59= ±15)	74.5 (81-69= ±12)	79.5 (83-75= ±8)
Education (Median & IQR)	12 (14-11= ±3)	12 (15-11= ±4)	11 (14-10= ±4)	12 (13-11= ±2)
Gender (% Female)	67%	61%	69%	75%
IQCODE (Median & IQR)	3.9 (4.3-3.5= ±0.8)	3.16 (3.7-3= ±0.7)	3.7 (4-3.6= ±0.4)	4.3 (4.7-4= ±0.7)
AD8 (Median & IQR)	5 (7-4 = ±3)	2 (5-0= ±5)	4 (5-3= ±2)	7 (8-6= ±2)
SMMSE (Median & IQR)	27 (29-25 = ±4)	29 (30-28= ±2)	26.5 (28-25= ±3)	20.5 (24-18= ±6)
Q*mci* (Median & IQR)	60 (71-47 = ±24)	71 (74-59= ±15)	54.5 (59-43= ±16)	40.5 (48-32= ±16)
MoCA (Median & IQR)	22 (25-17 = ±8)	25 (27-22= ±5)	18 (22-17.5= ±4.5)	14.5 (17-11= ±6)
GPCOG (Part 1: examination) (Median & IQR)	8 (9-4 = ±5)	8 (9-8= ±1)	7 (9-4= ±5)	2.5 (4-1= ±3)
GPCOG (Part 2: informant) (Median & IQR)	4 (6-2 = ±4)	6 (6-4= ±2)	4 (4-3= ±1)	2 (3-0= ±3)
GPCOG (% Cognitive impairment)	34%	3.6%	36%	93%

10.4 Discussion

This study presents a comparison between the commonly used SMMSE, the primary care specific GPCOG and the Q*mci*. It shows that the Q*mci* was statistically significantly more accurate in differentiating patients presenting to general practice with SMC from those with MCI. The GPCOG had poor accuracy (AUC 0.65) in MCI and was significantly less able to distinguish MCI from SMC compared with the Q*mci* and MoCA. The study also shows that that all three instruments had statistically similar accuracy in identifying cognitive impairment (either MCI or dementia) and dementia (from MCI or SMC). All three instruments had a median administration

time less than 10 minutes with the GPCOG and Q*mci* having median times less than 5 minutes. The Q*mci* had excellent IRR. This study provides further evidence that the Q*mci* is an accurate instrument in identifying impairment across the cognitive spectrum (O'Caoimh et al., 2012) and confirms that it has comparable accuracy but is shorter than the MoCA (O'Caoimh et al., 2013). To our knowledge this is the first study validating the MoCA in general practice. Again, this study shows that while accurate, its administration time is longer than other short screens potentially limiting its use in busy general practice clinics.

The strengths of the study include the detailed assessment and work-up for cognitive impairment. Limitations include the small number of participants, underpowering the study to show superiority of one instrument over another and limiting this study to a non-inferiority study.

Although evidence for routine screening for cognitive impairment is lacking, there is increasing opinion that early recognition of symptomatic individuals benefits patients, relatives and services alike [Iliffe et al., 2003],[Clionsky 2014]. Due to time and other constraints, short accurate screening instruments, that are easy to interpret and administer, are required in general practice. The brevity of the Q*mci* compared with the MoCA and its higher accuracy in MCI over the GPCOG suggest that it may represent the ideal brief screen in general practice, able to screen across the cognitive spectrum. Further study with a much larger sample size is required to confirm these findings.

Chapter 11

Reliability and validity of the Q*mci* in a Hospital Rehabilitation unit

11.1 Introduction

Cognitive impairment is frequently under-diagnosed among patients in rehabilitation units [Ruchinskas & Curyto, 2003]. The Irish National Audit of Dementia (INAD) 2013 [http://www.ucc.ie/en/inad/], [de Siún et al 2014] investigated the management of dementia in acute hospital settings in Ireland and found that only 43% of patients with dementia had a standardised cognitive test recorded and only 14% of patients with dementia had their level of cognitive impairment summarised and recorded at discharge [de Siún et al 2014]. The INAD found that the average length of stay for a person with dementia admitted from and discharged to their home was 22 days with this figure increasing to 59 days for discharge to nursing home care [de Siún et al 2014]. Cognitive impairment adversely affects the quality of rehabilitation, lengthening the rehabilitation stay [Wang et al., 2002] and increasing risk of adverse outcomes, mortality and institutionalisation [Poynter et al., 2011]. The MoCA is more sensitive and specific than the MMSE in a geriatric rehabilitation setting [Sweet et al., 2011].

Given that few studies have investigated the utility of different short cognitive screening instruments in this population of older adults, this study compared the SMMSE, MoCA and Q*mci* screen in their ability to differentiate cognitive impairment from normal cognition in a general older adult rehabilitation unit in St Finbarrs Hospital, Cork City.

11.2 Methods

Consecutive stable inpatients, newly admitted to a university hospital rehabilitation unit, were screened for cognitive impairment. The unit comprises a male and female general rehabilitation and a mixed 15 bed stroke rehabilitation unit. A diagnosis of cognitive impairment (MCI or dementia) was determined independently by multi-disciplinary team assessment. The team was asked to confirm whether patients were cognitively impaired or not based on usual practice (using the SMMSE and MoCA as screens and the Rowland Universal Dementia Assessment Scale to confirm the diagnosis). This diagnosis was made independently of the trained raters who scored three short cognitive screens (SMMSE, Q*mci* and MoCA), blinded to the decision and to the patients' medical notes. Patients who were medically unstable, screened positive for depression using the GDS Short Form, or who were unable to communicate verbally due to dysphasia were excluded. This was confirmed after discussion with the Clinical Nurse Manager for the unit and the multi-disciplinary team. Descriptive statistics were performed and accuracy was determined from the AUC of ROC curves. IRR was measured using Pearson's correlation coefficient. Additional data were collected as part of a medical students (Brian Daly) final year project and these results are currently in preparation for publication but are not included in this PhD.

11.3 Results

In total, 32 patients were assessed, of which 30 were included: 13 with NC and 17 with cognitive impairment. In all, 9/30 (30%) were post stroke. Two patients were excluded because of dysphasia. IRR was tested a median of four days following the initial assessment for a small sample (n=13), r =0.77. Characteristics of inpatients

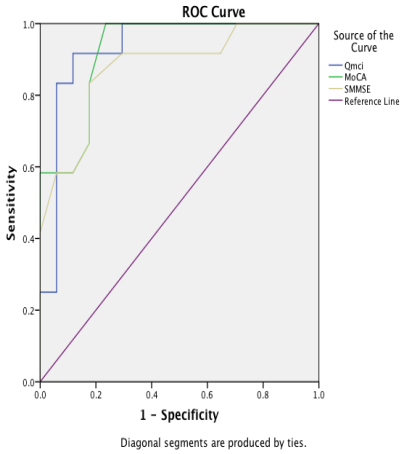
included in this analysis are presented in Table 11.1. The median age of patients was 81.5 (IQR ±9.75) years; 18 (60 %) were female. The median SMMSE score for those with normal cognition was 27 (±4), compared to 22 (±7.5) for the MoCA and 61 for the Q*mci*. Median scores for cognitive impairment for the SMMSE, MoCA and Q*mci* were 19 (±7), 12 (±4.75) and 35 (±18) respectively. ROC curves demonstrating the accuracy of the Q*mci*, MoCA & SMMSE and the Q*mci* subtests, in differentiating cognitive impairment from normal cognition, are presented in Figure 11.1.

The Q*mci* and MoCA had similar accuracy in differentiating cognition impairment from normal (AUC of 0.93, 95% CI: 0.84-1.00 for the Q*mci* and 0.92, 95% CI: 0.83-1.00 for the MoCA). Both were greater than the SMMSE (AUC of 0.88, 95% CI: 0.75-1.00) although this was not a statistically significant difference for either (p >0.05). The most accurate Q*mci* subtest was DR (AUC 0.95) followed by VF (AUC 0.87) and LM (AUC 0.83). All subtest CI overlapped suggesting that there is no statistically significant difference between them. Median administration times for the SMMSE, MoCA and Q*mci* were 5 min, 11 s (±1 min, 35s), 8min, 37s (±1 min, 27s) and 4 min, 25s (± 50 seconds) respectively.

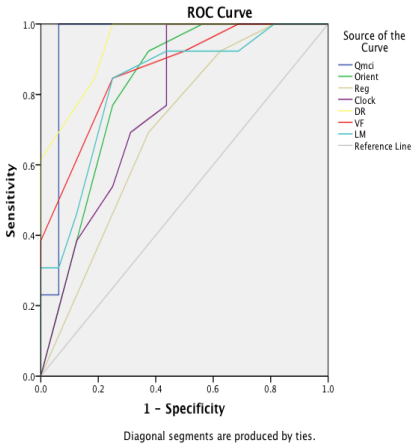
Table 11.1. Characteristics of rehabilitation inpatients including their median and interquartile (IQR) Quick Mild Cognitive Impairment (Q*mci*) screen, Montreal Cognitive Assessment (MoCA) and Standardised Mini-Mental State Examination (SMMSE) scores according to patient diagnosis.

Variable			Normal Cognition	Cognitive Impairment
Number of subjects			13	17
Indication for rehab		Post Stroke	3	6
		Other	10	11
Age	Median		81	81.5
	Interquartile range (IQR)		(+/-10)	(+/-10)
	range		57-87	70-94
Q*mci* (median score +/- IQR)			61 (+/-7.5)	35 (+/-18)
MoCA (median score +/- IQR)			22 (+/-7.75)	12 (+/-4.5)
SMMSE (median score +/- IQR)			27 (+/-4)	19 (+/-7)

Figure 11.1 Receiver Operating Characteristic curves demonstrating the accuracy as measured by the area under the curve (AUC) of the Quick Mild Cognitive Impairment (Q*mci*) and Standardised Mini-Mental State Examination (SMMSE) a) total scores and b) Q*mci* subtests in differentiating cognitive impairment from normal cognition.



a.



b.

Q*mci* Subtest	**AUC**	**95% Confidence Interval**
Orientation	0.82	0.66-0.98
Registration	0.70	0.51-0.89
Clock	0.77	0.60-0.95
Recall	0.95	0.87-1.00
Verbal Fluency	0.87	0.74-1.00
Logical Memory	0.83	0.68-0.93

11.4 Discussion

This small pilot study shows the accuracy of the Q*mci* in a stable inpatient rehabilitation population compared to two commonly used instruments in geriatric rehabilitation units, the MoCA and SMMSE. The results suggest that all three instruments are useful (accurate) but that the Q*mci* has a shorter administration time. As shown in other studies in this PhD, the median score for normal cognition for the MoCA was below its established cut-off for cognitive impairment (<26), suggesting that it is less useful in clinical practice. The study showed that the most accurate Q*mci* subtest was DR, which is different to both the memory clinic and movement disorder clinic studies described above, where LM was the most accurate subtest. This likely reflects the different sampling strategies employed and the particularly small sample included in this initial pilot, presented at the Irish Gerontological Society meeting [O'Caoimh et al., 2013, abstract] and part of an ongoing study. Although most patients were general medical or orthopaedic patients, a proportion were stroke patients. The MoCA is a well established valid cognitive screen in stroke [Godefroy et al., 2011] and this study suggests that the Q*mci* may also be of use, albeit in stable inpatients in a rehabilitation unit. However, given the very small sample of these patients it is difficult to generalise on the utility of the Q*mci* in this population.

In summary, all three of the cognitive screens were accurate, at differentiating cognitive impairment from normal cognition. The Q*mci* was the most accurate although this did not reach statistical significance. Delayed recall was the most accurate Q*mci* subtest. This study reaffirms the accuracy and short administration time of the Q*mci*, in this case quicker than both the SMMSE and MoCA. Futher study is required with much larger sample sizes to confirm these findings, in particular, whether the Q*mci* is sensitive and specific in Stroke and in acute medical inpatients.

Section 4

Additional Studies

Chapter 12

Utility of the Q*mci* in predicting disease progression: Using the Q*mci* in a Memory Gym

12.1 Introduction

There is growing interest in developing interventions to prevent cognitive impairment [Kivipelto et al., 2013] or prevent conversion from MCI to dementia [Gates et al., 2011]. The Study of Mental and Resistance Training trial [Fiatarone et al., 2014] compared two interventions: progressive resistance training and cognitive training, either in isolation or combination, in patients with MCI showing that resistence training alone improved global cognitive function. While combining treatment modalities is not new, multi-modal approaches are now increasingly being trialed in MCI and dementia. Tailored intervention strategies incorporating combinations of diet, exercise, stress reduction and cognitive stimulation have shown potential in patients with aMCI [Bredesen 2014] but the evidence for the efficacy of single or combined interventions remains limited.

This study investigated the effects of a "memory-gym" suite of lifestyle interventions and education strategies delivered in group therapy in a subgroup of patients with MCI attending the memory clinic in St Finbarrs Hospital. The hypothesis was that the "memory-gym" would slow or prevent conversion to dementia and that the Q*mci* could be used as a measure of progession, showing predictive validity.

12.2 Methods

The study was designed as a case-control trial comparing a six week "memory-gym" group-therapy programme with one three-month booster session to usual care, among consecutive patients recently diagnosed with MCI attending a university hospital memory clinic. MCI was diagnosed as described in Chapter 7. The "memory-gym" suite of stratgies included weekly cognitive training exercises (using three commercially-available apps, on tablet computers, according to an established protocol [Scanlon et al., 2014]), for one hour per week with an additional hour of either compensatory techniques, dietary advice, exercise instructions, stress management, mindfulness techniques or art therapy. Patients were included if baseline and end-point (standardised at six months apart) SMMSE, Q*mci* and Caregiver Burden scores were available. The Caregiver Burden score is a shortened version of the Zarit burden score. It is composed of six questions and describes the degree to which caring affects the caregiver from 0 (none of the time) to 6 (all of the time). Completed by the caregiver, scores <15/30 suggest no significant burden, scores suggest severe burden or burnout, see Appendix 2.7. The Caregiver Burden score is routinely self-administered by caregivers attending the memory clinic in St Finbarr's Hospital. In this study, it was collected by a retrospective chart review.

12.3 Results

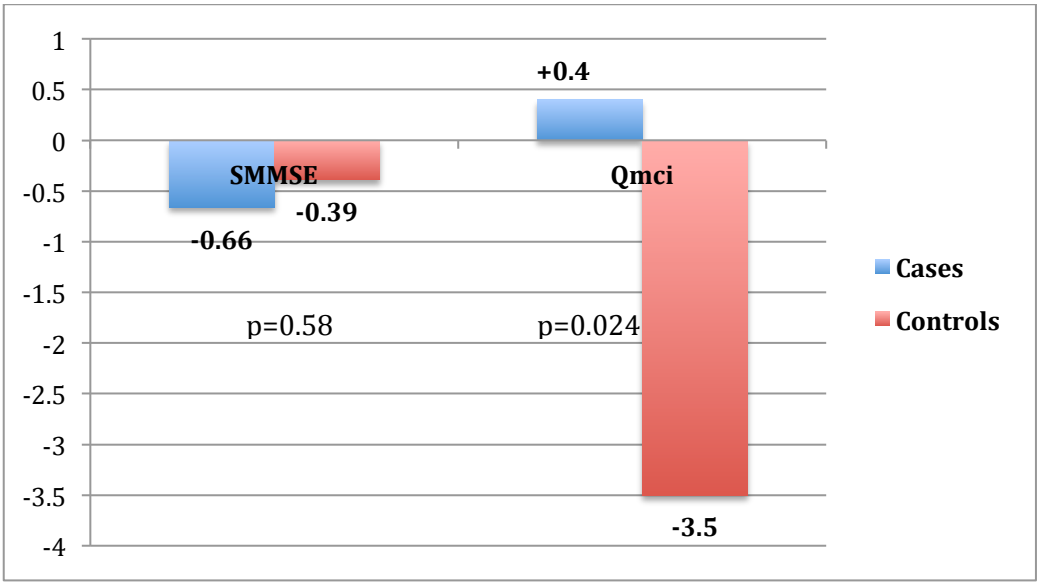
In all, 13 participants completed the intervention in two groups, median age 72 years (interquartile +/-6) compared to 76 (+/-11) for controls, (n=17). The median follow-up was 18 months versus 18.5 months respectively, p=0.72. No significant differences in baseline age, gender, education, SMMSE, Q*mci* or caregiver scores were found (see Table 12.1). There was a significant difference in median six month rate of

change in Q*mci* scores for those with MCI, +0.4/100 points versus -3.5/100 points, p= 0.024. No significant differences in SMMSE (-0.66/30 versus -0.39/30, p=0.58), or Caregiver Burden (0 versus 0, p=0.55) scores were shown (see Figure 12.1). Only 15% (2/13) of participants with MCI converted to dementia compared to 47% (8/17) of controls, p =0.12.

Table 12.1. Baseline characteristics, median and interquartile range (IQR), of participants (cases) and non-participants (controls) including median six-month rates of decline in Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment screen (Q*mci*) scores.

Group	**Participants (Cases)**	**Non Participants (Controls)**	P=X
Number	13	17	-
Follow-up in months (Median & IQR)	18 (+/-5)	18.5 (+/-7.75)	0.72
Age (Median & IQR)	72 (+/-6)	76 (+/-11)	0.26
Gender (% female)	71%	70%	1.0
Education in years (Median & IQR)	14 (+/-3)	12 (+/-6)	0.71
Diagnosis -MCI -Early dementia	 -13 -1	 -7 -3	-
SMMSE (Median & IQR)	29 (+/-4)	28.5 (+/-3)	0.51
Q*mci* (Median & IQR)	59.5 (+/- 15)	56 (+/-11)	0.98
Caregiver scores (Median & IQR)	2 (+/-5)	6 (+/- 11)	0.41
Δ SMMSE (Median & IQR)	-0.66 (+/-0.9)	-0.39 (+/- 1.1)	0.58
Δ Q*mci* scores (Median & IQR**)**	-0.13 (+/- 2.9)	-3.08 (+/- 5.5)	0.057
Δ Q*mci* scores (MCI only)	0.4 (+/- 2.9)	-3.5 (+/-5.5)	0.024
Δ Caregiver Burden Scores (Median & IQR**)**	0 (+/- 0.4)	0 (+/-4.6)	0.55
Percentage with Δ diagnosis	15% (2/13)	47% (8/17)	0.12

Figure 12.1. Comparison of median six-month rates of decline in Standardised Mini-Mental State Examination (SMMSE) and Quick Mild Cognitive Impairment screen (Q*mci*) scores in those with mild cognitive impairment, between participants (cases) and non-participants (controls).



12.4 Discussion

This study shows that there was a significant difference in the median 6-month rate of decline in Q*mci* scores between cases and controls and although it did not reach significance, almost half (47%) of controls converting from MCI to dementia compared to only 15% of participants. There were large differences in the six-month rate of change of Q*mci* scores between cases and controls (>3/100 points per six months, p =0.057) that reached statistical significance (again >3/100 points per six months, p =0.024) when patients with early dementia were excluded to leave only those with a diagnosis of MCI. No such difference was seen for the SMMSE, which may suggest it is less sensitive at detecting these small but significant differences. No differences in caregiver burden (as measured by the Caregiver Burden score) were found between groups, though baseline levels of burden were low (median score of

zero), as would be expected for carers managing the care of patients with mild cognitive deficits and who are more or less functionally independent (MCI).

These results suggest that a multi-modality intervention using educational strategies, delivered in the form a "memory-gym", by trained therapists aligned to a memory clinic, may slow progression in MCI. Although changes associated with the "memory-gym" were small and of uncertain clinical significance, if sustained over years, the compounding effects may have significant clinical benefits. A strength of this case control study is that both cases and controls were well matched with no significant differences in baseline demographics. Limitations include the small sample size, short training duration, short period of follow-up, lack of randomization or blinding and the inability to isolate individual components of the "gym". Furthermore, no recognized global assessment such as the ADAS-cog or SADAS-cog was used. However, this study shows the potential of the Q*mci* to measure progession of MCI, supporting the results presented in Chapter 8 where the Q*mci* was shown to correlate with the SADAS-cog, CDR and the Lawton-Brody ADL scale in a clinical trial. The patients included in this case control trial remain under follow-up but without booster sessions any beneficial effects of the "gym" are unlikely to be sustained. To confirm the preliminary findings and the ability of the Q*mci* to predict those who will convert from MCI to dementia a larger same size, followed for longer, is required. A randomised controlled trial is planned to investigate the potential benefits of the "memory gym" intervention.

Chapter 13

Shortening the Q*mci* to develop a caregiver administered cognitive screen; The Quick Memory Check (QMC)

13.1 Introduction

Traditionally, cognitive screens can be divided into directly administered performance-based instruments scored by trained raters in a clinical setting or informant-based observer rated scales. Interest in self-diagnosis including home-administered screening is increasing and is widely reported in the media [Adelman & Karlawish, 2013], particularly social media [Robillard & Johnson 2013]. Computerised neuropsychological batteries have potential to replace traditional "paper-based" assessments [Scanlon et al., 2014]. A wide variety of performance-based instruments are available [Lonie et al., 2009],[Cullen et al., 2007] though it is suggested that none will fit all situations [Cullen et al., 2007]. Informant-based scales, administered in conjunction with family or caregivers, provide a collateral, documenting symptoms suggestive of cognitive impairment. Although widely validated, they are long and not useful in detecting decline in cognition over time [Eramudugolla et al., 2012]. Informant-based scales may not be objective and collateral histories can be unreliable [Nieuwenhuis-Mark et al., 2009].

Another method of testing cognition is with home assessment. This has several potential advantages. Psychosocial stress is known to impair memory retrival [Kulmann et al., 2005] and there is evidence [Cockburn & Smith 1994], albeit conflicting [Hoffman & alAbsi, 2004], that anxiety affects performance on neuropsychological testing. While white coat effects are well established in hypertension, white coat effects related to the administration of cognitive screening testing are less well established and little is known about their effect on patients with

cognitive impairment. Home administration in a familiar setting could potentially reduce the anxiety associated with assessment in busy clinics. As time is limited in clinical practice, assessment prior to clinic may reduce waiting times. Home-administration may identify variation in patient scoring, allowing more frequent assessments at different time intervals, capturing variability that may suggest the presence of subtle cognitive impairment [Kaye et al., 2014]. With the growing use and availability of the internet, particularly on mobile devices, there has been an increase in the propagation of internet-based, self-administered tests for dementia [Robillard 2013, abstract]. Most however, have poor reliability and validity, with ethical concerns raised over data collection, privacy and follow-up [Robillard 2013, abstract]. To date, only a few self-administered cognitive screens have been validated in clinical practice and of those that are most still require supervision. Their potential was first demonstrated by the Test Your Memory (TYM) instrument [Brown et al., 2009], the most widely studied self-administered cognitive screen though it requires supervision. Other validated self-administered tests include the Computerized Self Test (CST) [Dougherty et al., 2010] and the Self-Administered Gerocognitive Examination (SAGE) [Scharre et al., 2010].

While increasingly used and validated, these tests are limited by the need for supervision by trained staff (TYM), lack of comparison with established short cognitive screens (SAGE and CST), particularly accurate tests identifying MCI and early dementia. A potential solution to this is to utilise caregivers or those close to patients. Although there is evidence that caregivers actively wish to engage with the diagnosis [Beauchamp et al., 2005], little information is available on the ability of caregivers to administer cognitive screens. As yet, no cognitive screens scored by caregivers of persons with symptomatic memory loss have been validated. Given the

increasing use of "home administered" cognitive screens, we sought to shorten the Q*mci* in order to develop and validate a new caregiver-administered cognitve screening test, which was christened the Quick Memory Check (QMC), to be used in conjunction with a thorough healthcare assessment as a novel way to screen cognition.

13.2 Methods

Development of the Quick Memory Check

The QMC is based upon the Q*mci* screen [O'Caoimh et al., 2012],[O'Caoimh et al., 2013]. Previous analyses of the Q*mci* subtests revealed that verbal fluency VF and LM best differentiated MCI from normal cognition, while orientation best differentiated MCI from dementia [O'Caoimh 2013]. Based upon this analysis, the Q*mci* was shortened and reweighted to produce the QMC, see Table 13.1. Orientation was increased to 15 points (from 10 points), VF (for animals as initial piloting found that animals were the easiest to score) from 20 to 40 points and LM from 30 to 45 points. The QMC was designed to be completed in three minutes, 30 seconds for the caregiver report and two and half minutes for the caregiver assessment (one minute for the orientation and VF subtests each and 30 seconds for LM). The QMC along with scoring instructions are provided in Appendix 1.3.

Table 13.1. Comparison of the Quick Mild Cognitive Impairment (Q*mci*) Screen and Quick Memory Check (QMC).

Q*mci*	Score	QMC	Score
Orientation	**10**	**Orientation**	**15**
Registration	**5**	**Verbal fluency**	**40**
Clock drawing	**15**	**Logical Memory**	**45**
Delayed recall	**20**		
Verbal fluency	**20**		
Logical Memory	**30**		
Total	**100**	**Total**	**100**

Participants

Consecutive patients attending a university hospital memory clinic were screened and assessed for cognitive impairment. All patients had a complete assessment including history, physical examination and work-up for causes of cognitive impairment including a brain CT, an electrocardiogram and blood tests where appropriate. Patients were classified as having NC (age associated memory loss), MCI or dementia. Dementia was diagnosed using DSM-R, (4th edition revised) criteria [APA 2000]. Dementia severity was correlated with the Reisberg FAST scale [Reisberg 1988]. MCI was diagnosed clinically based upon the presence of collaborated and progressive memory loss, without obvious loss of functional impairment using Petersens criteria [Petersen et al., 1999]. Patients were excluded if they were aged under 45 years, if they were depressed or if they were unable to provide a caregiver (spouse, child, friend or other person known to the person including a healthcare professional) . Depression was diagnosed clinically and screened using the GDS Short Form [Yesevage 1988], using a cut-off of ≥7, to optimize specificity [Marc et al., 2008]. After assessment those with LBD or PD were also excluded and analysed

separately as these often present atypically with a different MCI syndrome [Caviness et al., 2007]. Test-retest reliability was calculated by comparing the test completed at home and a repeat performed by a different caregiver in clinic. Inter-rater reliability (IRR) was determined by comparing the home-administered result to a repeat performed by a clinic nurse on arrival, for a sample of patients chosen by simple randomisation, n = 30.

Data Collection

The QMC with scoring instructions was posted with the appointment letter prior to clinic. Data were collected between 2013 and 2014. The scoring instructions, posted in advance with the QMC, stipulated that the test be dated (including time of day) and completed just before attending clinic. Caregivers were asked to provide their personal details including age, gender, occupation, educational level and time spent with the patient (days per week). In clinic, each patient had demographic data collected including age, gender and number of years of education. Each patient had the Q*mci* screen and MoCA administered sequentially but randomly by two trained raters, blind to the final diagnosis as part of the same data collection described in Chapter 7. Alternative forms of the Q*mci* were used to reduce learning effects and bias [Cunje et al., 2007]. Caregiver satisfaction was measured using anonymous self-completed questionnaires, developed by the researchers. Caregivers were asked ten questions (using a five-point Likert scale from strongly agree to strongly disagree) about their experience using the QMC including their willingness to use it again.

Statistical analysis

Data were entered into SPSS version 20.0. Subjects were subdivided according to age, > or <75 years and educational level, > or <12 years, the mean number of years in formal education in North America. The Shapiro–Wilk test was used to test normality and found that the majority of data were non-parametric. The accuracy of the individual screening tests was determined from the AUC using ROC curves. Youden's Index was used to calculate cut-off scores for the QMC [Youden 1950]. Sensitivity, specificity, PPV and NPV were calculated for each of the cognitive screens. IRR and test-retest reliability were determined using Pearson's correlation coefficient.

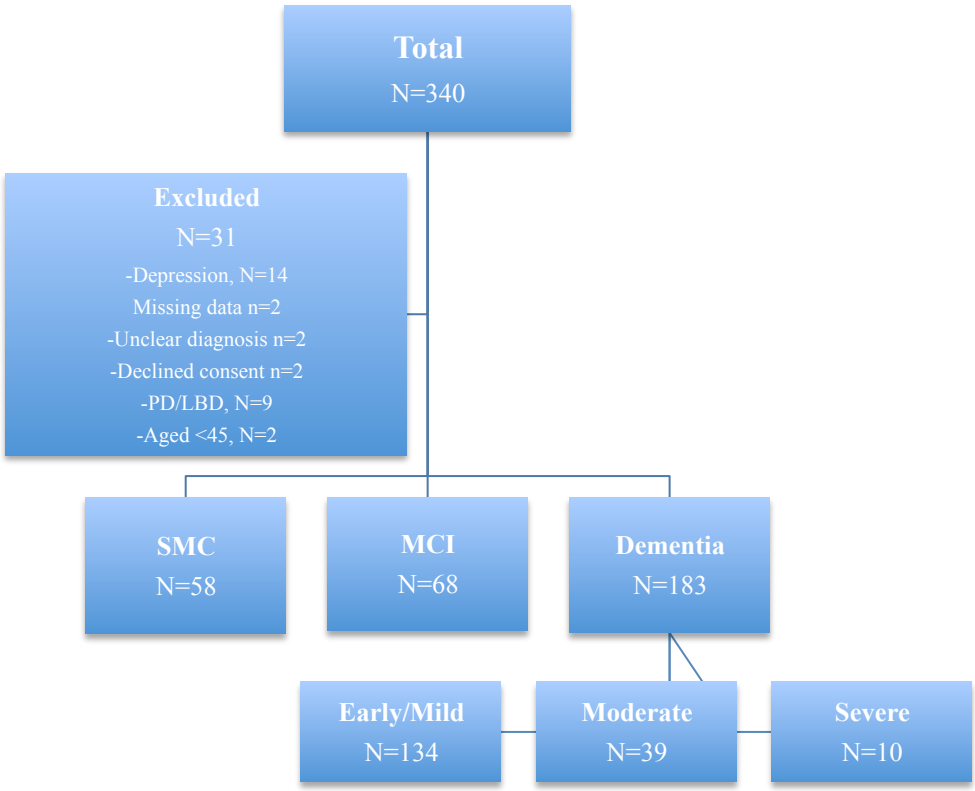
13.3 Results

Patient characteristics

In total, 340 assessments, were available for analysis. Of these, 309 assessments were included. An additional 34 normal controls, recruited from bridge clubs in Cork City, were also included. Normal controls were scored by untrained raters (with normal cognition), who also attend the clubs, to demonstrate the ability of older untrained raters to score the instrument. This normative data is part of a medical students final year project and although their demographic details are included for comparison their data is not included in this analysis. Thirty one were excluded because of missing data (n=2), refusal to consent (n=2), unclear diagnosis (n=2), active depression (n=14), LBD/PD (n=9) and age <45 years (n=2). Overall, 58 had NC (22%), 68 MCI (20%) and 183 had dementia (58%). Of those with dementia, 134 were classed as early-mild dementia, 39 as moderate and 10 as severe. Patient selection is presented graphically in Figure 13.1. The median age at assessment of those included was 76, interquartile

range (IQR) 11 years. Of those included 81 (34%) were male. Patients with dementia were similar in age to those with MCI (median age of 77 verus 75 years, p=0.1), but were significantly older than those with normal cognition, (median age 72 years, p=0.08).

Figure 13.1. Flow chart of participants included in the validation of the Quick Memory Check, including number of assessments, excluding those with Parkinson's disease (PD) and Lewy Body dementia (LBD).



Caregiver characteristics

The median age of caregivers at the time of assessment was 52 years (IQR =68-43= +/- 25), and the majority (70%) were female. In all, 9% of assessments were scored by caregivers that had completed primary education only, 44% secondary and 47% third level. Most caregivers scoring the QMC were the child of the patient (50%) followed by their spouse (38%) and other relationship (12%). The caregiver was currently in employment in 50% of cases, retired in 21% and not working outside the home in 29% of QMC assessments. Older caregivers, ≥65 years, were also predominantly female (58%), mainly retired (60%) and the majority (89%) were spouses. In keeping with this 94% saw the patient seven days a week.

Performance of the QMC

The median time between home testing and attending clinic was one month. Test-retest reliability was 0.95. IRR was 0.82. Median administration time for a sample of 30 patients, timed in clinic, was 2.5 minutes. The median QMC score for those with SMC was 64 points (IQR 19) compared to 52 (19) for MCI and 31 (21) for dementia. Normal controls had a median QMC score of 73 (16). Median and IQR scores of each of the outcome measues are presented in Table 13.2. Of the four tests, the Q*mci* most accurately identified patients with cognitive impairment, AUC of 0.95 (95% confidence interval: 0.93–0.98). The QMC however, compared favourably with the other tests with an AUC of 0.89 (95% confidence interval: 0.85–0.93), for differentiating cognitive impairment from SMC (see Table 13.3). Each of the cognitive assessments also accurately differentiated MCI from NC, although again the Q*mci* was most accurate, with an AUC of 0.84 (95% confidence interval: 0.76–0.91). The QMC was the next best performing test, AUC 0.75 (95% confidence interval:

0.66–0.84), compared with 0.71 (95% confidence interval: 0.61–0.80) for both the SMMSE and MoCA. The QMC also had excellent accuracy in its ability to differentiate MCI from dementia, AUC of 0.82 (95% confidence interval: 0.75–0.86). ROC curves comparing the accuracy of the instruments are presented in Figure 13.2.

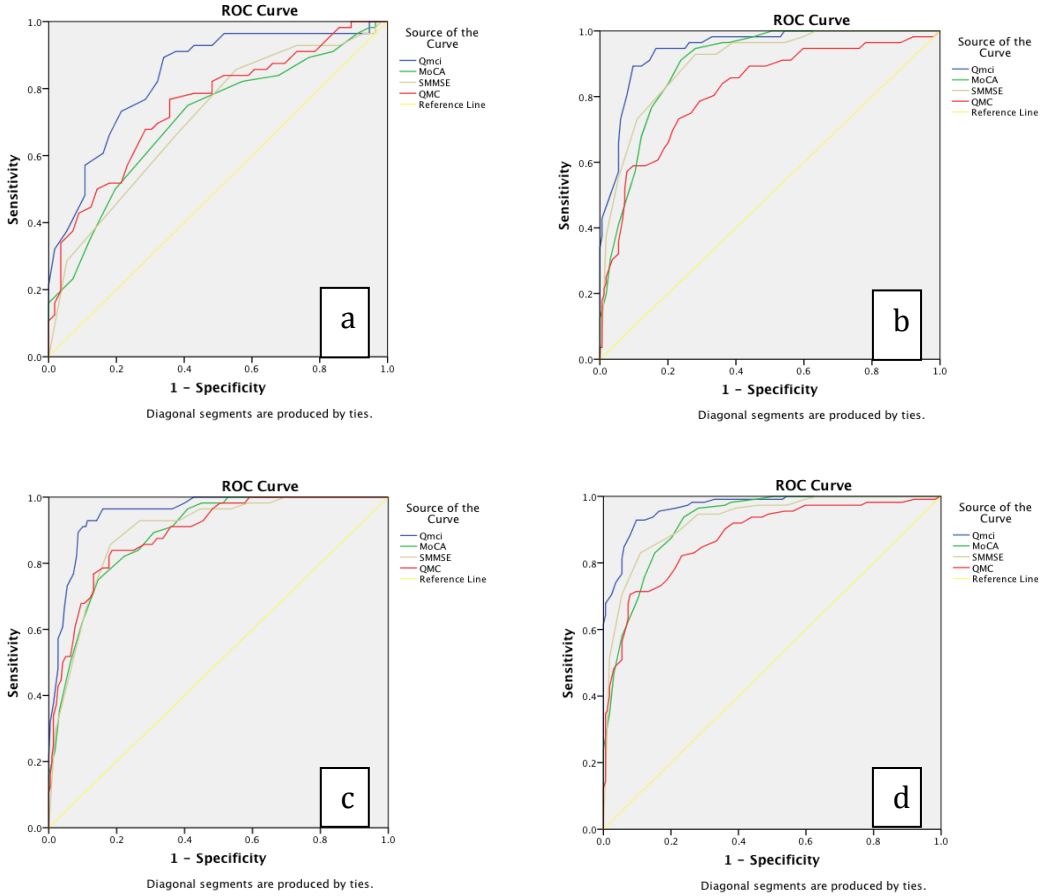
Table 13.2. Characteristics of the total sample, controls, those with subjective memory complaints (SMC), mild cognitive impairment (MCI), dementia and combined cognitive impairment (CI) groups, including median Quick Memory Check (QMC), Quick Mild Cognitive Impairment screen (Q*mci*), Standardised MMSE and Montreal Cognitive Assessment (MoCA) scores with inter-quartile range (IQR), (Q1–Q3 = IQR; Q1 = 1st Quartile, Q3 = 3rd Quartile).

Group		Total	Controls	SMC	MCI	Dementia	CI
Number of patients		n=239	n=34	n=52	n=49	n=138	n=187
Number of assessments		n=309	n=34	n=58	n=68	n=183	n=251
Age (years)							
	Median	76	71	72	75	77	77
	IQR	(81-70=11)	(76-65=10)	(81-65=16)	(80-70=10)	(81-71=10)	(81-71=10)
	Range	46-92	58-84	46-89	59-91	48-92	48-92
Education (years)							
	Median	11	14	12	12	11	11
	IQR	(14-10=4)	(16-12 =4)	(14-9.5=4.5)	(14-10=4)	(13-10=3)	(13-10=3)
	Range	7-18	8-18	8-18	8-18	7-18	7-18
QMC (median with IQR)		39 (55-27=28)	73 (82-66 =16)	64 (73-54=19)	52 (59.5-40.5=19)	31 (40-19=21)	45 (50-30=20)
Q*mci* (median with IQR)		46 (59-31=28)	76 (83-70 =13)	66 (72-61.5=10.5)	56 (62-52=10)	36 (45-22=23)	42 (51-26=25)
SMMSE (median with IQR)		25 (28-20=8)	30 (30-29 =1)	29 (30-28=2)	28 (28-26=2)	21 (25-16=9)	23 (27-19=8)
MoCA (median with IQR)		18 (23-11=12)	26.5 (29-24 =5)	25 (26.5-23=3.5)	22 (23-20=3)	13 (18-7=11)	16 (21-8.5=12.5)

Table 13.3. Comparison of area under the curve (AUC) values with 95% confidence intervals for the QMC, Q*mci*, SMMSE and MoCA in their ability to differentiate cognitive impairment (CI) from those with subjective memory complaints (SMC), mild cognitive impairment (MCI) from SMC, MCI from dementia and dementia from MCI and SMC.

Diagnosis	Test	AUC	95% Confidence Interval
CI from SMC	QMC	0.89	0.85-0.93
	Q*mci*	0.95	0.93-0.98
	SMMSE	0.89	0.85-0.94
	MoCA	0.89	0.85-0.93
MCI from SMC	QMC	0.75	0.66-0.84
	Q*mci*	0.84	0.76-0.91
	SMMSE	0.71	0.61-0.80
	MoCA	0.71	0.61-0.80
MCI from Dementia	QMC	0.82	0.75-0.86
	Q*mci*	0.95	0.92-0.98
	SMMSE	0.90	0.86-0.95
	MoCA	0.90	0.86-0.95
Dementia (from MCI & SMC)	QMC	0.88	0.84-0.92
	Q*mci*	0.97	0.95-0.99
	SMMSE	0.93	0.90-0.96
	MoCA	0.93	0.89-0.95

Figure 13.2. ROC curve demonstrating the accuracy of the Q*mci*, MoCA, SMMSE and QMC in differentiating (a). Mild cognitive impairment (MCI) from subjective memory complaints (SMC), (b). MCI from dementia, (c). Cognitive impairment from SMC and (d). Dementa from SMC and MCI.



Developing cut-off scores for the QMC

Using Youden's Index [Youden 1950] the estimated QMC cut-off score for cognitive impairment was ≤50. At this cut-off the QMC had a sensitivity of 85%, specificity of 80%, PPV of 96% and NPV of 50%. The optimal cut-off that differentiated MCI from SMC was ≤53, yielding a sensitivity of 79% and specificity of 55%. The cut-off that best differentiated dementia was ≤48 with a sensitivity of 72% and specificity of 91%. These results are presented in Table 13.4.

Acceptibility of the QMC

In total 50 caregivers returned the questionnaire, a response rate of 67%. The results of the questionnaire suggest that the majority of caregivers were happy with screening and would be willing to do it again. These results are presented in Figure 13.3.

13.4 Discussion

This paper presents the results of a caregiver "home" administered cognitive screen, administered by caregivers to patients with symptomatic memory loss, prior to attending a memory clinic, in comparison to a selection of short cognitive screens including the progenitor of the QMC, the Q*mci*. Caregivers, scoring the QMC, were predominantly middle-aged, female, children with a median age of 52 years. Half were in employment. This reflects the profile of other caregivers of patients with dementia [Sink et al., 2006]. Older caregivers (≥65) had similar profile except they were more often spouses living with the patient. The results demonstrate that the QMC accurately (AUC 0.89) differentiated those with SMC from cognitive impairment and compared well with formal cognitive screening using validated instruments including the SMMSE, MoCA and Q*mci* screen. The accuracy of the

QMC, in differentiating established cognitive impairment from SMC but normal cognition, also compares well with the results of other home-administered instruments such as the TYM, AUC of 0.94 [Hancock & Larner 2011] and the SAGE, AUC of 0.92 [Scharre et al., 2010]. In this sample a QMC cut-off score of <50 appears appropriate for differentiating cognitive impairment (either MCI or dementia) from SMC. At this score, calculated using Youden's Index, the QMC had 85% sensitivity and 80% specificity. A slightly higher cut-off of <53 produced the optimal cut-off for MCI and slightly lower (<48) the optimal cut-off for dementia. The cut-off for MCI however, had poor sensitivity (55%). It was instead more sensitive at its optimal cut-off for dementia suggesting that while useful in separating cognitive impairment of any type from SMC but normal cognition than specifically identifying MCI.

The advantage of home-administered instruments are that they allow subjects to complete cognitive screening, a key part of any memory assessment, at home, away from the busy atmosphere of clinic. In this way, the QMC potentially reduces the "white-coat" effect associated with cognitive testing in clinical environments and allows raters more time to compare the reliability of more detailed cognitive testing performed in clinic. There are several disadvantages. Physicians cannot see and assess the conditions under which the test was administered. Tests may create unnecessary anxiety for patients or their caregivers in advance of attending clinic. However, the results of the user questionnaires, administered to caregivers, suggest that these effects are minimal. The QMC itself is simple and quick to administer with considerably shorter administration times (median 2.5 minutes) compared to similar home-administered tests [Brown et al 2009],[Scharre et al 2010]. This is at the expense of the inclusion of fewer cognitive domains potentially reducing its accuracy in early cognitive impairment. That said, the QMC includes three key domains:

orientation, semantic memory (VF) and episodic memory (LM). LM even as a single subtest, is highly sensitive and specific for MCI [O'Caoimh et al., 2013].It should also be remembered that the QMC, as with all short cognitive screens, is not designed to provide a diagnosis but instead to be used as part of a screening and assessment pathway, either prior to clinic, as in this case, or in conjunction with other short cognitive screens administered by trained healthcare professionals. Given that the QMCs construct is similar to the Q*mci*, it would seem reasonable to compare the results of these two instruments in clinic as a form of 'white coat effect' screening. Instruments such as the TYM have shown the potential of home-administered screens to reduce indiscriminate assessment of asymptomatic patients, reducing the numbers of false positives. Until further validation in the community is available and better treatments provide justification for unselected community screening [Lin et al., 2013], its use outside of a memory clinic cannot be advised.

Strengths and limitations

The strengths of this study are that it validates a home-administered cognitive screen against standardised instruments that are widely used and validated in clinical practice, including the SMMSE, Q*mci* and MoCA. The use of standardised scoring instructions may have reduced variability in scoring, as witnessed by the high test-retest reliability. In addition, this is the first study to provide age and educational cut-off scores for a home-administered instrument. It also includes large numbers of patients, particularly those with MCI, compared with other studies of home-administered tests [Brown et al., 2009],[Scharre et al., 2010]. There are a number of limitations. The QMC was not compared to any other home-administered cognitive screens and none of the short instruments it was compared against can be considered a

gold standard. That said, no gold standard has been established [Lin et al., 2013] and the MMSE and MoCA are widely validated in patients with SMC. A relatively low IRR (caregiver versus trained rater) compared with high test-retest reliability (caregiver versus caregiver) may suggest that instructions provided to caregivers, posted with the QMC in advance of the clinic, were insufficient. Further, the median administration time obtained in clinic may not reflect the time taken by caregivers. More study is now required to clarify this, although only 4% of respondents strongly agreed that the test was too time consuming, suggesting that home-administration times were similarly brief. The use of caregivers rather than patients or trained raters may also have created bias. Although it is unknown whether caregiver administration affects subject performance, evidence from informant-based observer-rated instruments suggests that results may be biased [Nieuwenhuis-Mark et al., 2009], particularly as caregiver stress may affect caregiver cognition [MacKenzie et al., 2007]. That said, bias may also occur through self-administration/reporting of any test. Also, as this study was conducted with older adults (median age 76 years) attending a memory clinic with symptomatic memory loss, the sample was heavily weighted towards those with CI, prevalence of 78% (187/239 patients). This may also affect the accuracy of the proposed cut-off scores. That said, unlike other studies of home-administered tests [Brown et al., 2009], [Scharre et al., 2010], this study included relatively large numbers of symptomatic older adults with normal cognition (SMC) rather than including a random sample of older adults that were presumed normal. One limitation is that only a small sample of controls were available. However, the QMC was designed for patients referred for assessment of memory loss in a memory clinic and not for use by asymptomatic older adults in the community. Further study would be required to confirm utility of the test in this population but

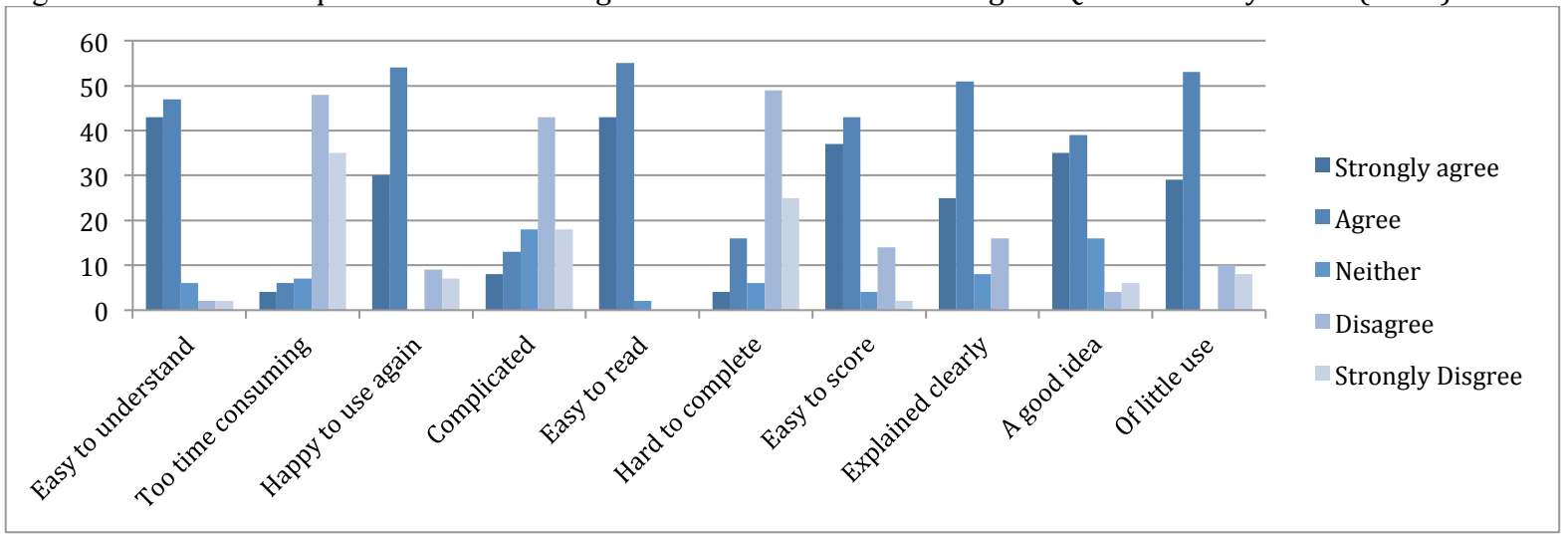
evidence/guidelines recommend against/suggest that asymptomatic adults should not be routinely screened [Lin et al., 2013]. Finally, that it was conducted in a single centre may also reduce the generalisability of the results.

The QMC now requires external validation with larger numbers and in different clinical settings e.g. general practice, where the test could arguably be best suited. Future research should focus on refining its different domains and cut-off scores and investigating if the QMC is also valid as a self-administered screen by comparing it with instruments such as the TYM [Brown et al., 2009] and the SAGE [Scharre et al., 2010]. In summary, the QMC is a home-administered cognitive screen validated for use by caregivers. It is short (median 2.5 mins), acceptable, easy to use and can be administered in an informal setting without direct clinical supervision. Based upon these results, the authors recommend that low scores (cut-off <50) on the QMC should prompt the need for further assessment. The QMC suggests that caregiver-administered cognitive screening tests may have a role in the assessment pathway for cognitive impairment, potentially reducing testing time and patient stress (white coat effects). It may also be useful as a pre-screen for MCI and early dementia in community settings, supporting the utility of shortening and refining the Q*mci* further such that an additional reduction in administration time is not off-set by a large reduction in accuracy. It may also be useful when combined with short a self or caregiver rated questionnaire evaluating symptoms of cognitive impairment such as the AD8. These could be supervised by GPs in the community, particularly where patients or caregivers approach with concerns. Patients screening positive could then be assessed formally in primary care and prompt referral arranged if required. Further research is now required to confirm these findings and elucidate the benefits if any of these community-based referral pathways.

Table 13.4. Comparison of cut-off scores for the QMC, Q*mci*, SMMSE and MoCA to differentiate cognitive impairment from those with subjective memory complaints (SMC), mild cognitive impairment (MCI) from SMC, MCI from dementia and dementia from MCI and NC, including sensitivities, specificities, positive predictive values (PPV), negative predictive values (NPV), including 95% confidence intervals at each cut-off. * Calculated from Youden's Index.

Diagnosis	**Test**	**Cut-off***	**Sensitivity** (95% confidence interval)	**Specificity** (95% confidence interval)	**PPV** (95% confidence interval)	**NPV** (95% confidence interval)	**False Positive** (95% confidence interval)	**False Negative** (95% confidence interval)
Prevalence of CI of 81%								
Cognitive impairment from SMC	QMC	< 50	80% (75-85)	85% (72-92)	96% (92-98)	50% (40-60)	4% (2-8)	50% (40-60)
Prevalence of MCI of 53%								
MCI from SMC	QMC	< 53	55% (42-67)	79% (66-88)	75% (60-86)	60% (49-71)	25% (14-40)	39% (27-51)
Prevalence of Dementia of 73%								
MCI from Dementia	QMC	< 48	91% (85-94)	62% (49-74)	87% (81-91)	71% (57-82)	13% (9-19)	29% (18-43)
Prevalence of Dementia of 59%								
Dementia (from MCI & NC)	QMC	< 48	91% (86-95)	73% (64-80)	83% (77-88)	85% (76-91)	17% (12-23)	15% (9-33)

Figure 13.3. Results of questionnaire of caregiver satisfaction with scoring the Quick Memory Check (n=50).



Chapter 14

External Validation of the Q*mci* in English (Australia) and non-English (Dutch) speaking populations

14.1 Introduction

Few short cognitive screening instruments such as the Q*mci* are available to identify MCI. As the Q*mci* has not been externally validated outside of this PhD project, the objective of this chapter is to confirm the accuracy of the Qmci in different populations and languages. This aim of thus study is to compare the accuracy of the Q*mci* screen with the SMMSE in differentiating MCI from normal cognition and dementia in an Australian outpatient and community setting. In addition, given that, few short screening tools, able to discriminate properly between MCI and normal cognition or dementia, are available in the Dutch language, we chose to adapt the Q*mci* for use in Dutch-language countries and to validate the Dutch version of the Q*mci* (Q*mci*-D), against the Dutch translation of the SMMSE (SMMSE-D).

14.2 Methods

To date, in Australia 224 subjects (156 with dementia, 43 with MCI, and 25 normal controls) have been recruited. Each were reviewed in geriatric outpatients or in the community by the Aged Care Assessment Team in Perth, Western Australia. Trained raters independently scored the SMMSE and Q*mci*. In the Netherlands (Groningen) the Q*mci* was translated to Dutch with a combined qualitative and quantitative approach. In all, 90 subjects were recruited from a hospital geriatric clinic (25 with dementia, 30 with MCI, 35 controls). The Q*mci*-D and SMMSE-D were administered by a trained rater and results were compared. Accuracy was determined from AUC from ROC curves.

14.3 Results

In Australia the Q*mci* is, like in Ireland and Canada, proving to be more accurate than the SMMSE in differentiating MCI from normal cognition, AUC of 0.81 (95% confidence interval (CI) of 0.69-0.93), compared with 0.69 (95% CI:0.54-0.85). Comparing the two instruments showed the Q*mci* to be significantly better than the SMMSE (z=-0.168, p=0.046). Similar results were obtained after correction for age and education. Both the Q*mci* and SMMSE had similar accuracy in identifying dementia, AUC of 0.87 (95% CI:0.81-0.93) versus 0.92 (95% CI:0.88-0.96) respectively, (z=1.32, p= 0.19). In the Netherlands the Q*mci*-D was more sensitive than the SMMSE-D in discriminating MCI from dementia with a significant difference in the AUC (0.73 compared to 0.60 respectively, p= 0.024), and in discriminating dementia from controls with an AUC of 0.95 compared to 0.89 (p= 0.006). Both screening instruments discriminated MCI from NC with an AUC of 0.86 (Q*mci*-D) and 0.84 (SMMSE-D).

14.4 Discussion

Preliminary results from Australia, the first external validation of the Q*mci* outside of this PhD, reaffirm that the English language version of the Q*mci* is more accurate in differentiating MCI from normal cognition than the still widely used SMMSE. In the Netherlands, the Q*mci*-D is more sensitive and specific than the widely used SMMSE-D in differentiating MCI from dementia and dementia from controls. Given its diagnostic accuracy, brevity and ease of administration, the Q*mci*-D seems a useful cognitive screen in a Dutch population. Validation is ongoing in both countries and in different languages in other centres.

Section 5

Chapter 15

Discussion

5.1 Overview of results

Population ageing has resulted in an increased prevalence of cognitive impairment, including MCI [Plassman et al., 2008],[Nie et al., 2011]. Unlike dementia, MCI is not associated with functional decline and there is increasing interest in management strategies targeted at prevention of conversion to dementia [Fiatarone et al., 2014],[O'Caoimh et al., 2015]. Although screening large numbers of asymptomatic older adults is not recommended at present [Lin et al., 2013], targeted screening may be beneficial, particularly as new treatments and better preventative measures emerge. Studies are therefore required that investigate the benefits of early intervention i.e. therapies targeted to individuals with asymptomatic or occult disease. A key step in realising the potential benefits of cognitive screening is the development of short, easy to use and highly sensitive and specific instruments. This PhD presents and explores the development and the results of the validation of the Quick Mild Cognitive Impairment screen or Q*mci*, a new, short cognitive screen for differentiating MCI from SMC and early-mild dementia, using data gathered by Prof William Molloy in Canada. Building on the published evidence for a previous version of the instrument, the ABCS 135 [Molloy et al., 2005],[Standish et al., 2007], the initial validation showed that the Q*mci* has greater accuracy over the commonly used standardised MMSE [O'Caoimh et al., 2012]. It also shows comparable accuracy with its predecessor. Examination of the Q*mci*'s subtests showed that the new subtest, logical memory, added to transform the ABCS 135 into the Q*mci*, is the most accurate

at differentiating MCI from normal controls [O'Caoimh et al., 2013]. Median administration time was just over four minutes and it has excellent test-retest reliability [O'Caoimh et al., 2013]. The ABCS 135 had previously been used in another outpatient database and a RCT called the DARAD trial, both conducted in Canada. This data were pooled with the original Q*mci* data set providing a large sample of patients and normal controls from which to develop cut-off scores. The results of this analysis suggest that a cut-off score of <60 produces the optimal balance between sensitivity and specificity for the presence of cognitive impairment. This combined dataset provided cut-off scores adjusted for age and education confirming the requirement to adjust scores, particularly for those aged over 75 years. Analysis of this combined data set also showed that the Q*mci* has superior accuracy to the SMMSE across different dementia subtypes. It likewise confirmed the utility of its LM subtest in a large sample of patients. Data from the DARAD trial was also used to assess internal consistency and the responsiveness of the Q*mci* to change over time [O'Caoimh et al., 2014]. It showed that the Q*mci* had high internal validity, was responsive to change over time and correlated with a detailed neuropsychological battery (Standardised ADAS-cog), a global assessment of cognition (CDR) and an ADL scale (Lawton-Brody scale), suggesting that the Q*mci* could be substituted for a more detailed neuropsychological instrument in clinical trials [O'Caoimh et al., 2014].

As the Q*mci* had not yet been externally validated, data collection in an Irish memory clinic was conducted. This study included detailed independent neuropsychological and informant testing not included in the original validation. It showed that the Q*mci* had a shorter administration time, excellent accuracy, comparable sensitivity and greater specificity than the MoCA at their established cut-

off scores. This is the first validation of the MoCA against an instrument designed specifically to screen for MCI. Even though the study was likely underpowered to show superiority, given the brevity and arguably easier scoring instructions of the Q*mci* relative to the MoCA, it suggests that the Q*mci* may be the better instrument to use as a screen. This is particularly true in busy general practice.

This project demonstrated that GPs, after a brief education session had excellent IRR compared to trained raters working in a memory clinic. The Q*mci* compared well with a selection of instruments in primary care including the GPCOG and the MoCA, though again the study was underpowered to show superiority to the MoCA. Despite this, the brevity and ease of administration (no requirement for an informant unlike the GPCOG) suggest that it is useful in this setting. Other studies conducted during this PhD showed that the Q*mci* has good to excellent accuracy in patients with cognitive impairment (MCI and or dementia) attending a movement disorder clinic [O'Caoimh et al., 2012 abstract] and among inpatients in a university hospital rehabilitation unit [O'Caoimh et al. 2013, abstract]. Additional concurrent validity was confirmed against another commonly used short cognitive screen, scored periodically in the Memory clinic during the period of data collection, the 6CIT [O'Caoimh et al. 2014, abstract].

Another important component of the PhD was an attempt to shorten the Q*mci* further without compromising its ability to detect either MCI or dementia. This shortening was based on the results of the subtest analysis and led to the development of another screening instrument called the Quick Memory Check or QMC [Coughlan et al., 2013 abstract]. Analysis suggested that LM and VF were two highly accurate subtests for the detection of MCI and that orientation was most accurate in dementia. This test was trialed as a new "home" caregiver-administered instrument [Coughlan et

al., 2013 abstract] and ongoing data collection, the results of which are presented in Chapter 13, show that it has good to excellent accuracy in detecting MCI and dementia, comparing favourably to a battery of established cognitive screening instruments administered by trained raters. The Q*mci* was also used as an outcome measure in a case-control study investigating the effects of a suite of lifestyle interventions on the progression of MCI [O'Caoimh et al., 2015], suggesting its predictive validity. Finally, the Q*mci* has been translated into multiple languages and has been externally validated in Dutch and Australian populations. Validation is ongoing in Italy and Portugal.

5.2 Limitations of this research

This project has several limitations. The sample size of the external validation of the Q*mci* against the MoCA was small and likely underpowered the study to show superiority. Based upon previous analysis, conducted as part of this research, the overall sensitivity and specificity of the Q*mci* for detecting cognitive impairment was approximately 85% and 80% respectively, compared to a sensitivity of 90% and specificity of 75% for the MoCA, The effect size was deemed to be small to medium. To detect a 5-10% difference in sensitivity and specificity between the two tests at a significance level of 0.01, a total sample size of 300 paired analyses was required to give a power of 80%. Thus, this post-hoc analysis (power calculation) suggests that approximately 300 paired (MCI-SMC) observations would be required to demonstrate superiority of the Q*mci* over the MoCA. Given that the prevalence of cognitive impairment in this study was high (>70%) and that this was predominantly patients with dementia, data collection would have taken more time than was possible within the limits of this PhD. The issue of small sample size and high prevalence of

cognitive impairment was common to the studies conducted in this PhD and given that consecutive patients were sampled over periods when the principle investigator was in clinic, this likely reflects the nature of those attending hospital clinics (memory or movement disorder), general practice surgeries with symptomatic memory loss, and inpatients in a rehabilitation unit.

Another limitation is that the cut-off scores were derived from pooled data sets, potentially creating bias in that the baseline characteristics of participants may have been different. Age and education cut-offs were also derived from this data. This said, comparisons of the databases showed only marginal, albeit statistically significant, differences in their demographic details and all three data sets were coordinated by the same principle investigator Prof William Molloy. All three databases were collected in a Canadian population. Appling these cut-off scores outside of Canada may have created bias. However, that Canada is a large multi-cultural country suggests that findings can be extrapolated and used in similar populations.

5.3 Future research

This PhD and each of the studies within it suggest the need for and direction of further studies. The optimal extent, type and benefits of cognitive screening remain uncertain [Lin et al., 2013] with opposing views on the best way forward [Clionsky & Clionsky, 2014],[McCartan 2013],[Boustani 2013]. Undoubtedly there is a place for cognitive screening, especially in busy non-specialised outpatient clinics and in general practice. It is clear that what is required now to facilitate this is a short, easy to administer, sensitive and specific cognitive screening instrument. To date, most studies have assessed the accuracy of screens in highly selected samples, usually

patients attending memory clinics where the prevalence of cognitive impairment is generally high. High prevalence rates, like in this project, affect the sensitivity and specificity of instruments [Altman & Bland, 1994],[Larner AJ, Springer International Publishing, 2015]. Few instruments have been compared in general practice where the prevalence is low [Connolly et al., 2011] and the utility of and need for these instruments is arguably at its greatest. Further training of GPs and improved resources are also required to improve detection rates [Cahill et al., 2008] and studies to investigate the effects on patients with cognitive impairment are now required. In addition, the Q*mci* is as yet unvalidated in an acute hospital setting where the prevalence of cognitive impairment is high [Sampson et al., 2009],[Ryan et al., 2013].

Given the challenges associated with traditional rater-administered screening, there may also be a place for other forms of administration including self-adminstered screening [Brown et al., 2009],[Scharre et al., 2010] and, as shown in this project, a caregiver administered instrument delivered before clinic. These screening techniques, while still in their infancy, show potential, though further rigourous external validation is still required including demonstration of their concurrent validity against detailed neuropsychological batteries, other short screens and new diagnostic algorithms that take neuroimaging, blood and cerebrospinal fluid results into account [Pankratz et al., 2015].

Although the IRR of the Q*mci* was acceptable in this project, apart from the sample of GPs who scored the test, the Q*mci* was only administered by trained raters and all results were double checked to ensure the quality of scoring. The Q*mci* requires standardisation of its scoring instructions to improve IRR, a technique that has improved the scoring of the MMSE [Molloy et al., 1991] and ADAS-cog [Standish et al., 1996]. While the Q*mci* correlated with the SADAS-cog in the

DARAD, further validation against neuropsychological batteries is also required. Likewise although this project showed some evidence that the Q*mci* was responsive to change over time and useful in measuring conversion (in a memory gym-clinic sample)[O'Caoimh et al., 2015], it remains to be seen if the Q*mci* is useful in measuring and predicting progression from SMC to MCI and dementia. A computerised application for smart phones and tablets has been developed (www.doctot.ie). Comparing the paper-based Q*mci* to the application is ongoing to confirm convergent validity. This project sets out cut-off data for the Q*mci* including adjustments for age and education. Further adjustments for cultural background and pre-morbid intelligence quota (IQ) scores are also required [Alves et al., 2013]. Results show that premorbid IQ influences instruments like the MMSE and MoCA, predicting variance from 8.4% to 33.2% [Alves et al., 2013]. Obtaining IQ scores in particular represents a significant logistic challenge but the increasing use of these should allow their inclusion in future studies. Normative data is also required to place screening scores in context of normal ageing [O'Connor 1990]. Longitudinal studies of ageing offer the best opportunity and attempts to include the Q*mci* in the third wave of The Irish Longitudinal Study of Ageing [Kenny et al., 2013] should be made.

External validation of the Q*mci* is also ongoing in other countries and settings. As presented above, colleagues in Perth Australia are presently completing externally validation of the Q*mci* in another English speaking country. The Dutch version has been validated and is under review. Both Dutch and Italian versions are being used in the FP-7 funded PERsonalised ICT Supported Service for Independent Living and Active Ageing (PERSSILAA, see http://www.perssilaa.eu; project number 610359) [O'Caoimh, Van Velsen et al., 2014]. PERSSILAA is an integrated ICT model for the detection, assessment and management of pre-frailty in community-dwelling older

adults. As partners in the trial Prof Molloy and I have been allowed to externally validate the Q*mci* in the two study sites: one in Enschede the Netherlands, the other in the Campania region of Italy. Results are expected in 2016. This project is also determining whether the Q*mci* can be self-administered as the goal of PERSSILAA is to enable older adults to self-screen and participate actively in their health management.

15.4 Conclusion and context

This PhD represents an exploration of a new short screening instrument and suggests that the Q*mci* is brief, reliable, sensitive, specific and accurate in differentiating MCI from patients presenting with SMC and early to mild dementia. It compares favourably with the results of previously published systematic reviews investigating the utility of short cognitive screens in MCI [Lonie et al., 2009] and dementia [Cullen et al., 2007],[Woodford 2007]. Short cognitive screens need to be easy to administer, available in multiple formats, with high sensitivity but also specificity. Though at present there is still a paucity of evidence to support community screening for cognitive impairment [Lin et al., 2013], including in primary care, this may in a large part be due to a lack of suitable instruments. The Q*mci* may be close to the ideal of a short cognitive screen though further research is ongoing to confirm this.

In summary, this PhD thesis confirms the concurrent validity of the Q*mci* against a large selection of widely used and validated instruments. It also confirms its construct validity against global cognitive and functional scales and the gold-standard assessment used in clinical trials, the ADAS-cog. This exploration of a new and arguably much needed short but highly sensitive and specific cognitive screen shows that it is suitable for use where it is likely to be of most benefit, in busy outpatient

clinics and in general practice. It also demonstrates the potential of shortening the instrument to allow caregivers score patients at home in an attempt to reduce performance anxiety and reduce waiting times in busy clinics, though this requires further validation. This project suggests that the Q*mci* could be substituted for more detailed and longer instruments in a wide variety of settings as a rapid screening test for cognitive impairment, particularly where the suspicion is for MCI. Further research will focus on increasing the sample size to confirm superiority over highly sensitive instruments such as the MoCA, target validation is clinical settings with a lower prevalence of cognitive impairment, attempt to develop of normative data and externally validate the Q*mci* in other cultures and languages. Measuring its predictive validity against more detailed neuropsychological testing such as the ADAS-cog or CANTAB is also required and an important next step towards building recognition of its utility and versatility as a short cognitive screening instrument.

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Appendices

1. Q*mci* and QMC scoring templates and administration and scoring guidelines

Appendix 1.1. The Quick Mild Cognitive Impairment (Q*mci*) screen: double sided score sheet.

Quick *Mild Cognitive Impairment* screen (Q*mci*)

Name: DOB: Gender: Years in Education: Date: Time:

1. Orientation **To begin ask 5 questions.** ◷ One minute. ✎ Give **2 points for correct answer**, 1 if attempted but incorrect, 0 if no attempt.	**What country is it?** ___ / 2 **What year is it?** ___ / 2 **What month is it?** ___ / 2 **What is todays date?** ___ / 2 **What day of the week is it?** ___ / 2	**Score** __/ 10
2. Word Registration To begin say… **"I am going to say 5 words. After I have said these 5 words, repeat them back to me. Are you ready?"** ◷ 30 seconds. ✎ Give **1 point per word** repeated, in any order, no hints.	**Dog** **Rain** **Butter** **Love** **Door** Alternate word groups include… **Cat** **Dark** **Pepper** **Fear** **Bed** **Rat** **Heat** **Bread** **Round** **Chair**	**Score** __/ 5
3. Clock Drawing **"Use the circle provided over page to draw a clock face, set the time to 'ten past eleven'."** ◷ One minute approximately. ✎ Give 1 mark for each number, 1 for each hand & 1 for the pivot correctly placed or close to their ideal location. Loose 1 mark for each number duplicated or greater than 12, e.g, 15 or 45, i.e. errors.	**Score:** Numbers Correct + _____/ 12 Errors - _____ Hands + _____/ 2 Pivot + _____/ 1 **Total** + _____ **/ 15**	**Score** __/ 15
4. Delayed Recall **"A few minutes ago I named five words. Name as many of those words as you can remember."** ◷ 30 seconds. ✎ Recall in any order, within 30 seconds, giving **4 points per word**, no hints.	**Dog** **Rain** **Butter** **Love** **Door** Alternate word groups include… **Cat** **Dark** **Pepper** **Fear** **Bed** **Rat** **Heat** **Bread** **Round** **Chair**	**Score** __/ 20
5. Verbal Fluency **"Name as many animals as you can in one minute. Ready? Go."** ◷ One minute. ✎ Give **half a point per animal** named; to a maximum of 40. Accept all 'creatures' including birds, fish, insects etc. Do NOT count suffixes twice, e.g. mouse/mice but allow points for similar names calf, cow, bull.	Alternative forms include: ***fruit & veg*** or ***towns & cities***. **Score 0.5 x number of animals =** List here, in 'shorthand' if required:	**Score** __/ 20

6. Logical Memory

"I am going to read you ONE short story. After I have finished reading it completely, I want you to tell me as much of the story as you can. OK?"

◷ 30 seconds.

Give **2 points per highlighted word**, recalled exactly, immediately within 30 seconds, in any order, no hints. Two alternatives are provided.

Story 1		Alternative version 1		Alternative version 2	
The **red**	It was a **hot**	The **brown**	It was a **cold**	The **white**	It was a **warm**
fox	**May**	**dog**	**October**	**hen**	**September**
ran across the	**morning**.	**ran across**	**day**.	**walked across**	**afternoon**.
ploughed	**Fragrant**	the **metal**	**Ripe**	the **concrete**	**Dry**
field.	**blossoms**	**bridge**.	**apples**	**road**.	**leaves**
It was **chased** by	were **forming** on	It was **hunting**	were **hanging** on	It was **followed** by	were **blowing** in
a **brown**	the **bushes**.	a **white**	the **trees**.	a **black**	the **wind**.
dog.		**Rabbit.**		**cat.**	

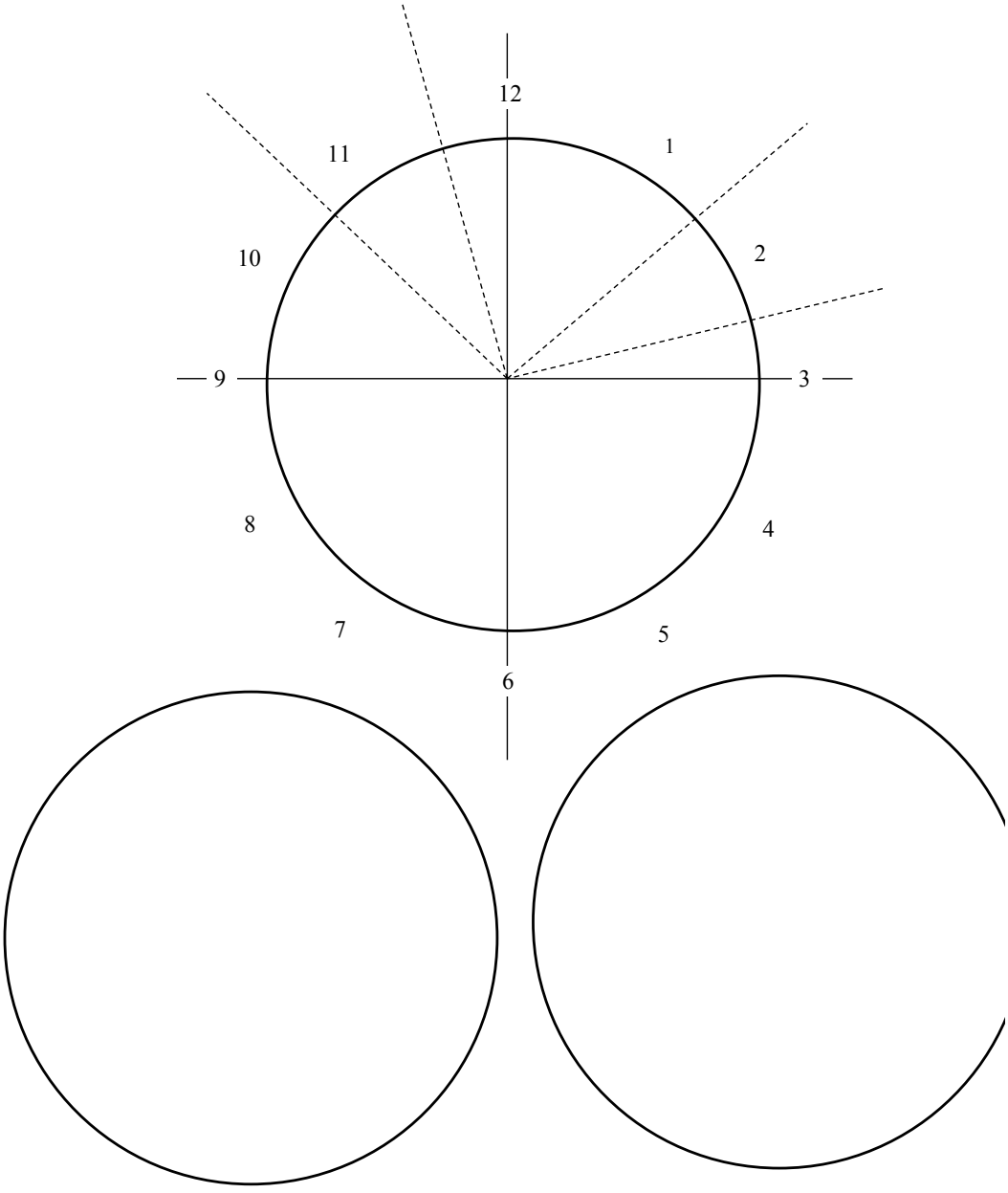
Score __/ 30

Q*mci* Total score *___/ 100

*adjust score for age & education (see over). **Administered by:**_____

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*Cognitive Impairment <60/100



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Appendix 1.2. Quick Mild Cognitive Impairment (Q*mci*) screen administration and scoring guidelines.

Quick *Mild Cognitive Impairment* screen (Q*mci)*

Administration and Scoring Guidelines

1. Orientation

Scoring

2 points for the correct answer, 1 point for wrong answers, and 0 points for no answer or a conceptually unrelated answer (see details below).

Timing

Maximum of 10 seconds for each answer.

Instructions and Scoring Guide

Year	If the person gives the correct year score 2 points, the incorrect year score 1 point, and 0 points if no year is given.
Country	Score 2 points for correct country, 1 point for incorrect country, and 0 if no country is named.
Month	Score 2 points for the correct month or for the previous or following month if within two days of the change of the month (for example, if the date is September 30th, score the full 2 points if person answers October. Similarly, if the date is October 2nd, score 2 points if person says September). Score 1 point if the month is incorrect and 0 if no month is named.
Date	Score 2 points for exact date or ± one day, 1 point for any other date, 0 if no date is named.
Day of week	2 points for correct day, 1 point for incorrect day, 0 if no day named.

To begin say...

"I'd like to ask you some questions and give you some problems to solve. Would that be OK?"

What country is this? _____

What year is this? _____

What month is this? _____

What is today's date? _____

What day of the week is this? _____

Score _____ / 10

2. Word Registration

Instructions and Scoring Guide



Scoring

Score 1 point for each word recalled after the first reading. If subject recalls all five, repeat the five items once and then go on to clock drawing. If subject does not repeat all 5, repeat the 5 items and ask the subject to repeat them. Do this until the subject correctly recalls all 5 items or for a maximum of 3 trials. Do not score for trials 2 and 3. These trials are to help the person learn in preparation for the delayed recall task.



Timing

Say the words very deliberately, one per second. Allow 10 seconds for the recall.

To begin say…

"I am going to say 5 words. After I have said these 5 words, repeat them back to me. Are you ready?"

Dog	**rain**	**butter**	**love**	**door**

Score _____ / 5

When finished, say… **"Remember these words because I'll ask you to recall them later."**

Alternate word groups include…

cat	**dark**	**pepper**	**fear**	**bed**
rat	**heat**	**bread**	**round**	**chair**

3. Clock Drawing

Instructions and Scoring Guide

Scoring

Place the circle of the transparent scoring template over the circle of the patient's completed clock. Rotate the template circle so that the "12" s align. Score 1 point each if the 1, 2, 4, 5, 7, 8, 10, and 11 are in the correct quadrants. Score 1 point each if the 12, 3, 6, and 9 touch their quadrant lines. Subtract one point for each number repeated or for numbers above 12. (Should the patient not have drawn a "12" align the template with the 3, 6, or 9.)

Score the placement of hands according to the tips and pivot. Give 1 point for each hand between the dashed lines. Score 1 point for hands connecting at the pivot.

Timing

One minute.

To begin…

Give the sheet of paper with the pre-drawn circle and a pencil to the patient. Say **"Now put in the numbers like the face of a clock."** Then say **"Set the hands to show ten past eleven." Place the numbers and hands as carefully as you can."**

You may prompt at each stage…"**put in the numbers…. put the time as ten past eleven**".

Score:	Numbers	Correct	+ _____/ 12
		Errors	- _____
	Hands		+ _____/ 2
	Pivot		+ _____/ 1
	Total		**+ _____/ 15**

4. Delayed Recall

Instructions and Scoring Guide

Scoring

Score 4 points for each word recalled. Subjects may recall words in any order.

Timing

10 seconds.

To begin say…

A few minutes ago I named five words. Name as many of those words as you can remember.

dog	**rain**	**butter**	**love**	**door**

Score _____ / 20

Alternate word groups include…

cat	**dark**	**pepper**	**fear**	**bed**
rat	**heat**	**bread**	**round**	**chair**

5. Verbal Fluency

Instructions and Scoring Guide

Scoring.

Give ½ point for each correct word recalled to a maximum of 40 words. Round up the final score. Do not count words with different suffixes twice (e.g. fish / fishes, mouse / mice, etc.). Accept alternate species (e.g. blue jay, robin, sparrow, duck, etc.). Alternate forms include fruits and vegetables, cities and towns.

Timing.

60 seconds. Write down each word the patient says. (You may need to develop some kind of "shorthand" for the speedier patients, such as writing the first 3 letters of each word and then completing them later.)

To begin say…

"Name as many *animals* as you can in one minute. Ready? Go."

Score _____ / 20

6. Logical Memory

Instructions and Scoring Guide

Scoring.

Give 2 points for each correct word item recalled verbatim. All bolded words within each section must be recalled for score 2 points. Otherwise score 0. Recall may be in any order.

Timing.

30 seconds. Check off each word unit recalled.

To begin say…

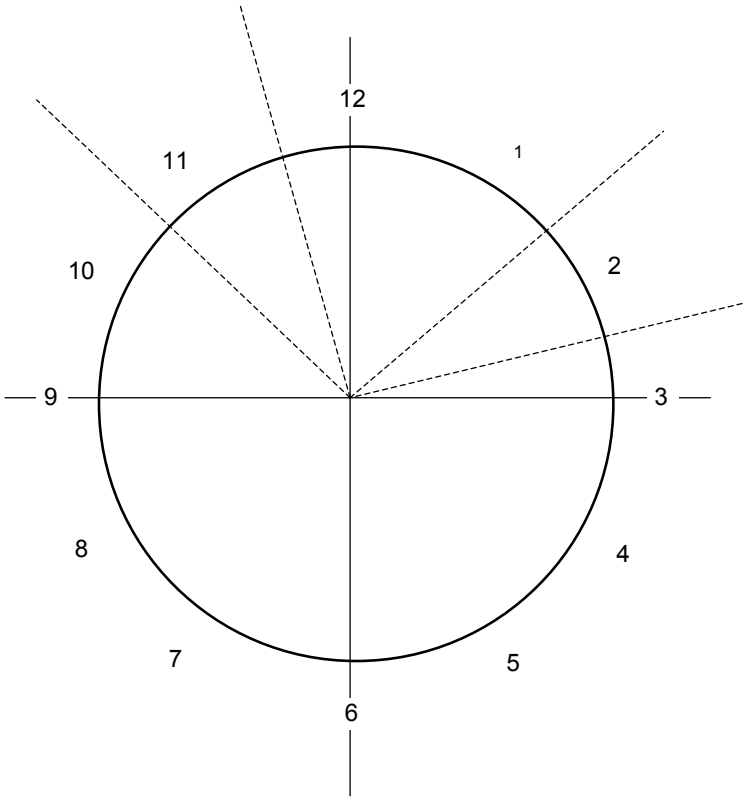
"I am going to read you a short story. After I have finished reading I want you to tell me as much of the story as you can. OK?" [patient signifies agreement, then begin reading the paragraph at about 1 second for each word unit] **"The red… fox… ran across..... the bushes."**

6. Logical Memory			
The **red**	The **brown**	The **white**	2 / 0
fox	**dog**	**hen**	2 / 0
ran across	**ran across**	**walked across**	2 / 0
the **ploughed**	the **metal**	the **concrete**	2 / 0
field.	**bridge**.	**road**.	2 / 0
It was **chased** by	It was **hunting**	It was **followed** by	2 / 0
a **brown**	a **white**	a **black**	2 / 0
dog.	**rabbit**.	**cat**.	2 / 0
It was a **hot**	It was a **cold**	It was a **warm**	2 / 0
May	**October**	**September**	2 / 0
morning.	**day**.	**afternoon**.	2 / 0
Fragrant	**Ripe**	**Dry**	2 / 0
blossoms	**apples**	**leaves**	2 / 0
were **forming** on	were **hanging** on	were **blowing** in	2 / 0
the **bushes**.	the **trees**.	the **wind**.	2 / 0

Score _____ / 30

Qmci Total Score _____ / 100

The Clock Transparency Scoring Template



Scoring
Place this scoring template over the completed clock with the template's "12 o'clock" line placed over the subject's 12. Adjust the template to maximize the score for the numbers and hands. The total score is 15. Record scores on the score sheet as follows:

Numbers

- For the numbers 12, 3, 6, and 9 score one (1) point if they touch their respective lines, zero (0) point if missed, and zero (0) if the number is omitted.
- For the numbers 1, 2, 4, 5, 7, 8, 10, and 11 score one (1) point for each number in the correct quadrant, zero (0) point if the number is outside the quadrant, and zero (0) if the number is omitted.
- **Subtract one point for each number repeated or more than 12.**

Hands

- Score the placement of the entire hand. If the hands are drawn within range, score one (1) point for each hand; if the hands are drawn outside the hatched line or are omitted score zero (0); Give one (1) point if the hands join at the pivot.

Appendix 1.3. The Quick Memory Check (QMC) template and scoring instructions

The *Quick Memory Check*

Instructions.

1. Make sure you have the full attention of the person being tested.

2. Get their permission to carry out the test.

3. Make sure the person being tested can hear you and that there is no background noise or distractions. Get their glasses or hearing aid.

4. Make sure you have a clock/watch to accurately time the test, **be strict with time!**

5. Try to avoid clues or feedback regarding their performance. Don't nod or smile when they answer correctly. Don't say, "yes, that's right" or "that was close" or "try again".

Thank you

Tell us about yourself first.

What relation are you to the person? Spouse ❑ Child ❑ Friend ❑
Other: ❑ Please state_____
How many days each week, on average, do you see this person?_____
What is your occupation? _____Your age?_____Male ❑ Female ❑
Level of education you've completed: Did not complete Primary ❑
Completed: Primary ❑ Secondary ❑ Third level ❑

Caregiver Report

What age is the person being assessed?_____
Describe the person over the last few years.

Circle the appropriate answer			
Q1	**Is there memory loss?** (Is the person forgetting names, appointments, birthdays, conversations? repeating questions, losing objects frequently? etc)	**Y**	**N**
Q2	**Is it getting worse recently?** (Has the memory loss been more obvious in recent months?)	**Y**	**N**
Q3	**Is the person unable to do anything now that he/she could do before the memory loss began?** (e.g. managing finances, medications, cooking, shopping, paying bills, dressing etc)	**Y**	**N**
Q4	**Does the person seem more confused in the last few months?** (e.g. getting lost, disorientated, not aware of the time, place or people around, difficulty with new tasks, unsure what to do in an emergency?)	**Y**	**N**
Q5	**Has there been a recent change to the quality of speech and conversation?** (e.g. word finding difficulties, mixing up names, forgetting what they were about to say).	**Y**	**N**

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Caregiver Assessment

To begin say "I'd like to ask you some questions and give you some problems to solve".

		Correct		Score
Q1 Orientation Test **Ask the person...**	**What country is this?** Score 3 points for correct country, accept exact country only.	**Y**	**N**	**/3**
	What year is this? Score 3 points for correct year, accept exact year only.	**Y**	**N**	**/3**
	What month is this? Score 3 points for the correct month or on the first day of the new month or last day of the previous, either.	**Y**	**N**	**/3**
	What day of the week is this? Score 3 points for correct day, accept exact day only.	**Y**	**N**	**/3**
	What is the date? Score 3 points for exact date or ± one day.	**Y**	**N**	**/3**
Q2 Naming Test **Ask them to name as many "animals" they can think of in one minute**. Give 1 point for each, to a maximum 40. *Accept all 'creatures', including animals, birds, fish or insects.* *Do not count repeated names or different suffixes twice e.g. mouse/mice but allow points for similar names e.g. calf, cow, bull.*	**List** Write down each word the patient says, in "shorthand" if fast.	**Number of animals named**		**/40**
Q3 Repeating a Short Story: Read ONCE only **"Once I have FULLY read this short story to you, repeat it for me, word for word".** *Give 3 points for each correct word recalled verbatim. Otherwise score 0. Recall may be in any order.* ***Read once*** *& count* ***underlined words*** *only.* **Give a max of 30 seconds for recall.**	**"**The **white hen walked across** the **concrete road.** It was followed by a **black cat**. It was a **warm September afternoon**. **Dry leaves** were **blowing** in the **wind.**	**Number of words recalled**		**/45**

Date / / **Time of day:** **Total Score: /100**

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2. Other Assessment Instruments

Appendix 2.1. The IQCODE Short Form.

Now we want you to remember what your friend or relative was like 10 years ago and to compare it with what he/she is like now. 10 years ago was in 19__. Below are situations where this person has to use his/her memory or intelligence and we want you to indicate whether this has improved, stayed the same or got worse in that situation over the past 10 years. Note the importance of comparing his/her present performance with 10 years ago. So if 10 years ago this person always forgot where he/she had left things, and he/she still does, then this would be considered "Hasn't changed much". Please indicate the changes you have observed by circling the appropriate answer.

Compared with 10 years ago how is this person at:

	1	2	3	4	5
1. Remembering things about family and friends e.g. occupations, birthdays, addresses	Much improved	A bit improved	Not much change	A bit worse	Much worse
2. Remembering things that have happened recently	Much improved	A bit improved	Not much change	A bit worse	Much worse
3. Recalling conversations a few days later	Much improved	A bit improved	Not much change	A bit worse	Much worse
4. Remembering his/her address and telephone number	Much improved	A bit improved	Not much change	A bit worse	Much worse
5. Remembering what day and month it is	Much improved	A bit improved	Not much change	A bit worse	Much worse
6. Remembering where things are usually kept	Much improved	A bit improved	Not much change	A bit worse	Much worse
7. Remembering where to find things which have been put in a different place from usual	Much improved	A bit improved	Not much change	A bit worse	Much worse
8. Knowing how to work familiar machines around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse

9. Learning to use a new gadget or machine around the house	Much improved	A bit improved	Not much change	A bit worse	Much worse
10. Learning new things in general	Much improved	A bit improved	Not much change	A bit worse	Much worse
11. Following a story in a book or on TV	Much improved	A bit improved	Not much change	A bit worse	Much worse
12. Making decisions on everyday matters	Much improved	A bit improved	Not much change	A bit worse	Much worse
13. Handling money for shopping	Much improved	A bit improved	Not much change	A bit worse	Much worse
14. Handling financial matters e.g. the pension, dealing with the bank	Much improved	A bit improved	Not much change	A bit worse	Much worse
15. Handling other everyday arithmetic problems e.g. knowing how much food to buy, knowing how long between visits from family or friends	Much improved	A bit improved	Not much change	A bit worse	Much worse
16. Using his/her intelligence to understand what's going on and to reason things through	Much improved	A bit improved	Not much change	A bit worse	Much worse

Appendix 2.2. The AD 8 Dementia Screening Interview.

AD8 Dementia Screening Interview

Patient ID#:_____
CS ID#:_____
Date:_____

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	**YES, A change**	**NO, No change**	**N/A, Don't know**
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. **Daily** problems with thinking and/or memory			
TOTAL AD8 SCORE			

Adapted from Galvin JE et al, The AD8, a brief informant interview to detect dementia, Neurology 2005:65:559-564

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Appendix 2.3. General Practitioner Assessment of Cognition (a) patient examination, (b) informant interview.

(a)

Patient name:_____ **Date:** _____

GPCOG Screening Test

Step 1: Patient Examination

Unless specified, each question should only be asked once

Name and Address for subsequent recall test

1. "*I am going to give you a name and address. After I have said it, I want you to repeat it. Remember this name and address because I am going to ask you to tell it to me again in a few minutes: John Brown, 42 West Street, Kensington.*" (Allow a maximum of 4 attempts).

Time Orientation	**Correct**	**Incorrect**
2. *What is the date?* (exact only)	☐	☐
Clock Drawing – use blank page		
3. *Please mark in all the numbers to indicate the hours of a clock* (correct spacing required)	☐	☐
4. *Please mark in hands to show 10 minutes past eleven o'clock* (11.10)	☐	☐
Information		
5. *Can you tell me something that happened in the news recently?* (Recently = in the last week. If a general answer is given, eg "war", "lot of rain", ask for details. Only specific answer scores).	☐	☐
Recall		
6. *What was the name and address I asked you to remember*		
John	☐	☐
Brown	☐	☐
42	☐	☐
West (St)	☐	☐
Kensington	☐	☐

(*To get a total score, add the number of items answered correctly*
Total correct (score out of 9) **/9**

If patient scores 9, no significant cognitive impairment and further testing not necessary.
If patient scores 5-8, more information required. Proceed with Step 2, informant section.
If patient scores 0-4, cognitive impairment is indicated. Conduct standard investigations.

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Brodaty et al, *JAGS* 2002; 50:530-534

(b)

Informant Interview

Date: _____

Informant's name: _____

Informant's relationship to patient, i.e. informant is the patient's: _____

These six questions ask how the patient is compared to when s/he was well, say 5 – 10 years ago

Compared to a few years ago:

	Yes	No	Don't Know	N/A
▪ Does the patient have more trouble remembering things that have happened recently than s/he used to?	☐	☐	☐	
▪ Does he or she have more trouble recalling conversations a few days later?	☐	☐	☐	
▪ When speaking, does the patient have more difficulty in finding the right word or tend to use the wrong words more often?	☐	☐	☐	
▪ Is the patient less able to manage money and financial affairs (e.g. paying bills, budgeting)?	☐	☐	☐	☐
▪ Is the patient less able to manage his or her medication independently?	☐	☐	☐	☐
▪ Does the patient need more assistance with transport (either private or public)? (If the patient has difficulties due only to physical problems, e.g bad leg, tick 'no')	☐	☐	☐	☐

(***To get a total score, add the number of items answered 'no', 'don't know' or 'N/A'***)

Total score (out of 6) ☐

If patient scores 0-3, cognitive impairment is indicated. Conduct standard investigations.

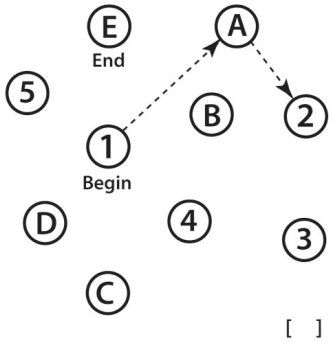
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Brodaty et al, *JAGS* 2002; 50:530-534

Appendix 2.4. The Montreal Cognitive Assessment (MoCA).

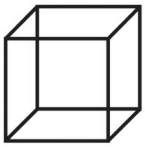
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE



Copy cube



[ ] [ ]

Draw CLOCK (Ten past eleven)
(3 points)

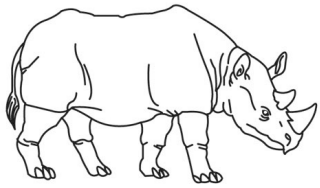
[ ] Contour [ ] Numbers [ ] Hands

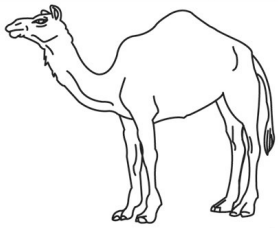
POINTS

__/5

NAMING







[ ] [ ] [ ]

__/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

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

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

__/2

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

__/1

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

__/3

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

__/2

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

__/1

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

__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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

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

Administered by: _____

Appendix 2.5. Alzheimer`s Disease Assessment Scale-Cognitive section

Alzheimer's Disease Cooperative Study

ADAS – Cognitive Behavior

SAMPLE FORM – Page 1 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

1. WORD RECALL TASK: Indicate the total number of ***correct*** responses for each trial

Trial 1	Trial 2	Trial 3

2. NAMING OBJECTS AND FINGERS: Check each object/finger named ***correctly*** or check "NONE."

NONE ☐

☐ Flower	☐ Rattle	☐ Wallet
☐ Bed	☐ Mask	☐ Harmonica
☐ Whistle	☐ Scissors	☐ Stethoscope
☐ Pencil	☐ Comb	☐ Tongs
☐ Thumb	☐ Index	☐ Ring
☐ Pinky	☐ Middle	

3. COMMANDS: Check each command performed ***correctly*** or check "NONE." NONE ☐

- ☐ Make a fist.
- ☐ Point to the ceiling, then to the floor.
- ☐ Put the pencil on top of the card, then put it back.
- ☐ Put the watch on the other side of the pencil and turn over the card.
- ☐ Tap each shoulder twice with two fingers keeping your eyes shut.

4. CONSTRUCTIONAL PRAXIS: Check each figure drawn ***correctly***.

- ☐ None: attempted but drew no forms correctly.
- ☐ Patient drew no forms; scribbled; wrote words.
- ☐ Circle
- ☐ Two overlapping rectangles
- ☐ Rhombus
- ☐ Cube

5. IDEATIONAL PRAXIS: Check each step completed ***correctly*** *or* check "NONE" NONE ☐

- ☐ Fold a letter.
- ☐ Put letter in envelope.
- ☐ Seal envelope.
- ☐ Address envelope.
- ☐ Indicate where stamp goes.

6. ORIENTATION: Check each item answered ***correctly*** or check "NONE." NONE ☐

☐ Full name	☐ Day
☐ Month	☐ Season
☐ Date	☐ Place
☐ Year	☐ Time of day

7. WORD RECOGNITION TASK: Scoring will be done by the A.D.C.S. Data Coordinating Center.

Trial 1	Trial 2	Trial 3
X	X	X

8. LANGUAGE: Check level of impairment.

- ☐ **None**: patient speaks clearly and/or is understandable.
- ☐ **Very Mild**: one instance of lack of understandability.
- ☐ **Mild**: patient has difficulty < 25% of the time.
- ☐ **Moderate**: patient has difficulty 25–50% of the time.
- ☐ **Moderately Severe**: patient has difficulty more than 50% of the time.
- ☐ **Severe**: one- or two-word utterances; fluent, but empty speech; mute.

9. COMPREHENSION OF SPOKEN LANGUAGE: Check level of impairment

- ☐ **None**: patient understands.
- ☐ **Very Mild**: one instance of misunderstanding.
- ☐ **Mild**: 3–5 instances of misunderstanding.
- ☐ **Moderate**: requires several repetitions and rephrasing.
- ☐ **Moderately Severe**: patient only occasionally responds correctly; i.e., yes – no questions.
- ☐ **Severe**: patient rarely responds to questions appropriately; not due to poverty of speech.

10. WORD FINDING DIFFICULTY: Check one response.

- ☐ **None.**
- ☐ **Very Mild**: 1 or 2 instances, not clinically significant.
- ☐ **Mild**: noticeable circumlocution or synonym substitution.
- ☐ **Moderate**: loss of words without compensation on occasion.
- ☐ **Moderately Severe**: frequent loss of words without compensation.
- ☐ **Severe**: nearly total loss of content words; speech sounds empty; 1– to 2-word utterances.

11. REMEMBERING TEST INSTRUCTIONS: Check level of impairment.

- ☐ **None**.
- ☐ **Very Mild**: forgets once.
- ☐ **Mild**: must be reminded 2 times.
- ☐ **Moderate**: must be reminded 3–4 times.
- ☐ **Moderately Severe**: must be reminded 5–6 times
- ☐ **Severe**: must be reminded 7 or more times.

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study

ADAS – Word Recall

SAMPLE FORM – Page 2 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

Present Word List #2.

Check EACH word correctly recalled.

TRIAL 1	
BOTTLE	
POTATO	
GIRL	
TEMPLE	
STAR	
ANIMAL	
FOREST	
LAKE	
CLOCK	
OFFICE	
TOTAL	

TRIAL 2	
FOREST	
TEMPLE	
BOTTLE	
STAR	
POTATO	
GIRL	
CLOCK	
ANIMAL	
LAKE	
OFFICE	
TOTAL	

TRIAL 3	
GIRL	
TEMPLE	
POTATO	
ANIMAL	
FOREST	
LAKE	
OFFICE	
CLOCK	
BOTTLE	
STAR	
TOTAL	

Indicate total number of words correctly recalled for EACH trial on the ADAS Cognitive Behavior Form.

12. Executive Function (Maze):

a. ☐☐ number of errors

b. ☐☐ time at completion or second error (total seconds)

13. Number Cancellation:

a. ☐☐ number of targets hit (Range: 0 - 40)

b. ☐☐ number of errors

c. ☐☐ number of times to remind of task

If any item(s) 1-13 are incomplete or not done, please specify reason:

☐ Subject too cognitively impaired to complete

☐ Subject was unable to complete for physical reasons

☐ Subject refused

☐ Not Done, for reason other than above explain: _____

_____

_____

_____

_____

_____

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study

ADAS – Delayed Recall

SAMPLE FORM – Page 3 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

Instructions: Say to the patient, **"NOW I WANT YOU TO TRY TO REMEMBER THE WORDS THAT I SHOWED YOU EARLIER ON PRINTED CARDS. CAN YOU TELL ME ANY OF THOSE WORDS?"**

Allow a maximum of two minutes for recall.

check EACH word correctly recalled.

BOTTLE	
POTATO	
GIRL	
TEMPLE	
STAR	
ANIMAL	
FOREST	
LAKE	
CLOCK	
OFFICE	
TOTAL	

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

Alzheimer's Disease Cooperative Study

ADAS – Word Recognition

SAMPLE FORM – Page 4 of 4

Center Name	Patient Number	Patient Initials	Examiner Initials	Examination Date
	P R – –			Month Day Year

Present Word List #2.

Check subject's response for each word. Subject should respond "yes" to original words which are bolded. INCORRECT responses are shaded. Three trials of reading and recognition are given.

	Yes	No
COST		
NATION		
CHIMNEY		
SPARROW		
DAMAGES		
TRAFFIC		
SANDWICH		
SERVICE		
SHELL		
SOLUTION		
YARD		
TUBE		
BODY		
GROUND		
STICK		
ENGINE		
RICHES		
GRAVITY		
SUMMER		
WISDOM		
MAN		
MEAL		
PASSENGER		
ACID		

	Yes	No
BATTLE		
MUCH		
TUBE		
TEAM		
COPY		
ENGINE		
GRAVITY		
COST		
JAR		
DISTANCE		
TRIUMPH		
TEMPER		
SENTENCE		
FOX		
PASSENGER		
SANDWICH		
SOLUTION		
WHISTLE		
CHIMNEY		
UNION		
ACID		
MEAL		
DAMAGES		
RICHES		

	Yes	No
VISITOR		
ACID		
SPEAK		
SOLUTION		
NAME		
MEAL		
LINE		
BILL		
CHIMNEY		
ENGINE		
WEALTH		
TUBE		
IMAGE		
COST		
SANDWICH		
DAMAGES		
ELEPHANT		
RICHES		
GRAVITY		
FUTURE		
PASSENGER		
STRING		
BANNER		
BERRY		

*see procedures manual for further clarification

WHITE- ADCS COPY YELLOW- INVESTIGATOR'S COPY PINK- CLINICAL MONITOR'S COPY

Appendix 2.6. The Quick Activities of Daily Living (Q*adl*) screen.

Q *Activities of Daily Living Score*

Tell us how the patient manages his / her "activities of daily living". How does he / she function every day? Circle the number that best applies in the past week. If the person does not do this activity, e.g. another person does shopping, circle "N/A" for not applicable.

Type of activity	**What is the level of care required?**	**How much of a problem is this?**
In the past week how well was he/she able to…	na Not applicable-never did this 0 Performs spontaneously and independently 1 Needs prompting (verbal) 2 Needs set-up (physical) 3 Needs supervision (stand by) 4 Needs assistance (physical) 5 Complete care required	0 None 1 Little 2 Moderate 3 Great 4 Extreme
manage their own medications	na 0 1 2 3 4 5	0 1 2 3 4
handle money (pay bills, shop, etc.)	na 0 1 2 3 4 5	0 1 2 3 4
use the telephone	na 0 1 2 3 4 5	0 1 2 3 4
prepare food	na 0 1 2 3 4 5	0 1 2 3 4
groom (hair, shaving, nails, etc.)	na 0 1 2 3 4 5	0 1 2 3 4
bath (bath, shower)	na 0 1 2 3 4 5	0 1 2 3 4
walk	na 0 1 2 3 4 5	0 1 2 3 4
toilet (urine / feces)	na 0 1 2 3 4 5	0 1 2 3 4
transfer (e.g. bed to chair)	na 0 1 2 3 4 5	0 1 2 3 4
feed themselves (eat and drink)	na 0 1 2 3 4 5	0 1 2 3 4

Is this person mainly limited or impaired by physical problems?

Check off if any of the following reduced the person's ability to care for him / her self.

❑ Blindness ❑ Hearing ❑ Weakness ❑ Arthritis ❑ Memory and thinking

Appendix 2.7. Caregiver Burden Score

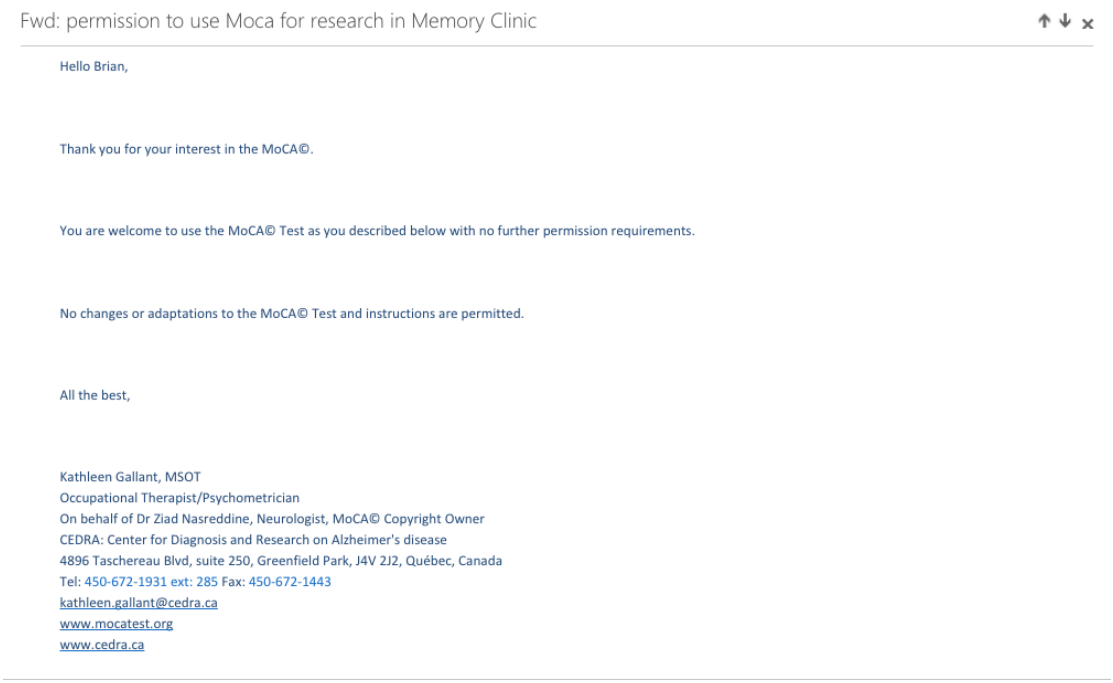
I feel...

0 None of the time
1 Almost none of the time
2 Hardly any of the time
3 A little bit of the time
4 Some of the time
5 Most of the time
6 All of the time

because of the time I spend with him / her, I don't have enough time for myself.	0	1	2	3	4	5	6
stressed between caring for him / her and trying to meet other responsibilities.	0	1	2	3	4	5	6
strained when I am around him / her.	0	1	2	3	4	5	6
uncertain what to do about him / her.	0	1	2	3	4	5	6
a great deal of burden caring for him / her.	0	1	2	3	4	5	6

3. Permissions and Ethical Approval

Appendix 3.1. Permission to use the Montreal Cognitive Assessment (obtained by Brian Daly, Medical student assisting me in the rating of controls and patients in the rehabilitation unit).



Fwd: permission to use Moca for research in Memory Clinic

Hello Brian,

Thank you for your interest in the MoCA©.

You are welcome to use the MoCA© Test as you described below with no further permission requirements.

No changes or adaptations to the MoCA© Test and instructions are permitted.

All the best,

Kathleen Gallant, MSOT
Occupational Therapist/Psychometrician
On behalf of Dr Ziad Nasreddine, Neurologist, MoCA© Copyright Owner
CEDRA: Center for Diagnosis and Research on Alzheimer's disease
4896 Taschereau Blvd, suite 250, Greenfield Park, J4V 2J2, Québec, Canada
Tel: 450-672-1931 ext: 285 Fax: 450-672-1443
kathleen.gallant@cedra.ca
www.mocatest.org
www.cedra.ca

Appendix 3.2. Ethical approval form for the external validation of the Q*mci* in Ireland.

Tel: + 353-21-490 1901
Fax: + 353-21-490 1919

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (aa) 03/04/12

23rd March 2012

Professor William Molloy
Professor of Geriatric Medicine
Centre for Gerontology and Rehabilitation
School of Medicine
University College Cork
College Road
Cork

Re: Development of a quick, screening test for mild cognitive impariment – validating and refining the Quick Mild Cognitive Impairment (Qmci) screen for use in a community and hospital setting.

Dear Professor Molloy

Expedited approval is granted to carry out the above study in:

- Memory Clinics and General Practices in Cork City.

The following documents were approved:

- Application Form
- Consent Form
- Quick Mild Cognitive Impairment Screen
- Montreal Cognitive Assessment
- Standardised Mini-Mental State Examination
- Study Protocol.

We note that the co-investigator involved in this study will be:

- Dr Rónán O'Caoimh.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 3.3. Ethical approval form for the extension of the external validation of the Q*mci* to include additional study sites.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 3 (kkk) 03/12/13

21st November 2013

Professor William Molloy
Professor of Geriatric Medicine
Centre for Gerontology and Rehabilitation
School of Medicine
University College Cork
College Road
Cork

Re: Development of a quick, screening test for mild cognitive impariment – validating and refining the Quick Mild Cognitive Impairment (Qmci) screen for use in a community and hospital setting.

Dear Professor Molloy

The Chairman approved the following:

- Amendment Application Form
- Additional Study Sites
- Addition of Brian Daly, Medical Student as a co-investigator in the above study.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Appendix 3.4. Ethical approval form for the validation of the Quick Memory Check (previous called the short caregiver dementia screen).

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 4 (ww) 03/07/12

2nd July 2012

Professor William Molloy
Department of Gerontology & Rehabilitation
University College Cork
Room 2.47
Western Gate Building
Western Road
Cork

Re: Assessing the role that caregiver reports could play in improving cognitive screening for dementia: the short caregiver dementia screen (SCADS)

Dear Professor Molloy

Expedited approval is granted to carry out the above study at:

- St Finbarr's Hospital.

The following documents have been approved:

- Application Form
- Study Protocol
- Questionnaire
- CV for Chief Investigator

We note that the co-investigators involved in this study will be:

- Patrick Coghlan, Medical Student, Dr Ronan O'Caoimh.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Appendix 3.5. Ethical approval form for the extension of the validation of the Quick Memory Check into community settings (bridge clubs) and its change of name.

UCC
Tel: + 353-21-490 1901
Fax: + 353-21-490 1919
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee
Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our ref: ECM 3 (rrrrrr) 06/01/15

5th January 2015

Professor William Molloy
Department of Gerontology & Rehabilitation
University College Cork
Room 2.47
Western Gate Building
Western Road
Cork

Re: Assessing the role that caregiver reports could play in improving cognitive screening for dementia: the short caregiver dementia screen (SCADS)

Dear Professor Molloy

The Chairman approved the following:

- Addition of Nurzakiah Mohd Zaki, Medical Student as a co-investigator in the study
- Addition of Bridge Clubs in Cork as study sites
- Changing the name of the Short Caregiver Dementia Screen to Quick Memory Check.

Please forward annual forms for this study for July 2013 and July 2014 if you wish to continue this study. We do not have a record of these documents on file.

Yours sincerely

Professor Michael G Molloy
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised by the Department of Health and Children to carry out the ethical review of clinical trials of investigational medicinal products. The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

4. Translations of the Q*mci*

Appendix 4.1. Turkish Translation of the Q*mci* with scoring instructions

Hızlı Hafif Kognitif Bozukluk Taraması (hHKB)

1. Yönelim

Hangi ülkedeyiz? _____

Hangi yıldayız? _____

Hangi aydayız? _____

Bugünün tarihi nedir? _____

Bugün haftanın hangi günü? _____

Skor _____ / 10

2. Kelime Kayıt Etme

Başlamak için şunu söyleyin:
"Size 5 kelime söyleyeceğim. Ben bu 5 kelimeyi söyledikten sonra bana onları tekrar edin. Hazır mısınız?"
Köpek yağmur tereyağı sevgi kapı

Skor _____ / 5

Alternatif kelime grupları şunları içerir:

kedi	**karanlık**	**biber**	**korku**	**yatak**
sıçan	**ısı**	**ekmek**	**yuvarlak**	**sandalye**

3. Saat Çizme

Skor:	Sayılar	Doğru	+ _____/ 12
		Hatalar	- _____
	Saatin kolları (akrep, yelkovan)		+ _____/ 2
	Merkez noktası		+ _____/ 1
	Toplam		**+ _____/ 15**

4. Gecikmiş Geri Çağırma

Başlamak için şunu söyleyin:

Birkaç dakika önce beş kelime söyledim. O kelimelerden hatırlayabildiğiniz kadar çok kelimeyi sayın.

köpek yağmur tereyağı sevgi kapı

Skor _____ / 20

5. Sözel Akıcılık

"Bir dakika içinde sayabildiğiniz kadar çok *hayvan* ismi sayın. Hazır mısınız? Başlayın."

Skor _____ / 20

6. Mantıksal Bellek

"Size kısa bir hikaye okuyacağım. Okumayı bitirdikten sonra bana hikayenin anlatabildiğiniz kadar çok kısmını anlatmanızı istiyorum. Tamam mı?" [hasta kabul ettiğini belirttikten sonra her kelime bölümünü yaklaşık 1 saniyede olmak üzere paragrafı okumaya başlayın] **"Kırmızı… tilki… sürülmüş……** üzerinde **oluşmaktaydı."**

6. Mantıksal Hafıza			
Kırmızı	**Kahverengi**	**Beyaz**	2 / 0
tilki	**köpek**	**tavuk**	2 / 0
sürülmüş	**metal**	**beton**	2 / 0
tarladan	**köprüden**	**yoldan**	2 / 0
koşarak geçti.	**koşarak geçti.**	**yürüyerek geçti.**	2 / 0
Kahverengi	**Beyaz**	**Siyah**	2 / 0
bir **köpek**	bir **tavşanı**	bir **kedi**	2 / 0
tarafından **kovalanıyordu.**	**avlıyordu.**	tarafından **izleniyordu.**	2 / 0
Sıcak bir	**Soğuk** bir	**Ilık** bir	2 / 0
Mayıs	**Ekim**	**Eylül**	2 / 0
sabahıydı.	**günüydü**.	**öğleden sonrasıydı.**	2 / 0
Güzel kokulu	**Olgun**	**Kuru**	2 / 0
çiçekler	**elmalar**	**yapraklar**	2 / 0
çalıların	**ağaçların**	**rüzgarda**	2 / 0
üzerinde **oluşmaktaydı**.	üzerinden **sarkıyordu**.	**savruluyordu**.	2 / 0

Skor _____ / 30

hHKB Toplam Skor _____ / 100

Hızlı Hafif Kognitif Bozukluk Taraması (hHKB)

Uygulama ve Puanlama Kılavuzu

1. Yönelim



Puanlama

Doğru cevap için 2 puan, yanlış cevaplar için 1 puan, hiç cevap yok veya kavramsal olarak ilişkisiz cevap için 0 puan (aşağıdaki detaylara bakınız).



Zamanlama

Her cevap için en fazla 10 saniye.

Yönergeler ve Puanlama Kılavuzu

Yıl	Doğru yılı söylerse 2 puan, yanlış yılı söylerse 1 puan, yıl söylemezse 0 puan verilir.
Ülke	Doğru ülke için 2 puan, yanlış ülke için 1 puan, ülke söylenmezse 0 puan verilir.
Ay	Doğru ay için veya ay değişiminin iki günü içerisinde iken önceki veya sonraki ay için 2 puan verilir (örneğin, tarih 30 Eylül ise, kişi Ekim cevabı verirse 2 puan verilir. Benzer şekilde tarih 2 Ekim ise, kişi Eylül derse 2 puan verilir). Ay yanlışsa 1 puan, ay söylenmezse 0 puan.
Tarih	Doğru tarih veya ± bir gün için 2 puan, herhangi başka bir tarih için 1 puan, tarih söylenmezse 0 puan verilir.
Haftanın günü	Doğru gün için 2 puan, yanlış gün için 1 puan, gün söylenmezse 0 puan verilir.

Başlamak için şöyle söyleyin:

"Size bazı sorular sormak ve çözmeniz bazı problemler vermek istiyorum. Sizin için uygun mu?"

Hangi ülkedeyiz? _____

Hangi yıldayız? _____

Hangi aydayız? _____

Bugünün tarihi nedir? _____

Bugün haftanın hangi günü? _____

Skor _____ / 10

2. Kelime Kayıt Etme

Uygulama ve Puanlama Kılavuzu



Puanlama

İlk okuma ardından hatırlanan her kelime için 1 puan verin. Kişi beşini birden hatırlarsa beş maddeyi bir seferde tekrarlayın ve saat çizme testine geçin. Kişi beşini birden hatırlayamazsa 5 maddeyi tekrarlayın ve hastanın tekrarlamasını isteyin. Bunu kişi doğru bir şekilde 5 maddeyi birden hatırlayana kadar ya da en fazla 3 deneme olacak şekilde tekrarlayın. İkinci ve üçüncü denemeler için puan vermeyin. Bu denemeler kişinin gecikmiş hatırlama testine hazırlanması için öğrenmesine yardım etmek içindir.



Zamanlama

Kelimeleri çok dikkatlice saniyede bir tane olacak şekilde söyleyin. Hatırlama için 10 saniye zaman tanıyın.

Başlamak için şöyle söyleyin:

"Size 5 kelime söyleyeceğim. Ben bu 5 kelimeyi söyledikten sonra bana onları tekrar edin. Hazır mısınız?"

Köpek **yağmur** **tereyağı** **sevgi** **Kapı**

Skor _____ / 5

Bitince şöyle söyleyin: **"Bu kelimeleri hatırlayın çünkü daha sonra sizden onları hatırlamanızı isteyeceğim."**

Alternatif kelime grupları şunları içerir:

kedi	**karanlık**	**biber**	**korku**	**yatak**
sıçan	**ısı**	**ekmek**	**yuvarlak**	**sandalye**

3. Saat Çizme

Uygulama ve Puanlama Kılavuzu

Puanlama

Transparan puanlama şablonunu hastanın tamamlanmış saatinin dairesinin üzerine koyun. “12” yi hizalamak için şablon dairesini döndürün. 1, 2, 4, 5, 7, 8, 10 ve 11 doğru kadranlardaysa her birine 1’er puan verin. 12, 3, 6 ve 9 kadran çizgilerine değiyorsa her birine 1’er puan verin. Tekrarlayan her sayı için veya 12’nin üzerinde her sayı için 1 puan çıkarın. (Hasta “12” yazmadıysa şablonu 3, 6, veya 9 ile hizalayın.)

Saatin kollarının yerleşimini uçlarına ve merkez noktasına göre puanlayın. Kesikli çizgiler arasındaki her kol için 1’er puan verin. Merkez noktasında birleşen kollar için 1 puan verin.

Zamanlama

Bir dakika.

Başlamak için:

Hastaya üzerinde önceden çizilmiş daire olan kağıdı ve kalemi verin. Şöyle söyleyin: **“Şimdi saat oluşturacak şekilde sayıları yerleştirin.”**. Sonra şöyle söyleyin: **“Saatin kollarını on biri on geçiyor olacak şekilde yerleştirin.” Sayıları ve kolları yapabildiğiniz kadar dikkatli yerleştirin.”**

Her evrede hatırlatma yapabilirsiniz… **“sayıları yerleştirin. … saati on biri on geçiyor olacak şekilde yapın”**.

Skor:	Sayılar	Doğru	+ _____/ 12
		Hatalar	- _____
	Saatin kolları (akrep, yelkovan)		+ _____/ 2
	Merkez noktası		+ _____/ 1
	Toplam		**+ _____/ 15**

4. Gecikmiş Geri Çağırma

Uygulama ve Puanlama Kılavuzu

 ***Puanlama***

Hatırlanan her kelime için 4'er puan verin. Kişiler kelimeleri herhangi bir sırayla hatırlayabilirler.

 ***Zamanlama***

10 saniye.

Başlamak için şöyle söyleyin:

Birkaç dakika önce beş kelime söyledim. O kelimelerden hatırlayabildiğiniz kadar çok kelimeyi sayın.

köpek **yağmur** **tereyağı** **sevgi** **kapı**

Skor _____ / 20

Alternatif kelime grupları şunları içerir:

kedi	**karanlık**	**biber**	**korku**	**yatak**
sıçan	**ısı**	**ekmek**	**yuvarlak**	**sandalye**

5. Sözel Akıcılık

Uygulama ve Puanlama Kılavuzu

 ***Puanlama***

En fazla 40 kelimeye kadar doğru hatırlanan her kelime için ½' şer puan verin. Son skoru yukarıya yuvarlayın. Farklı soneklere sahip kelimeleri iki kere puanlamayın (örn. balık/balıklar, fare/fareler gibi). Aynı grubun farklı türlerini kabul edin (örn. karga, bülbül, serçe, ördek gibi.).

Alternatif formlarında meyve ve sebzeler, şehirler ve kasabalar sorulabilir.

 ***Zamanlama***

60 saniye. Hastanın söylediği her kelimeyi yazın. (Daha hızlı hastalar için bir çeşit "kısayol" geliştirmeniz gerekebilir. Örneğin, her kelimenin ilk 3 harfini yazıp sonradan tamamlamak gibi.)

Başlamak için şöyle söyleyin:

"Bir dakika içinde sayabildiğiniz kadar çok *hayvan* ismi sayın. Hazır mısınız? Başlayın."

Skor _____ / 20

6. Mantıksal Bellek

Uygulama ve Puanlama Kılavuzu



Puanlama

Harfi harfine hatırlanmış her doğru kelime için 2'şer puan verin. 2 puan için her bölümdeki koyu belirtilmiş her kelimenin hatırlanması gerekir. Aksi takdirde 0 puan verin. Hatırlama herhangi bir sırayla olabilir.



Zamanlama

30 saniye. Hatırlanan her kelime ünitesine çek atın.

Başlamak için şöyle söyleyin:

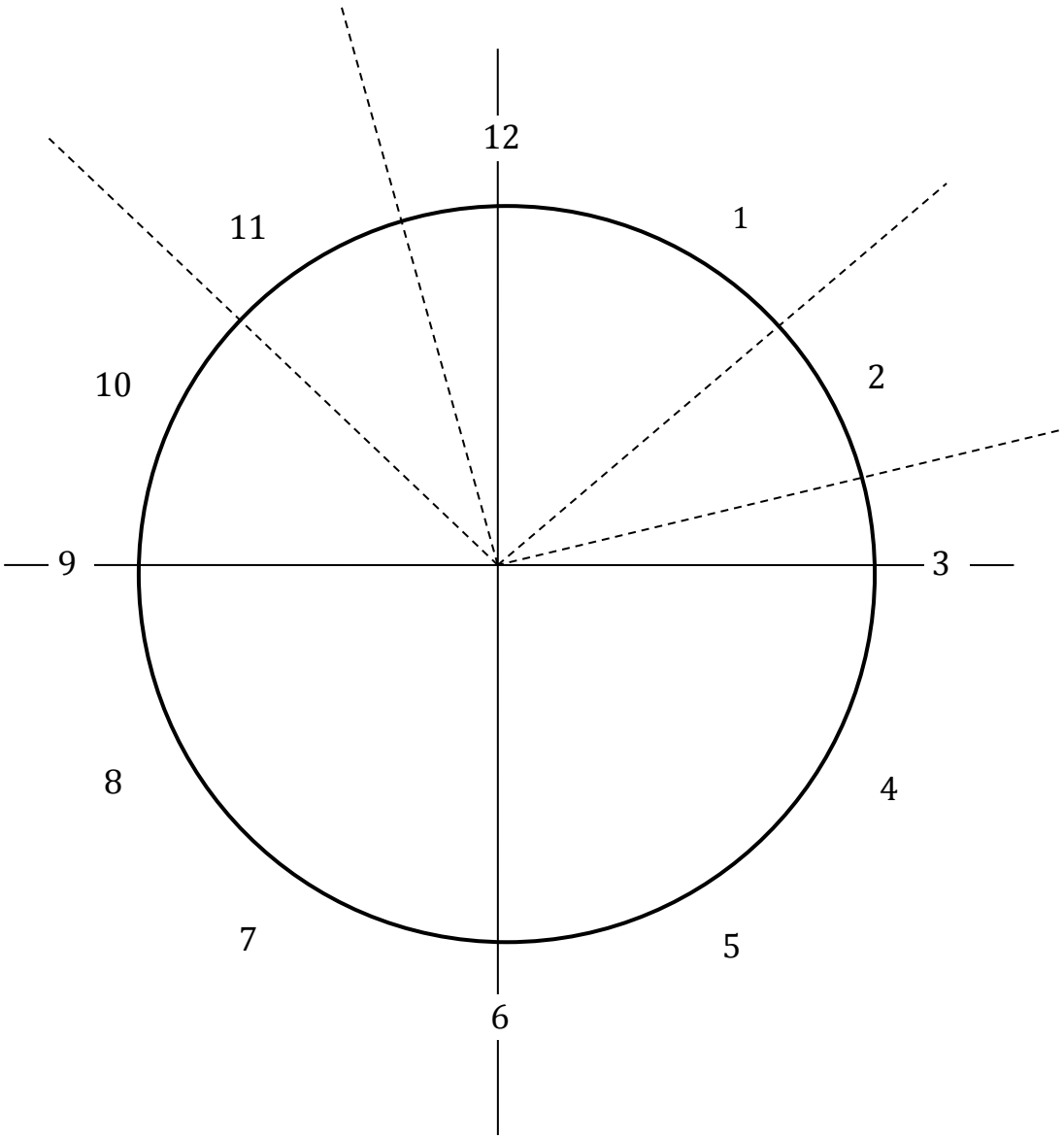
"Size kısa bir hikaye okuyacağım. Okumayı bitirdikten sonra bana hikayenin anlatabildiğiniz kadar çok kısmını anlatmanızı istiyorum. Tamam mı?" [hasta kabul ettiğini belirttikten sonra her kelime bölümünü yaklaşık 1 saniyede olmak üzere paragrafı okumaya **başlayın] "Kırmızı… tilki… sürülmüş..... üzerinde oluşmaktaydı."**

6. Mantıksal Hafıza			
Kırmızı	**Kahverengi**	**Beyaz**	**2 / 0**
tilki	**köpek**	**tavuk**	**2 / 0**
sürülmüş	**metal**	**beton**	**2 / 0**
tarladan	**köprüden**	**yoldan**	**2 / 0**
koşarak geçti.	**koşarak geçti.**	**yürüyerek geçti.**	**2 / 0**
Kahverengi	**Beyaz**	**Siyah**	**2 / 0**
bir köpek	**bir tavşanı**	**bir kedi**	**2 / 0**
tarafından kovalanıyordu.	**avlıyordu.**	**tarafından izleniyordu.**	**2 / 0**
Sıcak bir	**Soğuk bir**	**Ilık bir**	**2 / 0**
Mayıs	**Ekim**	**Eylül**	**2 / 0**
sabahıydı.	**günüydü.**	**öğleden sonrasıydı.**	**2 / 0**
Güzel kokulu	**Olgun**	**Kuru**	**2 / 0**
çiçekler	**elmalar**	**yapraklar**	**2 / 0**
çalıların	**ağaçların**	**rüzgarda**	**2 / 0**
üzerinde oluşmaktaydı.	**üzerinden sarkıyordu.**	**savruluyordu.**	**2 / 0**

Skor _____ / 30

hHKB Toplam Skor _____ / 100

Saat Çizme Transparan Puanlama Şablonu



Puanlama
Transparan puanlama şablonunu hastanın tamamlanmış saatinin dairesinin üzerine şablonun "12"si hastanın "12"sinin üzerine gelecek şekilde koyun. Şablonu sayı ve kolların puanlarının en yüksek olacağı şekilde ayarlayın. Toplam skor 15'dir. Skor sayfasına skorları aşağıdaki gibi kaydedin.
Sayılar

- 12, 3, 6 ve 9 için ilgili çizgilere değiyorsa her birine bir (1) puan verin, değmiyorsa sıfır (0) puan verin ve sayı ihmal edilmişse sıfır (0) puan verin.
- 1, 2, 4, 5, 7, 8, 10 ve 11 için doğru kadrandaki her sayı için bir (1) puan verin, sayı kadranın dışındaysa sıfır (0) puan verin ve sayı ihmal edilmişse sıfır (0) puan verin.
- **Tekrar eden her sayı için veya 12'nin üzerindeki her sayı için bir puan çıkarın.**

Saatin kolları (akrep, yelkovan)
Kolun bütününün yerleştirilmesine puan verin. Kollar aralık içerisine çizildiyse her kol için bir (1) puan verin; kollar hazırlanmış çizgilerin dışında çizildiyse veya çizilmediyse sıfır (0) puan verin. Kollar mer

Appendix 4.2. Dutch Translation of the Q*mci*.

Vragenlijst

Uitvoering en richtlijn voor het scoren

1. Oriëntatie

Scores

2 punten voor goede antwoorden, 1 punt voor foute antwoorden, en 0 punten bij geen antwoord of een conceptueel ongerelateerd antwoord (zie details onder).

Tijd

Maximaal 10 seconden voor elk antwoord.

Instructies en richtlijn voor het scoren

Jaar	Als de persoon het juiste jaar noemt tel 2 punten, het onjuiste jaar tel 1 punt, en 0 punten als geen jaar wordt genoemd.
Land	Tel 2 punten voor het juiste jaar, 1 punt voor het onjuiste jaar, en 0 als geen land wordt genoemd.
Maand	Tel 2 punten voor de juiste maand of de volgende of vorige maand wanneer binnen twee dagen van de maandwisseling (bijvoorbeeld, als de datum 30 september is, tel de volle twee punten als de persoon oktober noemt. Vergelijkbaar, als de datum 2 oktober is, tel 2 punten als de persoon september noemt). Tel 1 punt als de maand onjuist is en 0 als geen maand wordt genoemd.
Datum	Tel 2 punten voor de exacte datum of ± één dag, 1 punt voor elke andere datum, 0 als geen datum wordt genoemd.
Dag van de week	2 punten voor de juiste dag, 1 punt voor de onjuiste dag, 0 als geen dag wordt genoemd.

Geef de volgende instructie…

"Ik wil u graag enkele vragen stellen en geef u wat problemen om op te lossen. Vindt u dat goed?"

In welk land zijn we? _____

Welk jaar is het? _____

Welke maand is het? _____

Welke datum is het vandaag? _____

Welke dag van de week is het? _____

Score _____ / 10

2. Onthouden van woorden

Instructies en richtlijn voor het scoren



Scores

Tel 1 punt voor elk woord dat genoemd wordt na de eerste keer oplezen. Als de persoon zich alle vijf woorden herinnert, herhaal dan de vijf items één keer en ga vervolgens door met klok tekenen. Als de persoon zich niet alle vijf items herinnert, herhaal dan de 5 items en vraag de persoon ze opnieuw op te noemen. Herhaal dit tot dat de persoon zich alle vijf items juist herinnert, met een maximum van 3 keer. Geef bij de 2e en 3e keer geen scores. Deze herhalingen zijn bedoeld om de persoon te helpen de woorden te leren in voorbereiding op de opdracht bij uitgestelde herinnering.



Tijd

Lees de woorden heel bewust op, één per seconde. Sta 10 seconden toe voor het herinneren.

Geef de volgende instructie…

"Ik ga 5 woorden opnoemen. Nadat ik deze 5 woorden heb opgenoemd, herhaalt u ze voor me. Bent u er klaar voor?"

Hond regen boter liefde deur

Score _____ / 5

Daarna geef de volgende instructie **"Onthoud deze woorden want ik zal u later nog een keer vragen of u ze zich herinnert."**

Woordgroepen ter afwisseling zijn…

kat	**donker**	**peper**	**angst**	**bed**
rat	**hitte**	**brood**	**rond**	**stoel**

3. Klok Tekenen

Instructies en richtlijn voor het scoren



Scores

Plaats de cirkel van het transparente scoringssjabloon over de cirkel van de door de patiënt getekende klok. Roteer de sjablooncirkel zodanig dat de "12"-en op elkaar liggen. Tel 1 punt per correct cijfer als de 1, 2, 4, 5, 7, 8, 10, en 11 in de juiste kwadranten vallen. Tel 1 punt per correct cijfer als de 12, 3, 6, en 9 de kwadrantlijnen raken. Trek 1 punt af voor elk cijfer dat herhaald wordt or voor cijfers boven de 12. (Heeft de patiënt geen "12" getekend, zet het sjabloon dan gelijk aan de 3, 6, of 9.)

Geef de score voor het plaatsen van de wijzers aan de hand van de wijzers en het middelpunt. Geef 1 punt voor elke wijzer tussen de gestippelde lijnen. Tel 1 punt als de wijzers het middelpunt raken.



Tijd

Een minuut

Start met het volgende…

Geef het vel papier met de voorgetekende cirkel erop en geef een pen aan de patient. Zeg **"Zet de nummers erin als in een klok."** Zeg vervolgens **"Zet de wijzers op tien over elf. Plaats de nummers en wijzers er zo precies mogelijk in."**

U mag in elke fase onderbreken…"**zet de cijfers erin…. zet de tijd op tien over elf**".

Score:	Cijfers	Correct	+ _____/ 12
		Fouten	- _____
	Wijzers		+ _____/ 2
	Middelpunt		+ _____/ 1
	Totaal		**+ _____/ 15**

4. Uitgestelde herinnering

Instructies en richtlijn voor het scoren

Scores

Tel 4 punten voor elk woord dat wordt herinnerd. De woorden mogen in willekeurige volgorde genoemd worden.

Tijd

10 seconden.

Geef de volgende instructie…

"Enkele minuten geleden noemde ik 5 woorden op. Kunt u deze woorden nog eens opnoemen?"

hond	**regen**	**boter**	**liefde**	**deur**

Score _____ / 20

Woordgroepen ter afwisseling zijn…

kat	**donker**	**peper**	**angst**	**bed**
rat	**hitte**	**brood**	**rond**	**stoel**

5. Woordvlotheid

Instructies en richtlijn voor het scoren

Scores

Geef een ½ punt voor elk correct woord dat genoemd wordt met een maximum van 40 woorden. Rond de totale score af. Tel dezelfde woorden met verschillende achtervoegsels niet twee keer (bv. vis / vissen, muis / muizen, etc.). Accepteer verschillende soorten (bv. gaai, roodborstje, mus, eend, etc.). Verschillende soorten gelden ook voor fruit en groenten, steden en dorpen.

Tijd

60 seconden. Schrijf elk woord dat de patiënt zegt, op. (U zult misschien een soort "snelschrift" moeten gebruiken voor de snellere patiënten door bijvoorbeeld de eerste 3 letters van elk woord op te schrijven en ze dan later af te maken.)

Geef de volgende instructie…

"Noem zoveel mogelijk *dieren* als u kunt. U krijgt hiervoor één minuut. Klaar? Start."

Score _____ / 20

6. Logisch Geheugen

Instructies en richtlijn voor het scoren



Scores

Geef 2 punten voor elk correct genoemd woord, letterlijk, dat de patiënt zich herinnert. Alle vet gedrukte woorden in elk hokje moeten genoemd worden om 2 punten te tellen. Zo niet, tel dan 0 punten. De woorden mogen in elke volgorde worden genoemd.



Tijd

30 seconden. Vink elk woord dat genoemd wordt af.

Geef de volgende instructie…

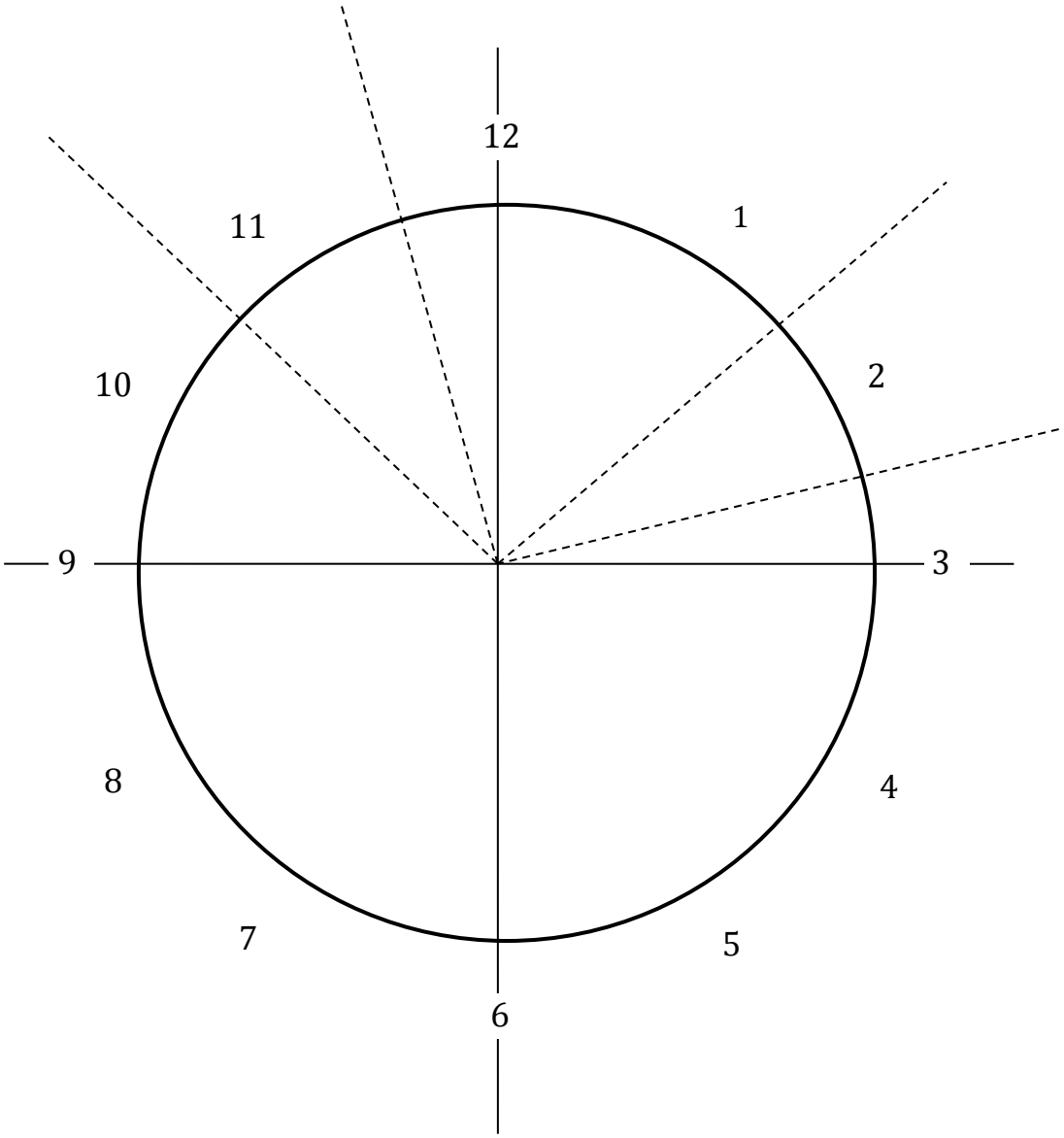
"Ik ga u een kort verhaaltje voorlezen. Nadat ik klaar ben met voorlezen probeert u zoveel mogelijk van het verhaaltje na te vertellen. OK?" [nadat de patiënt akkoord geeft, begin met het voorlezen van de paragraaf met een snelheid van ongeveer 1 seconde voor elke woordeenheid] **"De rode… vos… rende door…… het struikgewas."**

6. Logisch Geheugen			
De **rode**	De **bruine**	De **witte**	2 / 0
vos	**hond**	**kip**	2 / 0
rende over	**rende over**	**liep over**	2 / 0
het **omgeploegde**	de **metalen**	de **geasfalteerde**	2 / 0
veld.	**brug**.	**weg**.	2 / 0
Hij werd **nagejaagd** door	Hij **jaagde** op	Hij werd **gevolgd** door	2 / 0
een **bruine**	een **wit**	een **zwarte**	2 / 0
hond.	**konijn**.	**kat**.	2 / 0
Het was een **hete**	Het was een **koude**	Het was een **warme**	2 / 0
morgen	**dag**	**middag**	2 / 0
in **mei**.	in **oktober**.	in **september**.	2 / 0
Geurige	**Rijpe**	**Droge**	2 / 0
bloesems	**appels**	**bladeren**	2 / 0
bloeiden	**hingen**	**bewogen**	2 / 0
in het **struikgewas**.	in de **bomen**.	in de **wind**.	2 / 0

Score _____ / 30

Totale Score _____ / 100

De Klok Transparante Scoresjabloon



Scores
Plaats dit scoresjabloon over de getekende klok met de “12 uur”- lijn van het sjabloon geplaatst op de 12 van de patiënt. Verschuif het sjabloon om de score voor cijfers en wijzers te maximaliseren. De totale score is 15. Noteer de scores op het scorevel als volgt:

Cijfers

- Voor de cijfers 12, 3, 6, en 9 tel één (1) punt Als zij hun respectievelijke lijnen raken, nul (0) punten als dat niet zo is, en nul (0) als een cijfer ontbreekt.
- Voor de cijfers 1, 2, 4, 5, 7, 8, 10, en 11 tel één (1) punt voor elk cijfer in het juiste kwadrant, nul (0) punten als het cijfer buiten het kwadrant valt, en nul (0) als het cijfer ontbreekt.
- **Trek een punt af voor elk herhaald cijfer of cijfers hoger dan 12.**

Wijzers

- Geef een score voor de plaatsing van beide wijzers samen. Als de cijfers binnen de toegestane zone vallen, tel één (1) punt voor elke wijzer; als de wijzers buiten de gestippelde lijn zijn getekend of ontbreken tel dan nul (0) punten; Geef één (1) punt als de wijzers het middelpunt raken.

Appendix 4.3. German Translation of the Q*mci*.

Quick *Mild Cognitive Impairment* (Q*mci*) Fragenliste

Praktische Ausführung und Richtlinien für die Auswertung

1. Orientierung

Punkte

2 Punkte für jede gute Antwort, 1 Punkt für falsche Antworten und 0 Punkte für keine/konzeptuell unpassende Antworten (genauere Beschreibung im weiteren Text)

Zeit

Maximal 10 Sekunden für jede Antwort.

Anweisungen und Richtlinien für die Auswertung

Jahr	Falls die Person das richtige Jahr nennt gibt es 2 Punkte, das falsche Jahr jeweils 1 Punkt und 0 Punkte bei keiner Antwort.
Land	Jeweils 2 Punkte für das richtige Land, 1 Punkte für ein falsches Land und 0 Punkte bei keiner Antwort.
Monat	Jeweils 2 Punkte bei der richtigen Benennung vom Monat und des vorherigen und nächsten Monats falls der Test innerhalb von 2 Tagen rundum eines Monatswechsels abgehalten wird (zum Beispiel im Fall vom 30. September werden auch 2 Punkte vergeben wenn Oktober genannt wird oder am 2. Oktober warden 2 Punkte für September vergeben). Jeweils 1 Punkt für einen falschen Monat und 0 Punkte bei keiner Antwort.
Datum	Jeweils 2 Punkte für das korrekte Datum ± einem Tag, 1 Punkt für ein falsches Datum, 0 Punkte bei keiner Antwort.
Wochentag	Jeweils 2 Punkte für den korrekten Wochentag, 1 Punkt für einen falschen Wochentag, 0 Punkte bei keiner Antwort.

Gebe die folgenden Anweisungen…

'Ich möchte Ihnen einige Fragen stellen und ein paar Probleme geben, die Sie lösen sollen. Ist das in Ordnung?'

In welchem Land sind wir? _____

Welches Jahr ist es? _____

Welcher Monat ist es? _____

Was ist das Datum von heute? _____

Welcher Wochentag ist es? _____

Punktanzahl: _____ / 10

2. Das Erinnern an Wörter

Anweisungen und Richtlinien für die Auswertung

Punkte

Jeweils 1 Punkt für jedes auf der Liste stehende genannte Wort nach dem ersten Vorlesen. Falls sich die Person alle fünf Wörter erinnert, wiederhole alle fünf Wörter einmal und fange dann an mit nächsten Aufgabe (Uhr). Falls sich die Person nicht an alle fünf Wörter erinnert, wiederhole alle fünf Wörter und frage die Person um nochmal gut zu zuhören. Wiederhole den Prozess maximal drei Mal, bis sich die Person alle fünf Wörter gemerkt hat. Für den zweiten und dritten Versuch werden keine Punkte vergeben. Die Versuche sind dafür da um die Person vorzubereiten auf die spätere Aufgabe der verzögerten Erinnerung.

Zeit

Lese die Wörter sehr bewusst vor, jeweils ein Wort pro Sekunde. Ermögliche 10 Sekunden für das Erinnern.

Gebe die folgenden Anweisungen…

'Ich werde fünf Wörter vorlesen. Wenn ich fertig bin, möchte ich dass Sie die Wörter für mich wiederholen. Sind Sie soweit?'

Hund Regen Butter Liebe Tür

Punktzahl: _____ / 5

Gib danach die folgenden Anweisungen: **'Merke Sie sich bitte diese Wörter, ich werde Sie an einem späteren Zeitpunkt noch einmal nach den Wörtern fragen.'**

Verschiedene Wörtergruppen bei dieser Aufgabe zur Abwechslung sind….

Katze	**Dunkel**	**Pfeffer**	**Angst**	**Bett**
Ratte	**Hitze**	**Brot**	**rund**	**Stuhl**

3. Malen der Uhr

Anweisungen und Richtlinien für die Auswertung

Punkte

Lege den Zeiger der transparenten Schablone über den Kreis der durch die Person gezeichneten Uhr. Drehe den Zeiger so, dass die Nummer 12 der Schablone auf der Nummer 12 der gezeichneten Uhr liegt (sollte die Person keine 12 gezeichnet haben, lege die Schablone dann auf 3, 6 oder 9). Zähle jeweils 1 Punkt pro richtige Nummer, falls 1, 2, 4, 5, 7, 8, 10 und 11 auf die richtigen Quadranten fallen. Zähle jeweils 1 Punkt pro richtige Nummer, falls 12, 3, 6 oder 9 die Quadrantlinien berühren. Ziehe 1 Punkt ab für jede wiederholte Zahl oder für Zahlen über 12.
Gebe Punkte für das Anbringen der Zeiger an Hand der Zeiger des Mittelpunkts. Gebe jeweils 1 Punkt für jeden Zeiger zwischen den gestrichelten Linien. Ziehe 1 Punkt ab wenn die Zeiger den Mittelpunkt berühren.

Zeit

Eine Minute.

Fange an mit den folgenden Anweisungen:
Gib der Person ein Blatt Papier mit dem vorgezeichneten Kreis und gebe ihm/ihr einen Stift. Sage: **'Schreibe Sie bitte die Zahlen einer Uhr hier herein.'** Sage danach: **' Stelle bitte so genau wie möglich den Zeiger auf zehn nach elf.'**
Du kannst in jeder Phase unterbrechen…."**Schreibe die Zahlen…..stelle den Zeiger auf'.**

Punktanzahl:	Zahlen	Korrekt	+ _____/ 12
		Falsch	- _____
	Zeiger		+ _____/ 2
	Mittelpunkt		+ _____/ 1
	Total		**+ _____/ 15**

4. Verzögerte Erinnerung

Anweisungen und Richtlinien für die Auswertung

Punkte

4 Punkte für jedes erinnerte Wort. Die Wörter können genannt werden in einer willkürlichen Reihenfolge.

Zeit

10 Sekunden.

Gebe die folgenden Anweisungen…

'Vor einigen Minuten habe ich Sie gefragt um sich fünf Wörter zu merken. Können Sie mir diese Wörter nennen?'

Hund	**Regen**	**Butter**	**Liebe**	**Tür**

Punktzahl _____ / 20

Verschiedene Wörtergruppen zur Abwechslung sind….

Katze	**dunkel**	**Pfeffer**	**Angst**	**Bett**
Ratte	**Hitze**	**Brot**	**rund**	**Stuhl**

5. Wortflüssigkeit

Anweisungen und Richtlinien für die Auswertung

Punktzahl

Jeweils einen halben Punkt pro richtigem Wort aus der Liste mit einer maximalen Wörterzahl van 40. Runde die gesamte Punktzahl ab. Zähle ähnliche Wörter nicht doppelt (zum Beispiel Stuhl/Stühle, Maus/Mäuse). Akzeptiere verschiedene Wörter aus einer Wortgruppe, sowie Früchte, Gemüse, Städte oder Tiere (zum Beispiel Gans, Huhn, Papagei, Taube).

Zeit

60 Sekunden. Schreibe jedes Wort auf, was die Person sagt. Du musst eventuell Abkürzungen benutzen bei schnellen Personen, wie zum Beispiel die ersten drei Buschstaben eines Wortes.

Gebe die folgenden Anweisungen…

'Schreibe Sie so viele Tiere auf, wie sie können. Sie haben eine Minute Zeit. Sind Sie fertig? Los.'

Punktzahl _____ / 20

6. Logisches Denken

Anweisungen und Richtlinien für die Auswertung

Punkte

2 Punkte für jedes korrekt erinnerte Wort. Alle dickgedruckten Wörter in jeder Spalte zählen 2 Punkte. Falls nicht genannt, gib 0 Punkte. Die Wörter können in willkürlicher Reihenfolge genannt werden.

Zeit

30 Sekunden. Kreuze jedes genannte Wort an.

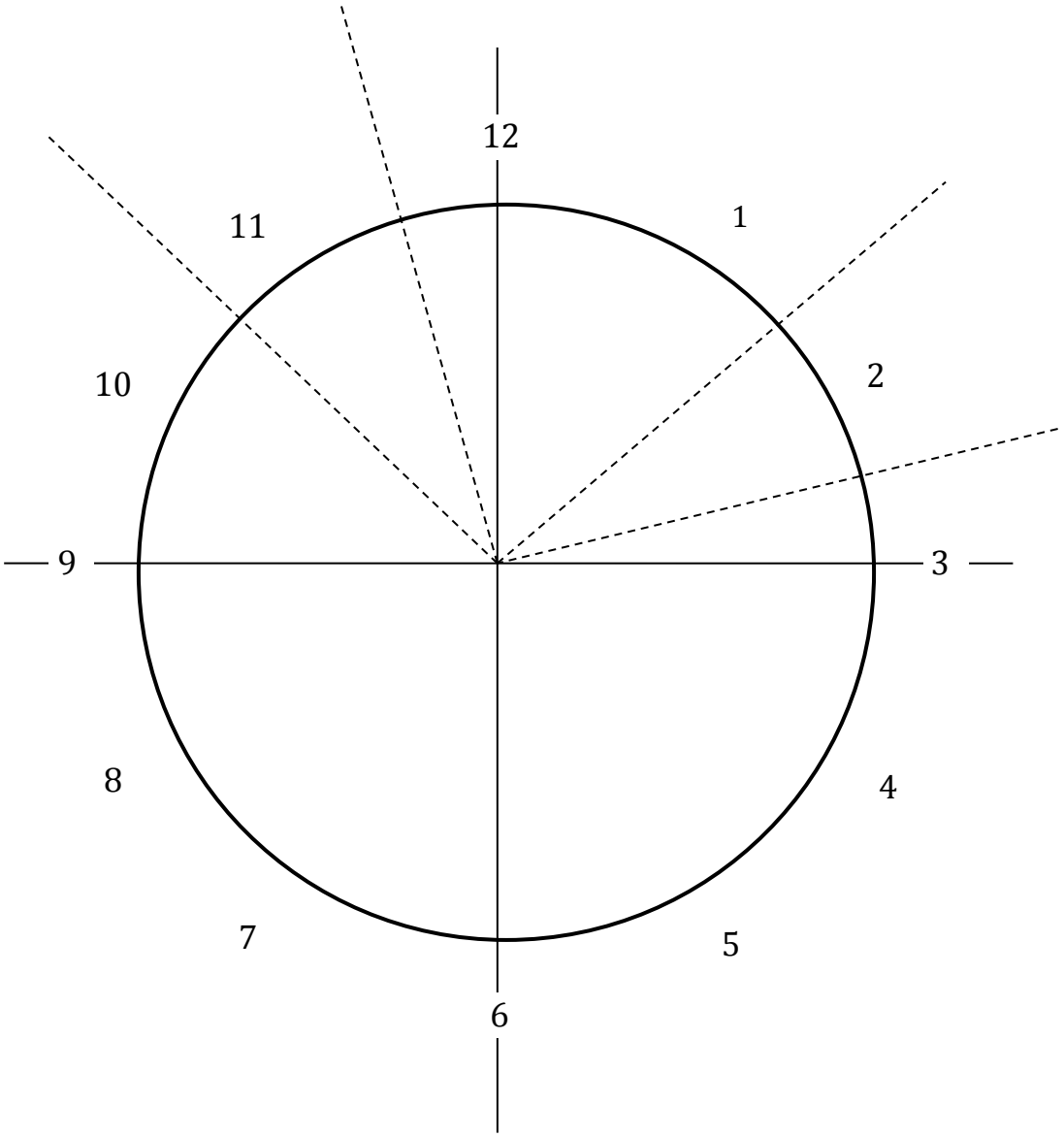
Gebe die folgenden Anweisungen…
'Ich werde Ihnen eine kurze Geschichte vorlesen. Wenn ich fertig bin, möchte ich dass Sie so gut Sie können die Geschichte wiederholen. Ok?'
[Wenn der Patient sich bereit erklärt, fange an die Geschichte vorzulesen mit der Geschwindigkeit von ungefähr einer Sekunde pro Worteinheit) ', **Der rote……..Fuchs……..lief durch……..die Büsche.,**

6. Logisches Denken			
Der **rote**	Der **braune**	Das **weiße**	2 / 0
Fuchs	**Hund**	**Hühnchen**	2 / 0
lief durch	**lief über**	**sprang über**	2 / 0
das **umgepflügte**	die **metallene**	die **asphaltierte**	2 / 0
Feld.	**Brücke.**	**Straße.**	2 / 0
Er wurde **verfolgt** von	Er **verfolgte**	Es wurde **verfolgt** von	2 / 0
einem **braunen**	einen **weißen**	einer **schwarzen**	2 / 0
Hund.	**Hasen.**	**Katze.**	2 / 0
Es war ein **heißer**	Es war ein **kalter**	Es war ein **warmer**	2 / 0
Morgen	**Tag**	**Nachmittag**	2 / 0
im **März**.	im **Oktober**.	im **September**.	2 / 0
Wohlriechende	**Reife**	**Trockene**	2 / 0
Blüten	**Äpfel**	**Blätter**	2 / 0
blühten	**hingen**	**bewegten**	2 / 0
in den **Büschen**.	in den **Bäumen**.	sich im **Wind**.	2 / 0

Punktzahl: _____ / 30

Gesamte Punkte: _____ / 100

Transparente Schablonen für die Uhrenaufgabe



Punktanzahl
Lege diese Schablone über die gezeichnete Uhr, wobei die 12-Uhr Linie der Schablone auf der 12 Uhr Linie von der gezeichneten Uhr vom Patienten liegt. Verschiebe die Schablone um die Punkte zu maximieren. Die maximale Punktzahl ist 15. Notiere die Punkte wie nachfolgend beschrieben:

Zahlen

- Für die Zahlen 12, 3, 6 und 9, gebe einen Punkt wenn diese die jeweiligen Linien berühren, gebe 0 Punkte wenn dies nicht so ist oder eine Zahl fehlt.
- Für die Zahlen 1, 2, 4, 5, 7, 8, 10 und 11 gebe einen Punkt für jede Zahl im richtigen Quadranten, 0 Punkte wenn die Nummer außerhalb des Quadranten liegt oder fehlt.
- **Ziehe einen Punkt ab für jede wiederholte Zahl oder Zahlen über 12.**
  Zeiger

- Gebe einen Punkt für beide Zeiger zusammen. Wenn die Nummern innerhalb der zugestandenen Zone fallen, gebe einen Punkt für jeden Zeiger. Liegen die beiden Zeiger außerhalb der gestrichelten Linie oder fehlen, gebe dann 0 Punkte; gebe einen Punkt falls die Zeiger den Mittelpunkt berühren.

Appendix 4.4. Italian translation of the Q*mci*.

QMCI- ***Quick Mild Cognitive Impairment screen***
(Test cognitivo Caoimh-Molloy)
Test da allegare alla scheda generale dati partecipante n…….

ANNO DI NASCITA SESSO M F Istruzione: Data:

1. Orientamento (un minuto)

(Dare 2 punti per risposta corretta, 1 se ha tentato e se non è corretta, 0 se nessun tentativo)

Che Paese è questo? _____

In che anno siamo? _____

In che mese siamo? _____

Quante ne abbiamo oggi? _____

Che giorno delle settimana è oggi? _____

Punteggio _____ / 10

2. Parole ricordate (30 secondi)

Per cominciare diciamo ...
"Sto per dire 5 parole. Dopo che le ho pronunciate, ripetile. Sei pronto?"
(Dare 1 punto per ogni parola ricordata, in qualsiasi ordineany order)

Cane	**pioggia**	**burro**	**amore**	**porta**

Punteggio _____ / 5

Gruppi di parole alternative includono …

gatto	**buio**	**pepe**	**paura**	**letto**
ratto	**calore**	**pane**	**turno**	**sedia**

3. Disegno dell'orologio (un minuto)

"Utilizzare il cerchio fornito per disegnare un orologio, impostare il tempo di '11:10'."
(Dare 1 punto per ogni numero, uno per ogni mano e 1 per il perno posizionato correttamente.

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Sottrarre 1 punto per ogni numero duplicato o maggiore di 12, ad esempio, 15 o 45).

Punteggio:	Numeri	Corretti	+ _____/ 12
		Errati	- _____
	Mani		+ _____/ 2
	Perno		+ _____/ 1
	Totale		**+ _____/ 15**

4. Ricordiamo (30 secondi)

Per cominciare diciamo ...
"Pochi minuti fa ho elencato cinque parole. Potresti ripetermele"
(Ricordate in qualsiasi ordine, entro 30 secondi, dare 4 punti per parola)

Cane pioggia burro amore Porta

Punteggio _____ / 20

5. Fluidità verbale (un minuto)

"Dimmi, in un minuto, il maggior numero di nomi di animali che ti vengono in mente. Pronto? Cominciamo."
(Dare ½ punto per ogni parola corretta ricordata fino ad un massimo di 40 parole. Arrotondare il punteggio finale. Non contare le parole con suffissi diversi per due volte (es. pesce / pesci, topo / topi, ecc.) Accettare specie alternative (ad esempio pettirosso, passero, anatra, ecc.) Forme alternative includono frutta e verdura, città e paesi).

Punteggio _____ / 20

Elencare qui, in 'stenografia' se necessario:

6. Memoria logica (30 secondi)

"Ho intenzione di leggere una breve storia. Dopo che ho finito di leggere voglio che tu mi ripeta gran parte della storia, OK? "[Se il paziente è d'accordo, iniziare la lettura del paragrafo]" La rossa volpe…… attraversava ..... i cespugli."
(Dare 2 punti per parola evidenziata, che ha ricordato esattamente, subito entro 30 secondi, in qualsiasi ordine. Sono fornite due storie alternative niente storie alternative).

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6. Logical Memory			
La **volpe**	Il **cane**	La **gallina**	2 / 0
rossa	**marrone**	**bianca**	2 / 0
corse attraverso	**corse attraverso**	**attraversò**	2 / 0
il **campo**	il **ponte**	la **strada**	2 / 0
arato	**metallico**	di **cemento**	2 / 0
e fu **inseguita**	Stava dando la **caccia**	Era **inseguita** da	2 / 0
da un **cane**	a un **coniglio**	un **gatto**	2 / 0
marrone.	**bianco**	**nero**	2 / 0
Era un **caldo**	Era un **freddo**	Era un **tiepido**	2 / 0
giorno	**giorno**	**pomeriggio**	2 / 0
di **Maggio.**	di **Ottobre**.	di **Settembre**.	2 / 0
Fiori	**Mele**	Le **foglie**	2 / 0
profumati	**mature**	**secche**	2 / 0
stavano **sbocciando** tra	**pendevano**	erano **soffiate** via	2 / 0
i **cespugli**.	dagli **alberi**.	dal **vento**.	2 / 0

Punteggio _____ / 30

Q*mci* Punteggio Totale _____ / 100

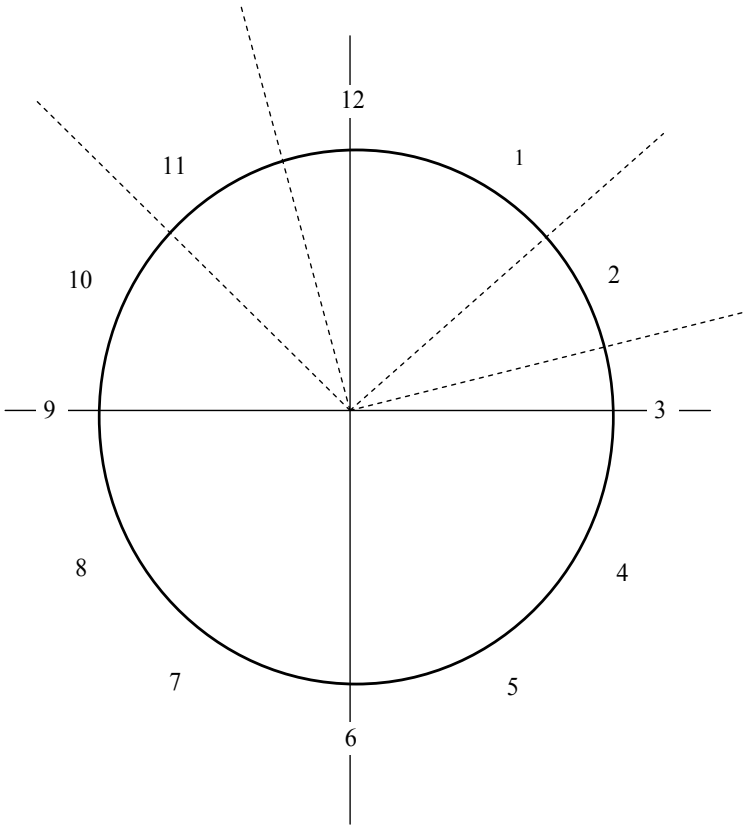
*Normale > 60
MCI=50-60
Demenza <50

Test eseguito da _____ Data / /

*aggiustare secondo l'età e l'istruzione

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The Clock Transparency Scoring Template



Punteggio

Mettere questo modello sopra l'orologio disegnato dal paziente sovapponendo le "12:00" Regolare il modello massimizzando il punteggio per i numeri e le mani. Il punteggio totale è 15.

Numeri

- Per i numeri 12, 3, 6 e 9, il punteggio 1 punto se toccano le rispettive linee, 0 punti se non toccano le rispettive linee, 0 se il numero viene omesso.
- Per i numeri 1, 2, 4, 5, 7, 8, 10, e 11 punteggio 1 punto per ogni numero nel quadrante corretto, 0 punti se il numero è fuori dal quadrante, 0 se viene omesso il numero.
- Sottrarre 1 punto per ogni numero ripetuto o superiore a 12.

Mani

Il punteggio per il posizionamento delle mani. Se le mani sono disegnate all'interno del campo, segnare 1 punto per ogni mano, se le mani sono disegnate al di fuori della linea tratteggiata o sono omessi punteggio 0; Lascia 1 punto se le mani si uniscono al perno.

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Appendix 4.5. Portugeuse translation of the Q*mci*.

Teste Rápido de Transtorno Cognitivo Leve (Q*mci, em inglês)*

Diretrizes de Administração e Pontuação

1. Orientação

Pontuação

2 pontos para a resposta correta, 1 ponto para as respostas erradas e 0 pontos no caso de não responder ou dar uma resposta não relacionada conceitualmente (ver detalhes abaixo)

Tempo

Máximo de 10 segundos para cada resposta

Instruções e Guia de Pontuação

Ano	Se a pessoa dá o resultado certo obtém 2 pontos, o ano incorreto pontua 1 ponto e 0 pontos se o ano não for indicado.
Pais	2 pontos para o país correto, 1 ponto para o país errado e 0 se nenhum país for pronunciada
Mês	Pontuação de 2 pontos para o mês correto ou para o mês anterior ou seguinte, se dentro de uma margem dois dias entre cada mês (por exemplo, se a data é 30 de setembro, pontua o total de 2 pontos se a pessoa responder outubro. Da mesma forma, se a data é 2 de outubro, a pontuação é de 2 pontos se a pessoa disser setembro). Pontuação de 1 ponto se o mês é incorreto e 0 se nenhum mês for pronunciada.
Data	Pontuação de 2 pontos para a data exata ou ± um dia, um ponto para qualquer outra data, 0 se nenhuma data for pronunciada
Dia da semana	2 pontos para o dia correto, 1 ponto para o dia incorreto, 0 se nenhum dia for pronunciado

Para começar, diga...

"Gostaria de lhe fazer algumas perguntas e alguns problemas para resolver. Está de acordo?"

Qual é este país? _____

Que ano é este? _____

Que mês é este? _____

Que data é hoje? _____

Que dia de semana é este? _____

Pontuação _____ / 10

2. Registro de Palavras

Instruções e Guia de Pontuação

Pontuação

Pontuação de 1 ponto para cada palavra recordada após a primeira leitura. Se a pessoa relembrar as cinco em total, repetir os cinco itens de uma vez só, em seguida, continuar com o desenho do relógio. Se a pessoa não repetir as 5 palavras, voltar a repetir os 5 itens e pedir á pessoa para repeti-las. Realizar este processo até que ela se lembre corretamente de todos os 5 itens ou repetir um máximo de três testes. Não pontuar os testes 2 e 3. Estes testes servem para ajudar a pessoa a aprender, em preparação para o exercício de memória tardia.

Tempo

Diga as palavras bem definidamente, uma por segundo. Aguarde 10 segundos para fazer memória.

Para começar, diga…
"Vou dizer 5 palavras. Depois de eu ter dito estas 5 palavras, repita-as. Esta preparado?"

Cão	**Chuva**	**Manteiga**	**Amor**	**Porta**

Pontuação _____ / 5

Quando finalizar, diga … **"Lembre-se destas palavras, porque eu vou pedir-lhe para recordá-las mais tarde."**
Os grupos de palavras alternativas incluem …

Gato	**Escuro**	**Pimenta**	**Medo**	**Cama**
Rato	**Calor**	**Pão**	**Redondo**	**Cadeira**

3. Desenho do Relógio

Instruções e Guia de Pontuação



Pontuação

Coloque o círculo do modelo de pontuação transparente sobre o círculo do relógio que o paciente completou. Gire o círculo modelo de modo a alinhar o "12". Pontuação de 1 ponto para cada caso se 1, 2, 4, 5, 7, 8, 10, e 11 estiverem nos quadrantes corretos. Pontuação de 1 ponto cada um, se o 12, 3, 6 e 9 tocarem as linhas do quadrante correspondente. Subtrair um ponto por cada número repetido ou acima de 12. (Caso o paciente não ter desenhado um "12" alinhar o modelo com o 3, 6 ou 9)

Pontuar o posicionamento das agulhas de acordo com as dicas e o ponto central. Atribuir um ponto para cada agulha situada entre as linhas tracejadas. Marcar um ponto para as agulhas unidas ao ponto central.



Tempo

Um minuto.

Para começar …

Dê a folha de papel com o círculo pré-desenhado e um lápis ao paciente. Diga "**Agora coloque os números, como se fosse a face de um relógio."** Depois diga **"Coloque as agulhas para indicar as 11h.10m.." Coloque os números e as agulhas tão cuidadosamente quanto puder**. "

Poder-se-á solicitar cada uma das fases: ... **"coloque os números ... marque as 11 horas y 10 minutos"**

Pontuação:	Números	Correto	+ _____/ 12
		Errôneo	- _____
	Agulhas		+ _____/ 2
	Ponto central		+ _____/ 1
	Total		**+ _____/ 15**

4. Memória tardia

Instruções e Guia de Pontuação

 ***Pontuação***

Pontuar 4 pontos por cada palavra recordada. Os sujeitos poderão recordar as palavras em qualquer ordem

 ***Tempo***

10 segundos.

Para começar, diga...

Há uns minutos eu nomeei cinco palavras. Diga todas as palavras que se lembrar.

Cão	**Chuva**	**Manteiga**	**Amor**	**Porta**

Pontuação _____ / 20

Os grupos de palavras alternativas incluem ...

Gato	**Escuro**	**Pimenta**	**Medo**	**Cama**
Rato	**Calor**	**Pão**	**Redondo**	**Cadeira**

5. Fluidez Verbal

Instruções e Guia de Pontuação

 *Pontuação.*

Atribuir ½ ponto para cada palavra correta recordada até um máximo de 40 palavras. Arredondar para cima a pontuação final. Não conte duas vezes as palavras com sufixos diferentes (por exemplo, peixe / peixes, rato / ratos, etc.) Aceite espécies alternativas (por exemplo, gralha azul, robin, pardal, pato, etc.) Formas alternativas incluem frutas e legumes, cidades e vilas.

 *Tempo.*

60 segundos. Anotar cada palavra que o paciente pronunciar. (Talvez seja necessário realizar uma espécie de "atalho" para os pacientes mais rápidos, como escrever as 3 primeiras letras de cada palavra e concluí-las mais tarde.)

Para começar, diga...

"Diga o maior número de *animais* que se lembrar em um minuto. Preparado? Comece."

Pontuação _____ / 20

6. Memória Lógica

Instruções e Guia de Pontuação



Pontuação.

Atribuir dois pontos para cada palavra correta lembrada textualmente. Todas as palavras ressaltadas em negrito dentro de cada seção deve ser recordada para pontuar 2 pontos. Caso contrário, marcar 0. A memorização pode ser feita em qualquer ordem.



Tempo.

30 segundos. Marque cada palavra recordada.

Para começar, diga...

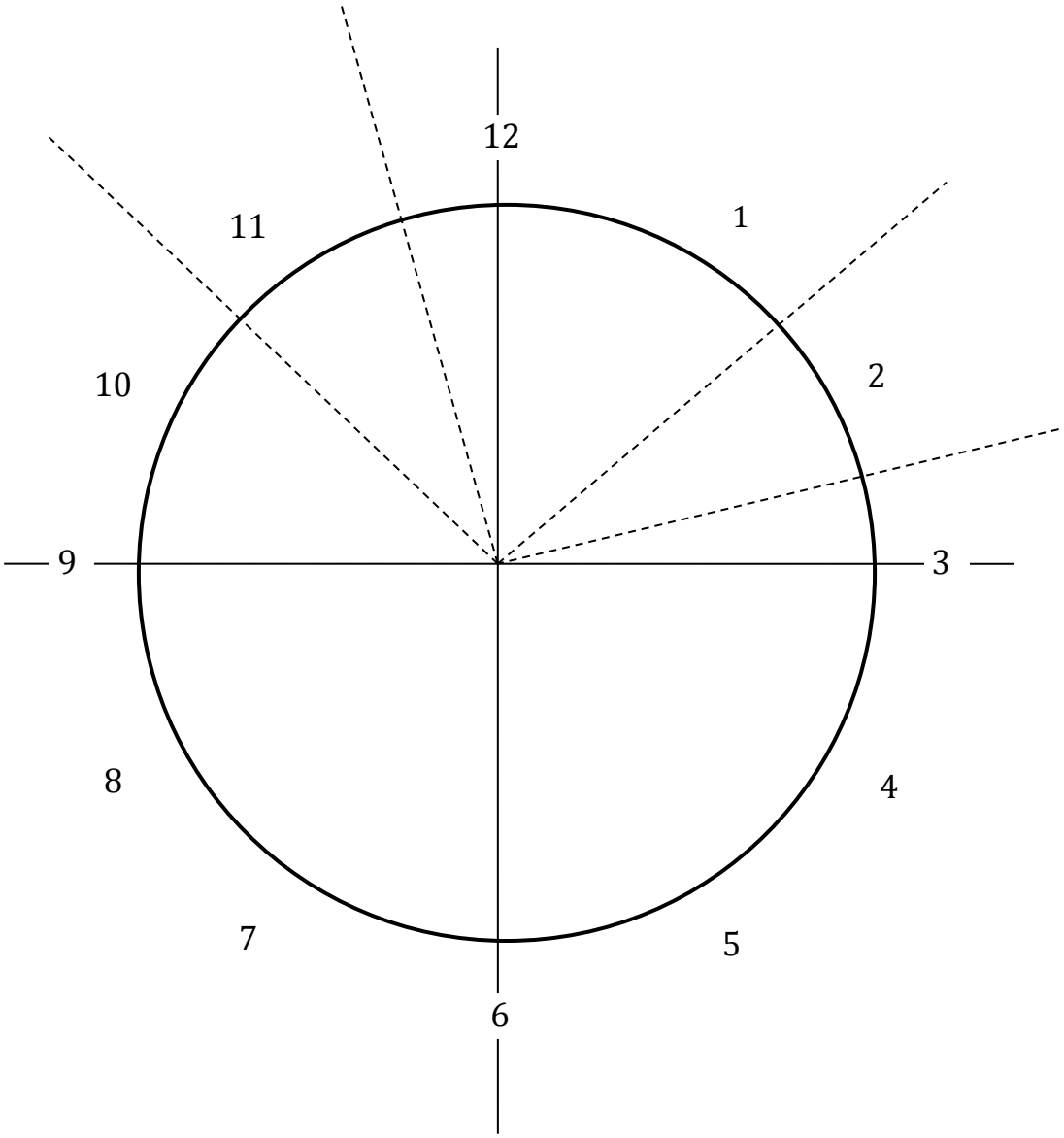
"Eu vou ler uma história curta. Depois que eu terminar de ler, quero que você me conte tudo o que puder da história. OK? "[Se o paciente indicar que está de acordo, então começar a ler o parágrafo em cerca de 1 segundo para cada unidade palavra]" **A raposa... vermelha .... corría através..... dos arbustos. "**

6. Memória Lógica			
A **raposa**	O **cão**	A **galinha**	2 / 0
Vermelha	**Castanho**	**Branca**	2 / 0
Corria através	**Corria através**	**Caminhava por**	2 / 0
De um **campo**.	De uma **ponte**.	Uma **estrada**.	2 / 0
arado	De **metal**	de **betão**	2 / 0
Ela era **perseguida** por	Estava a **caçar**	Era **perseguida** por	2 / 0
Um **cão**.	**Um coelho**.	**Um gato**.	2 / 0
castanho	**branco**	**preto**	2 / 0
Era uma **manhã**.	Era um **dia**.	Era uma **tarde**.	2 / 0
quente	**frio**	**calorosa**	2 / 0
De Maio	**De Outubro**	De **Setembro**	2 / 0
As **flores**	**As maçãs**	As **folhas**	2 / 0
Perfumadas	**maduras**	**Secas**	2 / 0
Floresciam	**Penduravam**	**Voavam**	2 / 0
Entre os **arbustos**.	Das **árvores**.	Com o **vento**.	2 / 0

Pontuação _____ / 30

Pontuação total Qmci **_____** / 100

O Modelo de Relógio de Pontuação Transparente



Pontuação

Colocar este modelo de pontuação sobre o relógio concluído com a linha "12 horas" do modelo sobre o número 12 desenhado pelo individuo. Ajustar o modelo para maximizar a pontuação correspondente aos números e às agulhas. A pontuação total é de 15. Gravar a pontuação no folha de classificação da seguinte forma

Números

- Para os números 12, 3, 6 e 9 marcar 1 (um) ponto, se tocarem as respectivas linhas, zero (0) ponto se falhar, e zero (0) se o número é omitido.
- Para os números 1, 2, 4, 5, 7, 8, 10 e 11 marcar 1 (um) ponto para cada número no quadrante correto, zero (0) ponto se o número estiver fora do quadrante, e zero (0), se o número for omitido.
- **Subtraia um ponto por cada número repetido ou superior a 12.**

Agulhas

- Pontuar a colocação completa da agulha. Se as agulhas estão desenhadas dentro da margem, pontuar com 1 (um) ponto cada agulha, se as agulhas estão desenhadas fora da linha tracejada ou são omitidas pontuar com zero (0); atribuir um (1) ponto, se as agulhas se juntarem no ponto central.

Appendix 4.6. Chinese (Mandarin) Translation of the Q*mci*

Quick *Mild Cognitive Impairment* screen (Q*mci*)
轻度认知功能障碍快速测试 （Q*mci*）

姓名: 出生年月: 受教育时间（年）: 日期:

1. 定向力 (1 分钟)

计分标准：答对得 2 分，答错或者试图回答得 1 分，不作答得 0 分

你现在在哪个国家? _____

今年是哪一年? _____

本月份是那个月? _____

今天几号? _____

今天星期几? _____

得分 _____ / 10

2. 词语即刻记忆 (30 秒)

开始说...

“我现在要说出 5 个词语。在我说完这 5 个词之后，把它们重复给我。准备好了吗?”

计分标准：不许提示，不管以任何顺序，每答对一个词得一分。

狗 **下雨** **黄油** **爱情** **门**

得分 _____ / 5

可供选择的词语还有...

猫	**黑暗**	**胡椒**	**害怕**	**床**
老鼠	**热**	**面包**	**圆形**	**椅子**

3. 临摹钟表 (1 分钟)

“画一个圆圈作为钟表的表盘，注明 12 个小时，并画出时间‘十一点十分’。”

计分标准：每标对一个数字得一分，每画对一个指针得一分，如能正确地放置轴心得一分。 数字如有重复，或者大于 12（例如 15 或 45），扣一分。

得分:	数字	正确	+ _____/ 12
		错误	- _____
	指针		+ _____/ 2
	轴心		+ _____/ 1
	共计		**+ _____/ 15**

4. 延迟复述 (30 秒)

开始说...

“几分钟前我说出过 5 个词语。请尽你最大的可能把它们复述给我。”

计分方法：不许提示，不管以任何顺序，在 30 秒内每答对一个词得 4 分

狗　　下雨　　黄油　　爱情　　门

得分 _____ / 20

5. 语言流畅性 (1 分钟)

“在一分钟之内说出你能想到的所有的动物名称。准备好了吗？开始。”

计分方式：每说出一个动物得半分，最多 40 个动物。动物种类，例如鸟，鱼，昆虫等也可以接受。

得分 _____ / 20

请记录下来:

6. 逻辑记忆 (30 秒)

“我将要给你读一个故事。在此之后我希望你能够复述给我尽可能多的内容。好吗？” [当病人表示同意后，以一秒钟一个词的速度读出下面的段落。] **“一只...红色的...狐狸...跑过.....灌木。”**

计分方式：不许提示，可以以任何顺序，在 30 秒之内正确复述出如下的下划体字/词，每一个字/词 2 分。（另外还有两个故事可供选择。）

6. 逻辑记忆			
一只**红色的**	一只**褐色的**	一只**白色的**	2 / 0
狐狸	**狗**	**母鸡**	2 / 0
跑过	**跑过**	**穿过**	2 / 0
耕种后的	一座**金属**	一条**水泥**	2 / 0
田野。	**桥**。	**马路**。	2 / 0
它正被一只**褐色的**	它正在**搜寻**	它的后面**跟随**着	2 / 0
狗	一只**白色的**	一只**黑色的**	2 / 0
追赶着。	**兔子**。	**猫**。	2 / 0
这是一个**炎热的**	这是一个**寒冷的**	这是一个**温暖的**	2 / 0
五月的	**十月的**	**九月的**	2 / 0
早晨.	**一天**。	**下午**。	2 / 0
芬芳的	**熟透了的**	**干枯的**	2 / 0
花朵	**苹果**	**叶子**	2 / 0
正在**灌木丛**中	正**悬挂**在	正在**风**中	2 / 0
生长着。	**树上**。	**摇摆着**。	2 / 0

得分 _____ / 30

Q*mci* 总分 _____ / 100

*正常 > 60
□度□知功能
障碍=50-60
痴呆症 <50

评分人 _____**日期** / /

*由年龄和教育年限决定

Appendix 4.7. Tamil Translation of the Q*mci*.

விரைவு மனநலக் குறைபாட்டு கேள்வித்தாள்

பெயர்: பிறந்த தேதி:

பாலினம்: படிப்பு:

தேதி: நேரம்:

1. நோக்குநிலை: (_____/10) (ஒரு நிமிடம்)
   நான் கேட்கும் கேள்விகளுக்கு விரைவாக பதில் சொல்ல முயற்சி செய்யுங்கள்.

   - இது எந்த நாடு (___/2)
   - இது எந்த ஆண்டு (___/2)
   - இது எந்த மாதம் (___/2)
   - இன்றைய தேதி என்ன (___/2)
   - இன்று எந்த கிழமை (___/2)

2. சொல் பதிவு: (_____/5) (30 வினாடிகள்)

   நான் உங்களிடம் ஐந்து சொற்கள் கூறுவேன் அதை நீங்கள் திரும்ப கூற வேண்டும்.

   - நாய், மழை, வெண்ணை, அன்பு, கதவு.

   மாற்று சொற்கள்:
   - பூனை, இருட்டு, மிளகு, பயம், மெத்தை.
   - எலி, வெப்பம், ரொட்டி, வட்டம், நாற்காலி.

3. கடிகாரம் வரைதல்: (____/15) (ஒரு நிமிடம்)

   உங்களுக்கு கொடுக்கப்பட்ட வட்டத்தில் கடிகாரம் வரைந்து பதினொற்று பத்து மணியை குறிக்கவும்.

   - எண்: (____/12)
   - முள்: (___/2)
   - மணி சரியாக குறித்தால்: (____/1)

4. நினைவூட்டுதல்: (___/20) (30 வினாடிகள்)

சிறிது நேரம் முன் கூறிய ஐந்து சொற்களை மறுபடியும் சொல்லவும்.

- நாய், மழை, வெண்ணை, அன்பு, கதவு.

மாற்று சொற்கள்:

- பூனை, இருட்டு, மிளகு, பயம், மெத்தை.
- எலி, வெப்பம், ரொட்டி, வட்டம், நாற்காலி.

5. வாய்மொழி சரள: (____/20) (ஒரு நிமிடம்)

உங்களுக்கு தெறிந்த விலங்கு பெயர்களை வரிசையாக கூறவும்.

- 0.5 * விலங்கின் எண்ணிக்கை : _____

6. தருக்க நினைவுத்திறம்: (_____/30) (30 வினாடிகள்)

நான் உங்களுக்கு ஒரு கதை சொல்லுவேன். அதை நீங்கள் முடிந்த வரை எனக்கு மறுபடியும் கூற வேண்டும்.

ஒரு **சிவப்பு நரி உழுத நிலத்**தில் ஓடியது அதை **விரட்டியடித்தது** ஒரு **பழுப்பு நாய்**.

அது ஒரு **சூடான மே** மாத **காலை**, **மணம்** வீசும் **பூக்கள் செடிகளில்** பூத்து கொண்டிருந்ததது.

மாற்று கதை:
அது **ஒரு குளி**ரான **அக்டோபர் தின**ம், **ஆப்பிள்** கனிகள் மரத்தில் காய்த்து **தொங்கி**க் கொண்டிருந்தன.

ஒரு பழுப்பு நாய் பாலத்தில் ஓடியது, அது ஒரு வெள்ளை முயலை வேட்டையாடியது.

மொத்த மதிப்பெண்: _____/100.

Appendix 4.8. Greek Translation of the Q*mci*.

Δοκιμασία Σύντομης Ανίχνευσης της Ήπιας Γνωστικής Διαταραχής (Q*mci*)

Όνομα: Ημ γενν: Φύλο: Έτη εκπαίδευσης:
Ημερ: Χρόνος:

1. Προσανατολισμός **Ξεκινήστε ρωτώντας 5 ερωτήσεις :** 🕒 Ένα λεπτό. ✎ Δώστε **2 βαθμούς για κάθε σωστή απάντηση**, 1 εφ΄όσον απάντησε λανθασμένα, 0 αν δεν απάντησε καθόλου.	**Σε ποια χώρα βρισκόμαστε;** __ / 2 **Τι έτος έχουμε;** __ / 2 **Τι μήνα έχουμε;** __ / 2 **Τι ημερομηνία έχουμε;** __ / 2 **Τι ημέρα της εβδομάδας έχουμε;** __ / 2	**Βαθμολ** **_/ 10**
2. Εγχάραξη λέξεων Ξεκινήστε λέγοντας… **"Πρόκειται να σας πω 5 λέξεις. Αφού σας πω και τις 5 λέξεις, να μου τις επαναλάβετε. Είστε έτοιμος/έτοιμη;"** 🕒 30 δευτερόλεπτα. ✎ Δώστε **1 βαθμό για κάθε λέξη που** επαναλήφθηκε, ανεξαρτήτως σειράς, χωρίς υποβοήθηση.	**Σκύλος Βροχή Βούτυρο Αγάπη Πόρτα** Εναλλακτικές λέξεις περιλαμβάνουν… **Γάτα Σκοτάδι Πιπέρι Φόβος Κρεβάτι** **Ποντικός Ζέστη Ψωμί Στρογγυλός Καρέκλα**	**Βαθμολ** **_/ 5**
3. Σχεδίαση ρολογιού **"Χρησιμοποιήστε τον κύκλο που υπάρχει πάνω στη σελίδα ώστε να σχεδιάσετε την όψη ενός ρολογιού και ορίστε να δείχνει την ώρα έντεκα και δέκα."** 🕒 Ένα λεπτό κατά προσέγγιση. ✎ Δώστε ένα βαθμό για κάθε αριθμό, ένα για κάθε δείκτη και ένα για τη σωστή τοποθέτησή τους, ή κοντά στην ιδανική τους θέση. Αφαιρέστε από ένα βαθμό για κάθε αριθμό που αναγράφεται για δεύτερη φορά, ή είναι μεγαλύτερος του 12, π.χ.15 ή 45.	**Βαθμολ: Αριθμοί** Σωστά + _____/ 12 Λάθοι - _____ Δείκτες + _____/ 2 Άξονας περιστροφής + _____/ 1 **Σύνολο + _____/ 15**	**Βαθμολ** **_/ 15**
4. Καθυστερημένη ανάκληση **"Λίγα λεπτά πριν σας ανέφερα πέντε λέξεις.**	**Σκύλος Βροχή Βούτυρο Αγάπη Πόρτα** Εναλλακτικές λέξεις περιλαμβάνουν…	**Βαθμολ**

Να μου επαναλάβετε όσες περισσότερες από αυτές θυμάστε." 🕒 30 δευτερόλεπτα. ✎ Ανάκληση ανεξαρτήτως σειράς, εντός 30 δευτερολέπτων, δίνει 4 βαθμούς για κάθε λέξη, χωρίς υποβοήθηση.	**Γάτα** **Σκοτάδι** **Πιπέρι** **Φόβος** **Κρεβάτι** **Ποντικός** **Ζέστη** **Ψωμί** **Στρογγυλός** **Καρέκλα**	**__/ 20**
5. Λεκτική ευχέρεια (ροή) **"Αναφέρετε όσο περισσότερα ονόματα ζώων μπορείτε μέσα σε ένα λεπτό. Είστε έτοιμοι; Πάμε."** 🕒 Ένα λεπτό. ✎ Δώστε μισό βαθμό για κάθε όνομα ζώου που αναφέρεται, με μέγιστο τα 40. Αποδεκτά γίνονται όλα τα "έμβια" συμπεριλαμβανομένων πουλιών, ψαριών, εντόμων κλπ. Δεν προσμετρούνται δυο φορές λέξεις με διαφορετική κατάληξη που αφορούν το ίδιο ζώο, π.χ. γάτα/γάτες, όμως επιτρέψτε και βαθμολογήστε παρόμοια ονόματα όπως μοσχάρι, αγελάδα, βόδι.	Εναλλακτικές κατηγορίες λέξεων συμπεριλαμβάνουν: **Φρούτα και Λαχανικά** **Βαθμολογήστε με 0.5 x αριθμό ζώων που αναφέρθηκαν =** Να σημειωθούν σύντομα εδώ εφόσον χρειαστεί:	**Score** **__/ 20**

6. Λογική μνήμη
"Πρόκειται να σας διαβάσω μια σύντομη ιστορία. Αφού ολοκληρώσω την ανάγνωση θέλω να μου πείτε όσες περισσότερες λεπτομέρειες από την ιστορία μπορείτε. Εντάξει;"
🕒 30 δευτερόλεπτα.
Δώστε **2 βαθμούς για κάθε λέξη με έντονη γραφή που ανακλήθηκε με ακρίβεια,** αμέσως μέσα σε 30 δευτερόλεπτα, ανεξαρτήτως σειράς, χωρίς υποβοήθηση. Δυο εναλλακτικές ιστορίες διατίθενται.

1η Ιστορία		**Εναλλακτική 1η Ιστορία**		**Εναλλακτική 2η Ιστορία**	
Η **κόκκινη**	Ήταν ένα **ζεστό πρωινό**	Ο **καφέ**	Ήταν μια **κρύα μέρα**	Η **άσπρη**	Ήταν ένα **ζεστό**
αλεπού	του **Μαΐου**	**σκύλος**	του **Οκτώβρη**	**κότα**	**απόγευμα**
διέσχισε	**Μυρωδάτα**	**διέσχισε**	**Ώριμα μήλα**	**περπάτησε**	του **Σεπτέμβρη**.
το **οργωμένο**	**άνθη**	τη **μεταλλική**	**κρέμονταν**	τον **τσιμεντένιο**	**Ξερά**
χωράφι.	**σχηματίζονταν**	**γέφυρα**.	από τα	**δρόμο**.	**φύλλα**
Την **κυνηγούσε**	στους **θάμνους**	**Κυνηγούσε**	**δένδρα**	Την **ακολούθησε**	ανέμιζαν
ο **καφέ σκύλος**		ένα **άσπρο κουνέλι**		η **μαύρη γάτα**	**στον αέρα**.

Βαθμολ
__/ 30

Q*mci* Συνολική Βαθμολογία
***__/ 100 *Να προσαρμοστεί η βαθμολογία για την ηλικία και εκπαιδευτικό επίπεδο** (βλέπε παρακάτω). **Χορηγήθηκε από:_____**